Studies on Reaction Conditions and New Entry to Chiral Ligands in the Chiral Lithium Amide-Mediated Enantioselective Aldol Reaction¹⁾

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Reaction conditions for the enantioselective aldol reaction of 2,2-dimethyl-3-pentanone (3) and benzaldehyde using the chiral lithium amide 1b as a chiral auxiliary were thoroughly investigated. All three procedures, that is, (1) the combined use of lithium diisopropylamide and the chiral lithium amide 1b, (2) the use of an excess of the chiral lithium amide 1b, and (3) the regeneration of the chiral lithium amide 1b, afforded the aldol 4 in about 90% yield and 70% enantiomeric excess (ee). Investigation of the effects of solvent by utilizing 1-naphthaldehyde revealed that in tetrahydrofuran, (*S,S*)-aldol 5 of 77% ee was obtained as the major product, while in ether (*R,R*)-5 became the major isomer (38% ee). Furthermore, addition of hexamethylphosphoric triamide caused a dramatic change of stereoselectivity, and (*S,S*)-5 of 70% ee was obtained in ether with 20 eq of hexamethylphosphoric triamide. The aldol 4 of 74% ee was obtained when the new chiral lithium amide 6b was used.

Keywords enantioselective aldol reaction; lithium enolate; lithium diisopropylamide; chiral lithium amide; chiral auxiliary; solvent effect; hexamethylphosphoric triamide

The aldol reaction is one of the most representative carbon-carbon bond-forming reactions and many researches have been concerned with the stereoselectivity of this reaction.²⁾ We have already reported³⁾ the enantioselective aldol reactions of ketone lithium enolates and aldehydes utilizing chiral lithium amides as chiral auxiliaries, covering the substituent effects of chiral lithium amides and the generality of this reaction. It was shown that the chiral lithium amides **1b** and **2b**, derived from (*S*)-2-isopropylamino-1-methoxy-3-methylbutane (**1a**) and (*R*)-2-isopropylamino-1-methoxy-2-phenylethane (**2a**), respectively, are very effective chiral auxiliaries. In the presence of these ligands, the reaction of the enolate of 2,2-dimethyl-3-pentanone (**3**) and benzaldehyde or 1-naphthaldehyde proceeded in good chemical yield (84–93%) and good enantioselectivity (68–77%) to give the aldol **4** or **5**, respectively (Chart 1).⁴⁾ With reference to the stereoselectivity of this reaction, we have thoroughly investigated the reaction conditions and have further become interested in using this reaction as a new entry to chiral ligands which possess two chiral centers. In this report, we would like to present the results of these investigations.

In our previous studies,^{3a)} it was clarified that the reaction of a lithium enolate and an aldehyde in the presence of a chiral lithium amide is very important to obtain an aldol

in good enantiomeric excess (ee), since the chiral lithium amide is a more effective chiral ligand than the chiral amine itself. We have therefore used the combination of lithium diisopropylamide (LDA) and a chiral lithium amide expecting that LDA would act as a strong base while the chiral lithium amide acts as a chiral auxiliary. We were able to obtain the aldol **4** in 93% chemical yield and 68% ee when the ketone **3** was treated with 1.2 eq of LDA and an equimolar amount of the chiral lithium amide **1b** at -10°C for 30 min and then the enolate was allowed to react with benzaldehyde at -70°C for 5 min. However, under these conditions, it seems possible that diisopropylamine, which is formed when the ketone **3** is converted to its enolate, might affect the reaction pathway to change the stereoselectivity. Furthermore, the above conditions, involving the reaction of the enolate in the presence of the chiral lithium amide, could also be produced in the following ways: (1) when the ketone is lithiated with excess chiral lithium amide and (2) when the chiral amine which results when the chiral lithium amide acts as strong base to form the ketone lithium enolate is reconverted to the lithium amide by adding *n*-butyllithium.⁵⁾ So we first examined these points. The results are summarized in Table I. When the ketone **3** was lithiated with 2.4 eq of the chiral lithium amide **1b** at -10°C for 30 min and then allowed to react with benzaldehyde, the *erythro* aldol **4**⁶⁾ was obtained in 84% yield and 70% ee. Neither lowering of the lithiation temperature to -70°C nor the use of 5.0 eq of the chiral lithium amide **1b** raised the stereoselectivity of the reaction. On the other hand, almost the same chemical yield (90%) and enantiomeric excess (67% ee) were also realized when 1.2 eq of the chiral lithium amide was employed if 1.0 eq of *n*-butyllithium was added after the lithiation of the ketone **3** with **1b** was completed.

Thus all three procedures, that is, (1) the combination of LDA and the chiral lithium amide **1b**, (2) the use of excess chiral lithium amide **1b** and (3) the regeneration of the chiral lithium amide **1b** after the lithiation of the ketone **3**, afforded the aldol **4** in about 90% yield and 70% ee. These results suggest that the same complex is formed from the enolate and the chiral lithium amide regardless of the formation method. In other words, the chiral amine **1a** or

Chart 1

TABLE I. Aldol Reaction of 2,2-Dimethyl-3-pentanone (3) with Benzaldehyde in the Presence of the Chiral Lithium Amide 1b

Run	1a (eq)	$((\text{CH}_3)_2\text{CH})_2\text{NH}$ (eq)	$n\text{-C}_4\text{H}_9\text{Li}$ (eq)	Lithiation conditions Temp (°C)	Time (min)	Isolated yield of 4 (%) ^{a)}	% ee (config.) ^{b)}
1	2.4		2.4	-10	30	84	70 (S, S)
2	2.4		2.4	-70	300	68	69 (S, S)
3	5.0		5.0	-10	30	59	60 (S, S)
4	1.2		1.2 + 1.0 ^{c)}	-10	30	90	67 (S, S)
5	1.2	1.2	2.4	-10	30	93	68 (S, S)
6	1.2	1.2	2.4	-70	30	88	33 (S, S)
7	1.2	1.2	2.4	-70	180	79	48 (S, S)

a) Only the *erythro* isomer was obtained. b) Determined by HPLC analysis using a chiral stationary phase column. c) This amount of *n*-butyllithium was added after the lithiation of the ketone 3 was completed.

TABLE II. Effects of Solvent and Additive

Run	Solvent	Additive ^{a)} (eq)	Isolated yield of 5 (%)	Ratio ^{b)} <i>Erythro</i> : <i>Threo</i>	% ee of <i>erythro</i> isomer (config.) ^{b)}	% ee of <i>threo</i> isomer (config.) ^{b)}
1	THF		85	97 : 3	77 (S, S)	21 (R, S)
2	Ether		76	92 : 8	38 (R, R)	36 (R, S)
3	Toluene		58	58 : 42	11 (R, R)	6 (S, R)
4	DME ^{c)}		92	85 : 15	24 (R, R)	59 (R, S)
5	THF	TMEDA (1.2)	94	97 : 3	78 (S, S)	28 (R, S)
6	THF	TMEDA (20.0)	87	95 : 5	75 (S, S)	18 (S, R)
7	Ether	TMEDA (1.2)	89	92 : 8	35 (R, R)	32 (R, S)
8	Ether	TMEDA (20.0)	71	91 : 9	20 (R, R)	2 (R, S)
9	THF	HMPA (1.2)	86	94 : 6	68 (S, S)	14 (S, R)
10	Ether	HMPA (1.2)	82	95 : 5	58 (S, S)	2 (R, S)
11	Ether	HMPA (20.0)	72	98 : 2	70 (S, S)	14 (S, R)

a) TMEDA: *N,N,N',N'*-tetramethylethylenediamine. HMPA: hexamethylphosphoric triamide. b) Determined by HPLC analysis. c) 1,2-Dimethoxyethane.

diisopropylamine would not participate in the chiral recognition of this reaction.⁷⁾ On the other hand, it has already been revealed^{3a)} that when the ketone was lithiated by utilizing 1.2 eq of LDA and 1.2 eq of the chiral lithium amide 1b at -70°C for 30 min, the enantiomeric excess of the aldol 4 fell to 33%. This temperature effect can be explained by considering the participation of diisopropylamine. When LDA deprotonates the ketone 3 to form the enolate, this enolate would form a complex with diisopropylamine and the conversion of this enolate–diisopropylamine complex to the enolate–chiral lithium amide complex would be slow at -70°C . In fact, when the ketone 3 was treated with LDA and the chiral lithium amide 1b at -70°C for 3 h, the enantiomeric excess of the aldol 4 rose to 48%. From the above investigations, we concluded that the most effective reaction conditions are as follows: the ketone is lithiated by using the combination of LDA and the chiral lithium amide at -10°C for 30 min, then allowed to react with aldehyde at -70°C for 5 min. We used these

reaction conditions for further studies.

Since tetrahydrofuran (THF) is the most widely used solvent in the reaction of lithium enolates and we had used this solvent for previous studies, we next examined the effects of solvent and then additive using the reaction of the ketone 3 and 1-naphthaldehyde in the presence of the chiral lithium amide 1b. The results are summarized in Table II. As previously reported,^{3b)} when this reaction was performed in THF the aldol 5 was obtained in 85% yield with good diastereoselectivity⁶⁾ (*erythro*:*threo*=97:3). The enantiomeric excess of the *erythro* isomer was 77% and the absolute configuration of the major enantiomer was (S,S).⁸⁾ On the other hand, when diethyl ether was used as the solvent, the diastereoselectivity was still high (*erythro*:*threo*=92:8). Interestingly, however, the absolute configurations of the major enantiomer were reversed and (R,R)-5 of 38% ee was obtained. Both diastereo- and enantioselectivities decreased in toluene or 1,2-dimethoxyethane.

We next studied the effects of additives in THF or

ether. The addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) had little effect on the stereoselectivity in both solvents. However, when hexamethylphosphoric triamide (HMPA) was added, the stereoselectivity changed dramatically. In THF, the addition of 1.2 eq of HMPA lowered the enantiomeric excess of the aldol **5** to 68%. In contrast, when the reaction was performed in ether with 1.2 eq of HMPA, reversal of the enantioselectivity was again observed and (*S,S*)-**5** of 58% ee was obtained as the major isomer. Furthermore, the increase of the amount of HMPA caused an increase of the enantiomeric excess and finally 70% ee was achieved when 20 eq of HMPA was added.

From the above results, it is clear that the enolate derived from the ketone **3** reacts with the aldehyde at opposite faces depending on the reaction conditions. In THF or ether-HMPA, the enolate mainly attacks from the *re*-face to afford the (*S,S*)-aldol while in ether it attacks from the *si*-face to afford the (*R,R*)-aldol. These facts indicate that the structure of the major complex which is formed from the enolate and the chiral lithium amide in THF or ether-HMPA is different from that formed in ether. Although the precise structure of the complex is still unknown,⁷⁾ it seems reasonable that the structure of the

chiral lithium amide, especially its conformation,⁹⁾ plays an important role in the stereoselectivity. According to this assumption, we have prepared many chiral amines which have various substituents on chiral carbon, nitrogen and the chelating group and have investigated the effects of these substituents.³⁾ However, we have not yet examined chiral amines possessing two chiral centers in the molecule. So we were next interested in the effects of a newly introduced chiral center.

Since the chiral lithium amide **2b** having the phenyl group on the chiral carbon has turned out to be a very effective chiral ligand,³⁾ we decided to introduce another phenyl group into this molecule. Thus, we designed new chiral amines **6**–**8** and prepared them by the method shown in Chart 2. At first we tried to convert (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**9**)¹⁰⁾ to its *N*-isopropyl-*O*-methyl derivative **6a** according to the method developed earlier.^{3b)} Although the reductive isopropylation using sodium cyanoborohydride and acetone proceeded smoothly, the yield of *O*-methylation utilizing sodium or potassium hydride and methyl iodide¹¹⁾ was unsatisfactorily low because of the concomitant formation of *N*-methyl and *N,O*-dimethyl derivatives. The use of silver oxide-methyl

Chart 2

TABLE III. Aldol Reaction of 2,2-Dimethyl-3-pentanone (**3**) and Benzaldehyde in the Presence of Various Chiral Lithium Amides

Run	Chiral lithium amide	Solvent	Isolated yield of 4 (%) ^{a)}	% ee (config.) ^{b)}
1	6b	THF	87	74 (R, R)
2	6b	Ether	70	17 (R, R)
3	<i>ent</i> - 6b	THF	88	62 (S, S)
4	7b	THF	79	58 (R, R)
5	<i>ent</i> - 7b	THF	73	59 (S, S)
6	<i>ent</i> - 7b	Ether	74	8 (S, S)
7	8b	THF	78	21 (R, R)
8	<i>ent</i> - 8b	THF	66	20 (S, S)
9	<i>ent</i> - 8b	Ether	65	5 (S, S)

a) Only the *erythro* isomer was obtained. b) Determined by HPLC analysis using a chiral stationary phase column.

iodide also proved to be unsuccessful. However, when the N-protected compound **10** was treated with sodium hydride and excess methyl iodide, the O-methylated derivative **11** was obtained in 79% yield. Acid hydrolysis of the *tert*-butoxycarbonyl group followed by reductive alkylation gave the desired chiral amino ether **6a** in good yield. In contrast to O-methylation, O-benylation of the N-isopropyl derivative **12** using potassium hydride and benzyl bromide afforded the O-benzyl derivative **7a** selectively in excellent yield. We further prepared the N,O-dimethyl derivative **8a** by treatment of the N-protected compound **10** with a large excess of sodium hydride-methyl iodide followed by acid hydrolysis. The enantiomers of **6–8** (*ent*-**6**—*ent*-**8**) were also prepared by the same methods from (1*R*,2*S*)-2-amino-1,2-diphenylethanol (*ent*-**9**).¹⁰⁾

Utilizing these chiral amino ethers, we investigated the aldol reaction of the ketone **3** and benzaldehyde. The results are summarized in Table III. When the chiral lithium amides **6b–8b** were used in THF, (*R,R*)-**4**⁸⁾ was obtained as the major isomer and as a matter of course, when *ent*-**6b**—*ent*-**8b** were used (*S,S*)-**4**⁸⁾ was predominant. Among them, the N-isopropyl-O-methyl derivative **6b** showed the highest enantioselectivity and 74% ee was realized. The N-isopropyl-O-benzyl derivatives **7b** and *ent*-**7b** gave the aldol **4** of about 60% ee, while the N,O-dimethyl derivatives **8b** and *ent*-**8b** showed poor selectivity. We also performed this reaction in ether in the presence of **6b–8b**. In contrast to the chiral lithium amide **1b**, the solvent effects were not so dramatic; we merely obtained the aldol **4** in low enantiomeric excess. Probably, these chiral lithium amides are too sterically bulky to form a complex of similar structure to that formed by the amide **1b** and the enolate of the ketone **3** in ether.

Thus we thoroughly investigated the reaction conditions of the aldol reaction using chiral lithium amide as the chiral auxiliary. We concluded that the combined use of LDA and the chiral lithium amide at -10°C to form the enolate-chiral lithium amide complex is the condition of choice. Furthermore, we found that both the solvent (THF or ether)

and the additive (HMPA) have a large influence on the stereoselectivity. We also examined new chiral ligands possessing two chiral centers in a molecule. Although the effects of the newly introduced chiral center are not as great as we had expected, we believe that further modification of the chiral lithium amide may provide more effective auxiliaries.

Experimental

Melting and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-2 spectrometer using nujol mulls or potassium bromide disks or as films. Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were recorded on a JEOL PMX-60, FX-100, EX-270 or GSX-400 spectrometer with tetramethylsilane as an internal standard in deuteriochloroform. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. High-performance liquid chromatography (HPLC) was carried out with an Erma Optical Works ERC-8710 high-performance liquid chromatograph using a Bakerbond TM (DNBPG) chiral column (RP-7103-0) (i.d. 4.6×250 mm, purchased from J. T. Baker Chemical Co.) as described earlier.^{3b)} Ether was distilled from lithium aluminum hydride and THF was distilled from benzophenone ketyl. Silica gel (BW-820 MH or BW-200, purchased from Fuji-Davison) was used for column chromatography. All reactions involving organometallic reagents were conducted under an argon atmosphere.

General Procedure for the Enantioselective Aldol Reaction First TMEDA or HMPA (if necessary) and then *n*-butyllithium (1.6 M in *n*-hexane, 1.5 ml, 2.4 mmol) were added to a solution of diisopropylamine (121 mg, 1.2 mmol) and the chiral amino ether (1.2 mmol) in a solvent (8 ml) at -10°C . After 30 min, the ketone **3** (114 mg, 1.0 mmol) in the same solvent (2 ml) was added over 5 min. The mixture was stirred at -10°C for 30 min then cooled to -70°C , and benzaldehyde or 1-naphthaldehyde (1.1 mmol) was added in one portion. After 5 min, saturated aqueous ammonium chloride (2 ml) was added and the mixture was warmed to room temperature. Water (20 ml) was added, and the mixture was extracted with ether. The organic layer was washed with 10% aqueous citric acid, water, and saturated aqueous sodium chloride and dried over sodium sulfate. After concentration *in vacuo*, the residue was purified by chromatography on silica gel using *n*-hexane-ethyl acetate (15:1, for **4**) or *n*-hexane-ether (15:1, for **5**) as an eluent. The enantiomeric excess of each aldol was determined by HPLC according to the method previously reported.^{3b)} The results are summarized in Tables II and III.

(1*S*,2*R*)-2-*tert*-Butoxycarbonylamino-1-methoxy-1,2-diphenylethane (11**)** Di-*tert*-butyl dicarbonate (5.98 g, 27.4 mmol) in dioxane (15 ml) was added to a solution of (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**9**)¹⁰⁾ (5.28 g, 25 mmol) in dioxane (35 ml), and the mixture was stirred at room temperature for 4.5 h. After addition of water, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over sodium sulfate. Removal of the solvent gave almost pure **10** (7.47 g, 96%), which was used for the next step without further purification. The *N*-protected alcohol **10** (313 mg, 1.0 mmol) and methyl iodide (0.62 ml, 10 mmol) were added to a suspension of sodium hydride (60% oil suspension, 42 mg, 1.1 mmol) in THF (10 ml), and the mixture was stirred at room temperature for 4 h. Water was added to the mixture, and the whole was extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane: ethyl acetate = 5:1 as an eluent) to give **11** (258 mg, 79%) as a colorless solid, mp $165.5\text{--}167^\circ\text{C}$ (ethyl acetate). $[\alpha]_D^{25} + 104.9^\circ$ ($c = 1$, CHCl_3). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3380, 1685, 1510, 1170, 1110, 695. $^1\text{H-NMR}$ δ ppm: 1.40 (9H, s), 3.29 (3H, s), 4.56 (1H, s), 4.84 (1H, brs), 5.49 (1H, brs), 6.9—7.0 (4H, s), 7.1—7.3 (6H, s). *Anal.* Calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.25; H, 7.66; N, 4.02.

(1*R*,2*S*)-2-*tert*-Butoxycarbonylamino-1-methoxy-1,2-diphenylethane (*ent*-11**)** This compound was prepared from (1*R*,2*S*)-2-amino-1,2-diphenylethanol (*ent*-**9**)¹⁰⁾ by the same procedure as described above. A colorless solid, mp 171.5°C (benzene). $[\alpha]_D^{25} - 97.7^\circ$ ($c = 1$, CHCl_3). The IR and $^1\text{H-NMR}$ spectra of this material were in agreement with those of the (1*S*,2*R*)-isomer **11**.

(1*S*,2*R*)-2-Isopropylamino-1-methoxy-1,2-diphenylethane (6a**)** Trifluoroacetic acid (2.5 ml) was added to a solution of the *tert*-butylurethane **11** (360 mg, 1.1 mmol) in dichloromethane (9 ml). The mixture was stirred at room temperature for 1.5 h and concentrated *in vacuo*. Benzene was added

to the residue and evaporated *in vacuo*. Water was then added to the residue and the solution was made basic with 10% aqueous sodium hydroxide. The solution was salted out with sodium chloride and extracted with ethyl acetate, and the organic layer was dried over sodium sulfate. Removal of the solvent gave the primary amine which was used for the next step without further purification. Sodium cyanoborohydride (117 mg, 1.9 mmol) and acetone (0.45 ml, 6.1 mmol) were added to a solution of the primary amine in methanol (13 ml), and the pH of the solution was adjusted to ca. 4 by adding acetic acid. The mixture was stirred for 3.5 h. Aqueous potassium carbonate (10%) was added to the mixture in an ice-bath, and the solution was extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium chloride, and dried over sodium sulfate. Concentration *in vacuo* provided the residue, which was purified by column chromatography on silica gel (*n*-hexane:ethyl acetate = 7:1—4:1 as an eluent) to give **6a** (270 mg, 91%) as a colorless oil, bp 140 °C (0.3 mmHg) (Kugelrohr). $[\alpha]_D^{20} + 103.2^\circ$ ($c = 1$, CH₃OH). IR $\nu_{\text{max}}^{\text{film}} \text{ cm}^{-1}$: 3300, 2950, 1450, 1105, 760, 700. ¹H-NMR δ ppm: 0.89 (3H, d, $J = 6.2$ Hz), 0.96 (3H, d, $J = 6.2$ Hz), 1.9 (1H, br s), 2.52 (1H, sept, $J = 6.2$ Hz), 3.18 (3H, s), 3.90 (1H, d, $J = 5.1$ Hz), 4.43 (1H, d, $J = 4.9$ Hz), 7.0—7.1 (2H, m), 7.1—7.2 (2H, m), 7.2—7.6 (6H, m). Anal. Calcd for C₁₈H₂₃NO: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.41; H, 8.77; N, 5.17.

(1*R*,2*S*)-2-Isopropylamino-1-methoxy-1,2-diphenylethane (ent-6a) This compound was prepared from the enantiomer of **11** (*ent*-**11**) by the same procedure as described above. A colorless oil, bp 145 °C (0.4 mmHg) (Kugelrohr). $[\alpha]_D^{23} - 99.3^\circ$ ($c = 1.4$, CH₃OH). The IR and ¹H-NMR spectra of this material were in agreement with those of the (1*S*,2*R*)-isomer **6a**.

(1*S*,2*R*)-1-Benzoyloxy-2-isopropylamino-1,2-diphenylethane (7a) (1*S*,2*R*)-2-Amino-1,2-diphenylethanol (**9**)¹⁰ was N-isopropylated by the same procedure as used for the preparation of **6a** to give **12**. The crude *N*-isopropyl derivative **12** was used in the next step without further purification. The amino alcohol **12** (79 mg, 0.3 mmol) was added to a suspension of potassium hydride (35% oil suspension, 181 mg, 1.6 mmol) in THF (1.5 ml) and the mixture was stirred for 30 min at room temperature. Benzyl bromide (0.18 ml, 1.5 mmol) was added and the mixture was stirred for another 30 min. Water was added, and the solution was extracted with ether. The organic layer was washed with saturated aqueous sodium chloride, and dried over sodium sulfate. The solvent was evaporated off *in vacuo*, and the residue was purified by chromatography on silica gel (*n*-hexane:ethyl acetate = 6:1 as an eluent). The desired amino ether **7a** was obtained (97 mg, 91%) as a colorless oil, bp 165 °C (0.2 mmHg) (Kugelrohr). $[\alpha]_D^{24} + 43.8^\circ$ ($c = 0.6$, CH₃OH). IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$: 3320, 2970, 1450, 1105, 1075, 760, 700. ¹H-NMR δ ppm: 0.85 (3H, d, $J = 6.2$ Hz), 0.91 (3H, d, $J = 6.3$ Hz), 1.62 (1H, s), 2.50 (1H, sept, $J = 6.3$ Hz), 3.94 (1H, d, $J = 6.0$ Hz), 4.19 (1H, d, $J = 11.8$ Hz), 4.41 (1H, d, $J = 11.9$ Hz), 4.57 (1H, d, $J = 5.9$ Hz), 7.0—7.3 (15H, m). Anal. Calcd for C₂₄H₂₇NO: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.60; H, 7.82; N, 3.67.

(1*R*,2*S*)-1-Benzoyloxy-2-isopropylamino-1,2-diphenylethane (ent-7a) This compound was prepared from (1*R*,2*S*)-2-amino-1,2-diphenylethanol (*ent*-**9**)¹⁰ by the same procedure as described above. A colorless oil, bp 175 °C (0.4 mmHg) (Kugelrohr). $[\alpha]_D^{23} - 43.7^\circ$ ($c = 1.1$, CH₃OH). The IR and ¹H-NMR spectra of this material were in agreement with those of the (1*S*,2*R*)-isomer **7a**.

(1*S*,2*R*)-1-Methoxy-2-methylamino-1,2-diphenylethane (8a) The *tert*-butylurethane **10** (626 mg, 2.0 mmol) and methyl iodide (2.5 ml, 40 mmol)

were added to a suspension of sodium hydride (60% oil suspension, 800 mg, 20 mmol) in THF (20 ml), and the mixture was stirred at room temperature for 2 h. The work-up procedure was the same as that for the preparation of **6a**. The crude *N*,*O*-dimethyl derivative **13** was used for the next step without further purification. Trifluoroacetic acid (1.5 ml) was added to a solution of **13** in dichloromethane (15 ml), and the solution was stirred at room temperature for 2 h. After concentration *in vacuo*, benzene was added to the residue and the mixture was again concentrated *in vacuo*. Saturated aqueous sodium bicarbonate was added to the residue and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium chloride and dried over sodium sulfate. The solvent was removed and the residue was purified by chromatography on silica gel (chloroform:methanol = 20:1 as an eluent) to give the *N*,*O*-dimethyl amino ether **8a** (432 mg, 90%) as a colorless solid, mp 133—134 °C (benzene). $[\alpha]_D^{24} + 39.6^\circ$ ($c = 1$, CHCl₃). IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$: 3330, 2900, 1450, 1100, 760, 700. ¹H-NMR δ ppm: 2.40 (3H, s), 3.28 (3H, s), 3.4—4.4 (1H, br s), 3.94 (1H, d, $J = 4.0$ Hz), 4.83 (1H, d, $J = 4.0$ Hz), 6.9—7.3 (10H, m). Anal. Calcd for C₁₆H₁₉NO: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.82; H, 8.07; N, 5.50.

(1*R*,2*S*)-1-Methoxy-2-methylamino-1,2-diphenylethane (ent-8a) This compound was prepared from the enantiomer of **10** (*ent*-**10**) by the same procedure as described above. A colorless solid, mp 129 °C (*n*-hexane). $[\alpha]_D^{23} - 38.2^\circ$ ($c = 1$, CHCl₃). The IR and ¹H-NMR spectra of this material were in agreement with those of the (1*S*,2*R*)-isomer **8a**.

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