Pergamon

Tetrahedron, Vol. 53, No. 21, pp. 7191-7200, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00422-5

Stereoselective Reactions. 26.[1] Solution Structures of a Chiral Bidentate Lithium Amide in Relation to the Solvent-Dependent Enantioselectivities in Deprotonation Reaction

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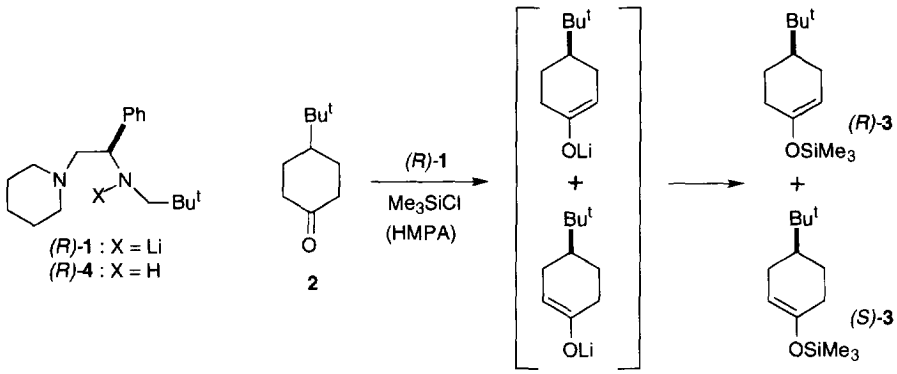
Abstract: ^{6}Li- and ^{15}N-NMR spectroscopic analyses of a labeled chiral bidentate lithium amide ([^{6}Li,$^{15}N_2$]-*(R)*-**1**) have shown that it exists as a chelated monomer (**5**) in THF and in DME, as a chelated dimer (**6**) in toluene and in ether, while as a chelated monomer (**5**) in any of these solvents in the presence of 2 equivalents of HMPA. Solvent-dependent enantioselectivities in deprotonation of 4-*tert*-butylcyclohexanone (**2**) by *(R)*-**1** appear to be correlated to these solution structures.

INTRODUCTION

Enantioselective asymmetric synthesis using chiral lithium amides has received much attention in recent years.[2] We have previously reported enantioselective deprotonation of prochiral 4-substituted cyclohexanones by various chiral bidentate lithium amides in several solvents in the presence of excess trimethylsilyl chloride (TMSCl) (internal quench method[3]) to give the corresponding chiral silyl enol ethers.[1,4] It is shown that enantioselectivities of the reactions are dependent on the solvent used, but are almost independent on the solvent in the presence of 2 equivalents of hexamethylphosphoric triamide (HMPA). We assumed that this interesting finding might be attributed to the difference in aggregation states of the lithium amide in solution, due to the high propensity of lithium dialkylamides to self-associate, a phenomenon that is markedly dependent on the solvent and conditions.[5] Our hypotheses at the design of these bidentate chiral lithium amides were: 1) they should be aggregated in solution to satisfy the valency of the lithium, 2) the degree of aggregation should be dependent on the solvent, since some solvents should also work as ligands for the lithium, and 3) the degree of aggregation in solution should possibly be controlled by addition of strongly-coordinating external ligands, such as HMPA.[1,4,6]

The present paper describes the results of enantioselective deprotonation of prochiral 4-*tert*-butylcyclohexanone (**2**) by a chiral bidentate lithium amide (*(R)*-**1**) in the presence of excess TMSCl to give the corresponding chiral silyl enol ether (**3**), ^{6}Li- and ^{15}N-NMR spectroscopic analyses of the solution structures of [^{6}Li,$^{15}N_2$]-*(R)*-**1** in several solvents in the absence and in the presence of HMPA, X-ray crystallographic confirmation of the structure of a chelated dimer (**6**) of *(R)*-**1**, and the relationship between enantioselectivities of deprotonation of **2** and the solution structures of *(R)*-**1**.[7]



RESULTS AND DISCUSSION

Deprotonation of 2 by *(R)*-1 Deprotonation of **2** by *(R)*-**1** was carried out at -78 °C in four representative solvents, THF, DME, ether, and toluene, in the presence and in the absence of HMPA (2 equivalents to *(R)*-**1** used). To trap the resulting enolate anion as quickly as possible, excess TMSCl was added at the start of the reaction, and the product was isolated as the corresponding silyl enol ether (**3**). In all cases examined, the product was found to be rich in *(R)*-enantiomer,[8,9] as summarized in Table 1.

Table 1. Enantioselective Deprotonation of **2** Using *(R)*-**1** to Give **3**

	In the absence of HMPA					In the presence of HMPA (2 equiv.)				
Solvent	Run	Reaction time (min)	Isolated y. (%)	E. e. (%)	Confign.	Run	Reaction time (min)	Isolated y. (%)	E. e. (%)	Confign.
THF	1	10	86	84	*R*	5	10	82	82	*R*
DME	2	10	86	70	*R*	6	10	87	81	*R*
ether	3	15	8	64	*R*	7	10	89	82	*R*
toluene	4	60	12	58	*R*	8	10	87	82	*R*

It is shown that the reaction is dependent on the solvent used in the absence of HMPA. Thus, the chemical yield of the product is higher in THF and in DME (runs 1 and 2), while lower in ether and in toluene (runs 3 and 4). E. e. of the product is relatively higher in the former solvents, while relatively lower in the latter solvents. In the presence of HMPA, the reaction is independent on the solvent used, giving the product in almost the same chemical and optical yields (runs 5~8).

^{6}Li- and ^{15}N-NMR Spectroscopic Studies on [^{6}Li,$^{15}N_2$]-*(R)*-1 in the Absence of HMPA The pioneering works by Jackman[10] and Collum[11] have demonstrated the potential of ^{6}Li-^{15}N double-labeled compounds such as [^{6}Li,^{15}N]-lithioenamines, [^{6}Li,^{15}N]-lithium anilides, and [^{6}Li,^{15}N]-lithium dialkylamides in conjunction with ^{6}Li- and ^{15}N-NMR spectroscopy for determining Li-N connectivities in solution. When the spin 1/2 ^{15}N coupling to lithium by ^{6}Li-NMR spectroscopy is observed, the number of nitrogens connected to the lithium can be readily determined. Conversely, monitoring the spin 1 ^{6}Li coupling to nitrogen by ^{15}N-NMR spectroscopy provides the number of lithiums connected to the nitrogen. The combined results offer essential information on the aggregation states of these compounds in solution.

A labeled chiral bidentate lithium amide ([^{6}Li,$^{15}N_2$]-*(R)*-**1**) was prepared from 99% [^{15}N]-NH_4Cl, 99% [^{15}N]-NH_3 gas, and 99.5% ^{6}Li metal. Thus, [^{15}N]-*dl*-phenylglycine was prepared by Strecker amino acid synthesis[12] using [^{15}N]-NH_4Cl, and was resolved by *d*-camphorsulfonic acid.[13] [^{15}N]-Piperidine hydrochloride prepared from [^{15}N]-NH_3 gas[14] was condensed with [^{15}N]-*(R)*-phenylglycine, and the product was converted to the labeled chiral bidentate amine ([$^{15}N_2$]-*(R)*-**4**) by the reported method.[6]

Since [^{6}Li,$^{15}N_2$]-*(R)*-**1** is unstable to air and water, solutions were prepared in NMR sample tubes by adding a solution of [^{6}Li]-butyllithium in hexane to a solution of [$^{15}N_2$]-*(R)*-**4** in anhydrous solvents under argon atmosphere at -78 °C, and the tubes were sealed immediately. From the data shown in Table 1, we selected THF-d_8, DME-toluene-d_8 (4:1), ether-toluene-d_8 (4:1), and toluene-d_8 as solvents. ^{6}Li- and ^{15}N-NMR spectra are shown in Figure 1.

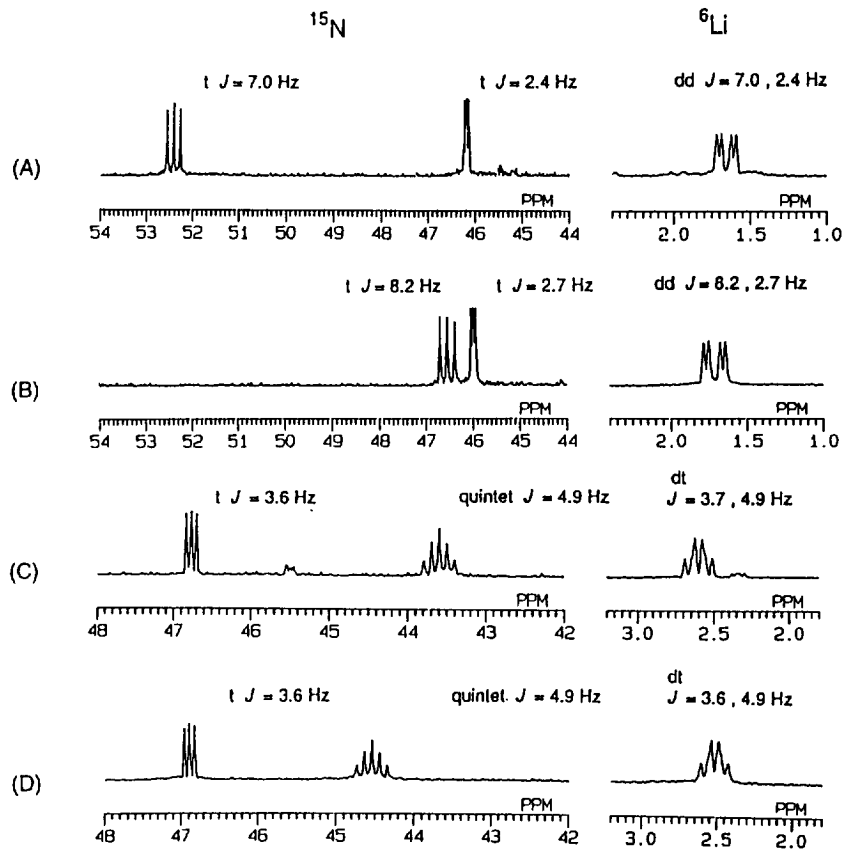
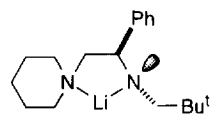


Figure 1. ^{6}Li- and ^{15}N-NMR spectra of 0.08 *M* solution of [^{6}Li,$^{15}N_2$]-*(R)*-**1** recorded at -80 °C. (A) in THF-d_8; (B) in DME-toluene-d_8 (4:1); (C) in ether-toluene-d_8 (4:1); (D) in toluene-d_8.

In THF-d_8 and in DME-toluene-d_8 (4:1), the ^{6}Li-NMR spectrum of [^{6}Li,$^{15}N_2$]-*(R)*-**1** shows a doublet of doublets (Figure 1, (A) and (B)), indicative of coupling to two neighboring ^{15}N nuclei. The corresponding ^{15}N spectrum displays two sets of triplets (1:1:1), indicating that each nitrogen atom couples to one neighboring

^{6}Li nucleus. This requires that each nitrogen is attached to one lithium. These observations suggest that *(R)*-**1** exists almost entirely as a five-membered chelated monomer (**5**) in THF and in DME-toluene (4:1). Evaluating the steric interaction between the phenyl group on the chiral carbon and the bulky neopentyl group on the amide nitrogen, the lone pair on the amide nitrogen is expected to orient itself exclusively *cis* to the phenyl group as shown. In ether-toluene-d_8 (4:1) and in toluene-d_8, the ^{6}Li-NMR spectrum of [^{6}Li,$^{15}N_2$]-*(R)*-**1** shows a doublet of triplets (Figure 1, (C) and (D)), indicative of coupling to three neighboring ^{15}N nuclei. The corresponding ^{15}N spectrum displays a triplet (1:1:1) and a quintet (1:2:3:2:1), indicating that one nitrogen couples to one neighboring lithium, while the other nitrogen couples to two neighboring lithiums. Thus, one nitrogen is connected to one lithium, and the other nitrogen is connected to two lithiums. It is therefore concluded that *(R)*-**1** exists almost entirely as a chelated dimer in ether-toluene-d_8 (4:1) and in toluene-d_8. Assuming that the dimer (**6**) is formed from the monomer (**5**) by coordination of the lone pair on the amide nitrogen of the monomer to the lithium of the other monomer at two sites, the structure of the dimer should be as shown in **6**, which has a 5-4-5 ring system, two phenyl groups on the same side, and two neopentyl groups on the other side.



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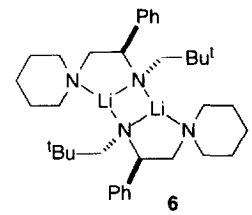

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^{6}Li- and ^{15}N-NMR Spectroscopic Studies on [^{6}Li,$^{15}N_2$]-*(R)*-1 in the Presence of HMPA ^{6}Li- and ^{15}N-NMR spectroscopic studies on [^{6}Li,$^{15}N_2$]-*(R)*-**1** were carried out in the same solvents in the presence of HMPA. The spectra are shown in Figure 2.

It is shown that addition of HMPA changes the situation dramatically. Thus, the ^{6}Li-NMR spectra show a doublet of doublets, and the corresponding ^{15}N spectra display two sets of triplets in all the solvents examined in the presence of 2 equivalents of HMPA-d_{18} (Figure 2, (A)~(D)). This observation clearly demonstrates that deaggregation from the dimer (**6**) to the monomer (**5**) occurs in ether-toluene (4:1) and in toluene solution, while the monomer (**5**) still holds in THF and in DME-toluene (4:1) solution by addition of 2 equivalents of HMPA.[15] As a result, the solution structure of *(R)*-**1** is chelated monomeric and common in these solvents in the presence of 2 equivalents of HMPA. It should be noted that addition of a large excess of HMPA-d_{18} to the solution of [^{6}Li,$^{15}N_2$]-*(R)*-**1** in THF-d_8 does not affect the five-membered chelated structure (**5**) (Figure 2, (E)).

To observe the change from the dimer (**6**) to the monomer (**5**), ^{15}N-NMR spectra of [^{6}Li,$^{15}N_2$]-*(R)*-**1** in toluene-d_8 were taken in the presence of limited amounts of HMPA-d_{18} as shown in Figure 3. As already discussed, the chelated dimer (**6**) predominates in the absence of HMPA-d_{18} (Figure 3, (A)), while the chelated monomer (**5**) predominates in the presence of 2 equivalents of HMPA-d_{18} (Figure 3, (E)). In the presence of 0.7 equivalent of HMPA-d_{18}, two species are observed, i.e., the one corresponds to the dimer (**6**), while the other corresponds to the monomer (**5**) (Figure 3, (C)). In the presence of 1 equivalent of HMPA-d_{18}, this chiral lithium amide exists almost entirely as the mononer (**5**) (Figure 3, (D)). Since HMPA is a monodentate ligand, this result means that lithium can exist stably in a tri-coordinated state.

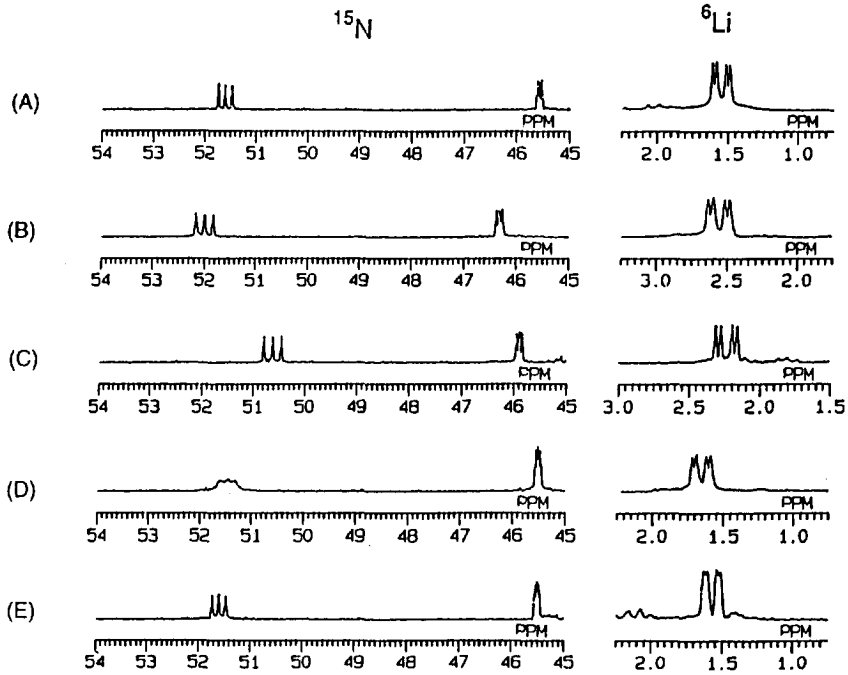

Figure 2. ^{6}Li- and ^{15}N-NMR spectra of 0.08*M* solution of [^{6}Li,$^{15}N_2$]-*(R)*-**1** at -80 °C. (A) in THF-d_8 with 2 equiv. of HMPA-d_{18}; (B) in DME-toluene-d_8 (4:1) with 2 equiv. of HMPA-d_{18}; (C) in ether-toluene-d_8 (4:1) with 2 equiv. of HMPA-d_{18}; (D) in toluene-d_8 with 2 equiv. of HMPA-d_{18}; (E) in THF-d_8 with 13 equiv. of HMPA-d_{18}.

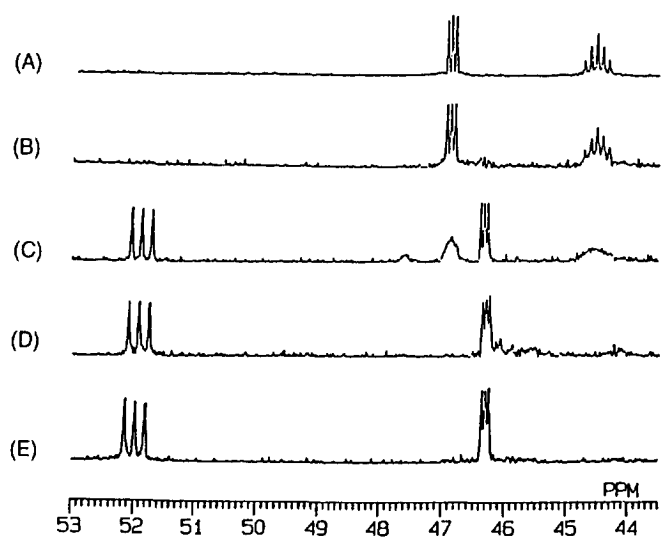

Figure 3. ^{15}N-NMR spectra of 0.08 *M* solution of [^{6}Li,$^{15}N_2$]-*(R)*-**1** in toluene-d_8 at -80°C. (A) without HMPA-d_{18}; (B) with 0.3 equiv of HMPA-d_{18}; (C) with 0.7 equiv. of HMPA-d_{18}; (D) with 1 equiv. of HMPA-d_{18}; (E) with 2 equiv. of HMPA-d_{18}.

Isolation and X-Ray Analysis of Crystalline *(R)*-1 (Dimer (6)) After many unsuccessful trials, we finally succeeded in obtaining crystalline *(R)*-**1** from ether-toluene (4:1), and in putting the crystal in a sealed capillary for low-temperature X-ray analysis.[16] The structure is shown in Figure 4.

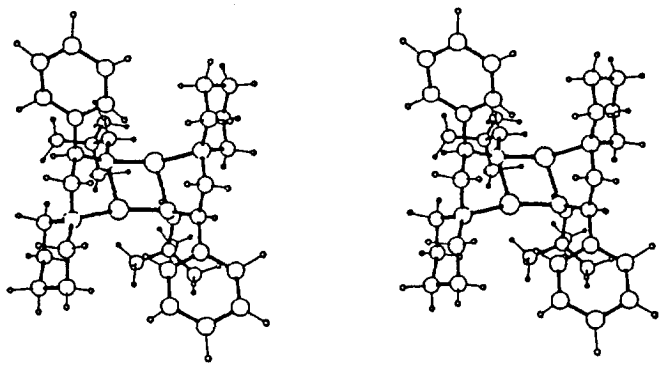

Figure 4. Crystal structure (stereoview) of *(R)*-**1** obtained from ether-toluene (4:1).

The X-ray crystal structure of *(R)*-**1** shown in Figure 4 confirms the structure of the chelated dimer (**6**), predicted by ^{6}Li- and ^{15}N-NMR spectra of [^{6}Li,$^{15}N_2$]-*(R)*-**1** taken in the same solvent system (ether-toluene-d_8 (4:1)) (Figure 1, (C)). The core of the dimer is an approximately diamond-shaped Li-O-Li-O four-membered ring. Both lithium atoms are tri-coordinated. A five-membered chelate is formed in each monomer unit that constitutes a dimer. The conformation of each monomer is very similar. The flexible neopentyl groups on the amide nitrogen adopt a slightly different conformation and are *trans* to the phenyl group. This means that the lone pair on the amide nitrogen is fixed *cis* to the phenyl group as expected, and dimer is formed by coordination of the lone pair on the amide nitrogen to the vacant orbital on the lithium atom from the same side of the phenyl group on the chiral carbon.

Relationship between Solution Structures of *(R)*-1 and Deprotonation Enantioselectivities It is shown in Figure 3 that the ratio of monomer (**5**) to dimer (**6**) of *(R)*-**1** in toluene depends upon the amount of HMPA. Deprotonation of **2** by *(R)*-**1** in toluene was carried out in such solvent systems. The results are shown in Table 2.

Table 2. Enantioselective Deprotonation of **2** Using *(R)*-**1** in Toluene to Give **3**

Run	HMPA (equiv.)	Reaction time (min)	Product (**3**)		
			Isolated y. (%)	E. e. (%)	Confign.
1	0	60	12	58	*R*
9	0.3	10	45	56	*R*
10	1.0	10	72	76	*R*
5	2.0	10	87	82	*R*

It is shown that chemical and optical yields of the *(R)*-**3** increase as the amount of HMPA increases. This phenomenon is parallel to the monomer (**5**)/dimer (**6**) ratio observed in Figure 3. It is reasonable to

assume that the reactivity of the monomer (**5**) is higher as a base to give the product in higher chemical and optical yields, compared to that of the dimer (**6**). The results in Table 1 support this explanation. Since the lithium in **5** is di-coordinated, while that in **6** is tri-coordinated (except the coordination by the solvent), Lewis acidity of the former is considered to be stronger than that of the latter. Evaluating the importance of the coordination of the carbonyl group of **2** to the lithium for deprotonation to occur,[17] the difference in reactivity between **5** and **6** is reasonable.

CONCLUSION

Solvent dependency in enantioselective deprotonation of prochiral 4-*tert*-butylcyclohexanone (**2**) by a chiral bidentate lithium amide (*(R)*-**1**) in the presence of excess TMSCl is correlated to the solution structures of *(R)*-**1**. NMR spectral studies have shown that *(R)*-**1** exists as a chelated mononer (**5**) in THF and in DME, as a chelated dimer (**6**) in ether and toluene, while as a chelated monomer (**5**) in any of these solvents in the presence of 2 equivalents of HMPA. This fact means that a chelated monomer (**5**) gives the product (**3**) in higher chemical and optical yields. By the crystal structure of **6** confirmed by X-ray analysis, it is suggested that a chelated monomer takes the conformation in which the lone pair on the amide nitrogen is *cis* to the phenyl group on the chiral carbon in the chelated ring.

EXPERIMENTAL SECTION

General All melting and boiling points are uncorrected. IR spectra were recorded on a JASCO IRQ-1 or a JASCO DS-402G spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Hitachi R-24B, a JEOL JNM-EX270, a JEOL GSX-400, or a JEOL GSX-500 spectrometer. The chemical shifts are given in δ (ppm) values using tetramethylsilane as an internal standard. Coupling constants (*J*) are given in hertz. The following abbreviations are used: br = broad, s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplets, t = triplet, q = quartet, quin = quintet, m = multiplet. Mass spectra (MS) were recorded on a JEOL JMS-01 SG-Z or a JEOL JMX-DX-300 spectrometer. Optical rotations were measured by a JASCO DIP-370 polarimeter. For anhydrous solvents, THF, DME, ether, toluene, THF-d_8, and toluene-d_8 were distilled from sodium/benzophenone ketyl under argon atmosphere. HMPA, HMPA-d_{18}, and TMSCl were distilled from CaH_2 under argon atmosphere.

Deprotonation of 2 by *(R)*-1 in the Absence of HMPA (run 1) Under argon atmosphere, a solution of BuLi in hexane (1.61 *N*, 0.93 mL, 1.50 mmol) was added to a solution of *(R)*-**4**[6] (432 mg, 1.58 mmol) in THF (18 mL) at room temperature, and the whole was stirred at -78°C for 5 min. A solution of **2** (193.5 mg, 1.25 mmol) and TMSCl (0.79 mL, 6.3 mmol) in THF (2 mL) was added during 90 sec, and the whole was stirred at -78°C for 10 min. After addition of triethylamine (2 mL) and saturated aqueous $NaHCO_3$ (6 mL), the reaction mixture was allowed to warm to room temperature, and was extracted with hexane (200 mL). The organic extract was washed successively with 0.1 *N* aqueous citric acid (50 mL) five times (until pH of the aqueous washings was nearly 4), water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a pale yellow oil, which was purified by column chromatography (silica gel, hexane) followed by bulb-to-bulb distillation to give **3** (243.5 mg, 86%) as a colorless oil of bp 160°C (bath temperature) (5 mmHg), $[\alpha]_{365}^{25}$ +198.5 (*c* = 1.01, benzene), corresponding

to be 84% ee *(R)*.[9] ^{1}H-NMR (CCl_4): 0.14 (9H, s), 0.87 (9H, s), 1.0-2.2 (7H, m), 4.65 (1H, br). MS *m/z*: 226(M^+).

Deprotonation of 2 by *(R)*-1 in the Presence of HMPA (run 8) Under argon atmosphere, a solution of BuLi in hexane (1.61 *N*, 0.99 mL, 1.59 mmol) was added to a solution of *(R)*-**4**[6] (459 mg, 1.68 mmol) in toluene (18 mL) at -78°C. The whole was warmed to room temperature, and was stirred for 15 min. After addition of HMPA (0.55 mL, 3.18 mmol), the resulting solution was cooled to -78°C, and was stirred for 5 min. A solution of **2** (205.3 mg, 1.33 mmol) and TMSCl (0.84 mL, 6.65 mmol) in toluene (2 mL) was added during 60 sec, and the reaction mixture was stirred at -78°C for 10 min. After addition of triethylamine (2 mL) and saturated aqueous $NaHCO_3$ (6 mL), the whole was treated as described above (run 1) to give **3** (263.3 mg, 87%) as a colorless oil of bp 170°C (bath temperature) (10 mmHg), $[\alpha]_{365}^{25}$ +193.5 (*c* = 0.97, benzene), corresponding to be 82% ee *(R)*.[9]

Rotational Values of 3 Obtained by the Reactions All reactions were carried out and the products (**3**) were isolated and purified as described above. Chemical and optical yields are written in Tables 1 and 2. Rotational values of **3** obtained were as follows.[9] run 2: $[\alpha]_{365}^{25}$ +164.8 (*c* = 1.04, benzene); run 3: $[\alpha]_{365}^{25}$ +151.5 (*c* = 0.82, benzene); run 4: $[\alpha]_{365}^{25}$ +136.3 (*c* = 0.98, benzene); run 5: $[\alpha]_{365}^{25}$ +193.5 (*c* = 1.09, benzene); run 6: $[\alpha]_{365}^{25}$ +191.7 (*c* = 1.18, benzene); run 7: $[\alpha]_{365}^{25}$ +194.1 (*c* = 1.09, benzene); run 9: $[\alpha]_{365}^{25}$ +132.0 (*c* = 1.06, benzene); run 10: $[\alpha]_{365}^{25}$ +179.5 (*c* = 1.19, benzene).

[$^{15}N_2$]-*(R)*-*N*-Neopentyl-1-phenyl-2-(1-piperidino)ethylamine ([$^{15}N_2$]-*(R)*-4) [^{15}N]-*dl*-Phenylglycine prepared by Strecker amino acid synthesis[12] using [^{15}N]-NH_4Cl was resolved by *d*-camphor-sulfonic acid[13] as reported to give [^{15}N]-*(R)*-phenylglycine of $[\alpha]_D^{25}$ -155.0 (*c* = 1.036, 1 *N* aqueous HCl) (reported[18] $[\alpha]_D^{25}$ -157 (*c* = 1, 1 *N* aqueous HCl) for *(R)*-phenylglycine). [^{15}N]-Piperidine was prepared from [^{15}N]-NH_3 gas as reported.[14] [$^{15}N_2$]-*(R)*-**4** was prepared from [^{15}N]-*(R)*-phenylglycine and [^{15}N]-piperidine and purified by recrystallizations of its dipicrate as reported.[6] The free [$^{15}N_2$]-*(R)*-**4** was obtained as a colorless oil of bp 170°C (bath temperature) (0.4 mmHg), $[\alpha]_D^{25}$ -100.2 (*c* = 0.786, MeOH). MS *m/z*: 277 (M^++1). Spectral data agree with those reported.[6]

^{6}Li- and ^{15}N-NMR Spectroscopic Analyses ^{6}Li- and ^{15}N-NMR spectra were recorded on a JEOL GSX-500 spectrometer (73.45 and 50.55 MHz, respectively). The ^{6}Li chemical shifts are reported in δ (ppm) using ^{6}LiCl in MeOH-THF-d_8 or in THF-toluene-d_8 (δ = 0.0) as an external standard. The ^{15}N chemical shifts are reported in δ (ppm) using [^{15}N]-aniline in THF-THF-d_8 or THF-toluene-d_8 (δ = 52.0) as an external standard.

The following is a representative procedure for preparing samples for ^{6}Li- and ^{15}N-NMR spectroscopic analysis. [$^{15}N_2$]-*(R)*-**4** (62.4 mg, 0.23 mmol) was placed in a dried NMR sample tube. The tube was placed under a septum, and the inside of the tube was substituted with argon. THF-d_8 (2.5 mL) was charged using a syringe to dissolve [$^{15}N_2$]-*(R)*-**4**. After addition of a solution of Bu^{6}Li in hexane (6.0 *N*, 40 μL, 0.24 mmol) using a micro-syringe, the tube was immediately dipped in a dry ice-acetone bath, and was sealed with a flame. This sample could be stored at -20°C without decomposition. In cases where HMPA-d_{18} was added, the sealed tube was once warmed to room temperature, and was vibrated to get a clear solution. The NMR spectra are shown in Figures 1, 2, and 3.

Preparation of Crystalline *(R)*-1 and X-Ray Analysis A solution of *(R)*-**4** (24.5 mg, 0.089 mmol) in ether (0.9 mL) was prepared in a glass tube under argon atmosphere. A solution of BuLi in hexane (8.3 *N*, 10.8 μL, 0.089 mmol) was added using a micro-syringe, and toluene (0.23 mL) was added. The glass tube

was dipped in dry ice-acetone bath, and sealed with a flame. After 30 min at -78°C, fine precipitates appeared. The tube was warmed to get a clear solution, and was then allowed to stand at -20°C. After 3 days, colorless prisms appeared. In a dry box under argon atmosphere, the tube was cut, a prism of 0.7 mm long was selected, and placed in a capillary. The capillary was placed under a rubber septum, taken out from the dry box, and sealed with a flame immediately. This sample was subjected to X-ray analysis at -20°C.

The dimer (**6**) crystallized in the orthorhombic space group $P2_12_12_1$ with unit cell parameters a = 29.163 (2) Å, b = 11.469 (1) Å, c = 10.722 (1) Å, and D_{calcd} = 1.038 g/cm^3. A total of 3024 reflections were observed using graphite-monochromated Cu K_α radiation (2θ values in the range of 0-120°), and the temperature of the crystal was kept at 253K. The structure was solved by direct methods using the computer program SIR 85 and the difference Fourier method. The final values are R = 0.047 and R_w = 0.046. No absorption corrections were applied. The X-ray structure is shown in Figure 4.[16]

Acknowledgment Financial support from the Ministry of Education, Science, Sports and Culture of Japanese Government, Ciba-Geigy Foundation for the Promotion of Science, and Japan Research Foundation for Optically Active Compounds is gratefully acknowledged.

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(*Received in Japan* 21 *February* 1997; *accepted* 8 *April* 1997)