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Stereoselective Reactions. 29.[1] Lithium-Hydrogen Interchange between Achiral Tridentate Lithium Amides and Chiral Bidentate Amines. An Approach to Catalytic Enantioselective Deprotonation

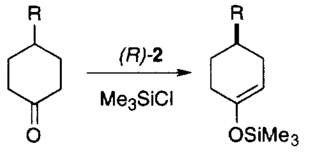
Toyoharu Yamashita, Daisaku Sato, Taro Kiyoto, Arvind Kumar, and Kenji Koga*

Graduate School of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: ^{1}H-NMR spectral studies have shown that lithium-hydrogen interchange between a chiral bidentate amine ((*R*)-**3b**) and an achiral tridentate lithium amide (**5a**) occurs rapidly in THF, favoring the exclusive formation of a chiral bidentate lithium amide ((*R*)-**2b**) at equilibrium. This finding was applied to catalytic asymmetric deprotonation of prochiral 4-substituted cyclohexanones (**1**) using 0.3 equivalent of (*R*)-**3b** in the presence of 2.4 equivalents of **5a** in THF in the presence of DABCO and HMPA. © 1997 Elsevier Science Ltd.

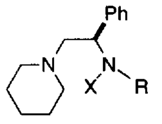
INTRODUCTION

Conversion of carbonyl compounds into the corresponding enolates is a fundamental and widely used process in synthetic organic chemistry, because enolates play a central role as carbon nucleophiles to undergo various reactions with electrophiles.[2] Recent advances in kinetic deprotonation by chiral lithium amides has established a method for enantioselective asymmetric synthesis of chiral lithium enolates from symmetrically substituted, prochiral cyclic ketones.[3]



1
a : R = Bu^t
b : R = Ph
c : R = Pr^i
d : R = Me

(*R*)-**4**
a : R = Bu^t
b : R = Ph
c : R = Pr^i
d : R = Me



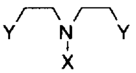
(*R*)-**2** : X = Li
(*R*)-**3** : X = H

a : R = CH_2CMe_3
b : R = CH_2CF_3
c : R = CH_2CHF_2
d : R = CH_2CH_2F
e : R = $CH_2CF_2CF_3$
f : R = $CH_2C(Me)_2NMe_2$
g : R = $CH_2C(Me)_2OMe$
h : R = $CH_2CH_2N(CH_2)_5$

We have previously reported enantioselective deprotonation of prochiral 4-substituted cyclohexanones (**1a**~**d**) using a little more than a stoichiometric amount of chiral bidentate lithium amides ((*R*)-**2a**~**e**) in the presence of excess trimethylsilyl chloride (TMSCl) (internal quench (IQ) method[4]) to isolate the corresponding chiral lithium enolates as their trimethylsilyl enol ethers ((*R*)-**4a**~**d**) in reasonably high chemical and optical yields.[5] It is also shown that the chemical yields of these reactions using a little more than a stoichiometric amount of chiral tridentate lithium amides ((*R*)-**2f**~**h**) are reasonably lower under the same conditions.[5i] Based on this finding, the present paper describes an approach to catalytic asymmetric deprotonation of **1a**~**d** using less than a stoichiometric amount of chiral bidentate amines in the presence of excess achiral tridentate lithium amides.[6]

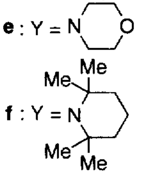
RESULTS AND DISCUSSION

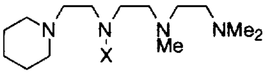
Strategy for Catalytic Asymmetric Deprotonation Deprotonation reactions of **1a** by 1.2 equivalents of bidentate ((*R*)-**2a**~**e**), 2 equivalents of tridentate (**5a**~**f**), and 2 equivalents of tetradentate (**5g**~**h**) lithium amides were carried out in THF in the presence of HMPA (2 equivalents to the lithium amide used) at -78 °C for 1 hr. Treatment of the resulting solution with excess TMSCl (external quench (EQ) method[7]) gave the product (**4a**) as summarized in Table 1.



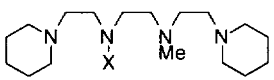
5 : X = Li
6 : X = H

a : Y = $N(CH_2)_5$
b : Y = $N(CH_2)_4$
c : Y = NEt_2
d : Y = NPr_2





5g : X = Li
6g : X = H



5h: X = Li
6h: X = H

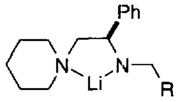
Table 1. Deprotonation of **1a** to Give **4a** by External Quench Method[a]

	Base		Product (**4a**)				Base		Product (**4a**)		
Run	Lithium amide	Euiv.	Chem. y. (%)	E. e. (%)	Confign.	Run	Lithium amide	Euiv.	Chem. y. (%)	E. e. (%)	Confign.
1	(*R*)-**2a**	1.2	86	77	*R*	8	**5c**	2.0	14	-	-
2	(*R*)-**2b**	1.2	85	81	*R*	9	**5d**	2.0	21	-	-
3	(*R*)-**2c**	1.2	83	77	*R*	10	**5e**	2.0	44	-	-
4	(*R*)-**2d**	1.2	49	47	*R*	11	**5f**	2.0	69	-	-
5	(*R*)-**2e**	1.2	64	68	*R*	12	**5g**	2.0	45	-	-
6	**5a**	2.0	37	-	-	13	**5h**	2.0	26	-	-
7	**5b**	2.0	42	-	-						

[a] For the procedure, see text and experimental section.

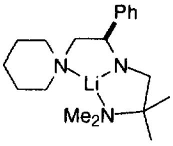
It is recognized that the chemical yields of **4a** depend upon the differences in the structure of lithium amides used. Thus, among chiral bidentate lithium amides, chemical yields were higher using (*R*)-**2a**~**c** (runs 1~3). Among tridentate lithium amides, those amides (**5a**~**e**) whose internal ligation sites are not bulky[8] gave

4a in lower chemical yields (runs 6~10). Tetradentate lithium amides (**5g~h**) also gave **4a** in lower chemical yields (runs 12, 13). It is already known by ^{6}Li- and ^{15}N-NMR spectroscopic studies that *(R)*-**2a** and *(R)*-**2b** (bidentate lithium amides) exist as a chelated monomeric form (**7**) in THF in the presence of HMPA (2 equivalents),[5b,c] and *(R)*-**2f** (a tridentate lithium amide) exists as a chelated monomer (**8**) in the same solvent system.[5i] It should be noted that the lithium in **7** is di-coordinated, while that in **8** is tri-coordinated intramolecularly. Since deprotonation of a carbonyl compound by a lithium amide is considered to occur *via* the coordination of the carbonyl oxygen to the lithium,[9] the difference in chemical yields of deprotonation discussed above suggests that the tridentate and tetradentate lithium amides are inferior to bidentate lithium amides as bases for the deprotonation due to the decrease in Lewis acidity of the lithium caused by additional intramolecular coordination.[1]



7

R = Bu^t or CF$_3$



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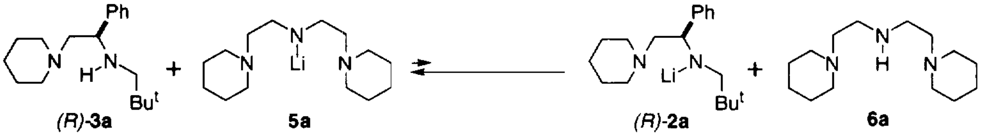
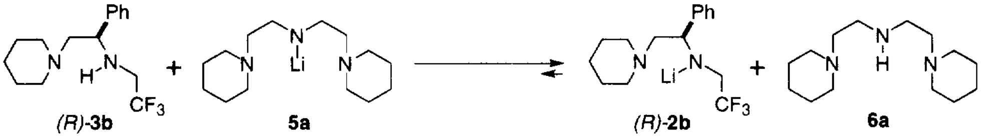
Based on the understanding that the rate of deprotonation by a bidentate lithium amide is generally faster than that by a tridentate and tetradentate lithium amide, it may be possible for the present enantioselective deprotonation reaction to be carried out by employing less than a stoichiometric amount of a chiral bidentate amine in the presence of a sufficient amount of an achiral tridentate or tetradentate lithium amide, if lithium-hydrogen interchange[10] between the former and the latter occurs rapidly in the reaction medium, favoring the formation of a chiral bidentate lithium amide at equilibrium.

^{1}H-NMR Spectroscopic Studies on Lithium-Hydrogen Interchange between Chiral Bidentate Amines ((*R*)-3a~b) and an Achiral Tridentate Lithium Amide (5a) In the ^{1}H-NMR spectra in THF-d_8 in the absence and in the presence of HMPA-d_{18}, chemical shifts of the benzylic proton signals (doublet of doublets at δ 4.18 and 4.17) of chiral bidentate lithium amides (*(R)*-**2a** and *(R)*-**2b**, respectively) differ from those (doublet of doublets at δ 3.71 and 4.00) of the corresponding chiral bidentate amines (*(R)*-**3a** and *(R)*-**3b**, respectively), while an achiral tridentate lithium amide (**5a**) and its corresponding amine (**6a**) have no signals in this region. Therefore, simply by taking the ^{1}H-NMR spectra of a mixture of *(R)*-**3a** and **5a**, *(R)*-**3b** and **5a**, *(R)*-**2a** and **6a**, or *(R)*-**2b** and **6a** in these solvents, it should be possible to examine whether lithium-hydrogen interchange occurs between them.

A solution was prepared by mixing *(R)*-**3a** (1 equivalent) and **5a** (2 equivalents) in THF-d_8 in the presence of HMPA-d_{18} (2 equivalents) at -78 °C. The ^{1}H-NMR spectrum of the resulting solution measured at -80 °C showed the presence of *(R)*-**3a** and the absence of *(R)*-**2a**. Three possibilities conceivably may account for this fact, i.e., 1) lithium-hydrogen interchange between *(R)*-**3a** and **5a** did not occur at all, 2) the equilibrium was not yet attained due to the slow rate of lithium-hydrogen interchange, and 3) the equilibrium was already attained due to the fast interchange, favoring the exclusive formation of *(R)*-**3a** at equilibrium. To check these possibilities, a solution was prepared contrariwise by mixing *(R)*-**2a** (2 equivalents) and **6a** (1 equivalent) in the same solvent system. The ^{1}H-NMR spectrum showed the presence of *(R)*-**2a** and *(R)*-**3a** in almost equal amounts. This result clearly indicates that the possibility 3) above was the case, as shown below. Assuming that the lithium prefers to be intramolecularly tri-coordinated rather than di-coordinated, this result is reasonable. This result clearly rules out the *in situ* generation of *(R)*-**2a** from *(R)*-**3a** using **5a**, and therefore, catalytic asymmetric deprotonation by this combination is not feasible.



Since the trifluoroethyl group is electron-withdrawing, it is conceivable that the amine proton of *(R)*-**3b** should be reasonably more acidic than that of *(R)*-**3a**,[11] and therefore, should be more easily metalated. Thus, a solution was prepared by mixing *(R)*-**3b** (1 equivalent) and **5a** (2 equivalents) in the same solvent system at -78 °C. The ^{1}H-NMR spectrum measured at -80 °C showed the presence of *(R)*-**2b** and the absence of *(R)*-**3b**. Contrariwise, a solution was prepared by mixing *(R)*-**2b** (1 equivalent) and **6a** (2 equivalents) in the same solvent system. The ^{1}H-NMR spectrum measured at -80 °C showed the presence of *(R)*-**2b** and the absence of *(R)*-**3b**. These data indicate that lithium-hydrogen interchange between *(R)*-**3b** and **5a** occurs to give *(R)*-**2b** exclusively at equilibrium.[12]



It is therefore conceivable that fluorine-containing chiral lithium amides (*(R)*-**2b**~**e**) may be generated from the corresponding chiral bidentate amines (*(R)*-**3b**~**e**) using tridentate achiral lithium amides (**5**) in the solvent of the deprotonation reaction, and that enantioselective deprotonation reaction may be carried out using less than a stoichiometric amount of *(R)*-**3b**~**e** under the presence of a sufficient amount of **5**.

Catalytic Asymmetric Deprotonation of 1 Based on the above lithium-hydrogen interchange data, the possibility of catalytic asymmetric deprotonation of **1a**~**d** was examined under EQ conditions using 0.3 equivalent of chiral amines (*(R)*-**3b**~**e**) in the presence of excess achiral lithium amides (**5a**~**h**) in THF. The results are summarized in Table 2.

We first examined deprotonation of **1a**. Under stoichiometric conditions[13] using *(R)*-**2b**, the product (*(R)*-**4a**) was obtained in 83% yield (79% ee) in the absence of HMPA (run 1), and in 85% yield (81% ee) in the presence of HMPA (2 equivalents to *(R)*-**2b**) (run 3). These chemical and optical yields are the goals under catalytic conditions[13] in the present study.

Deprotonation of **1a** under catalytic conditions was then examined using a combination of *(R)*-**3b** and **5a** under various conditions (runs 2, 4~18). In spite of the fact that lithium-hydrogen interchange occurs between *(R)*-**3b** and **5a** in THF in the absence of HMPA, the reaction gave *(R)*-**4a** in 31% ee in the absence of HMPA (run 2), indicating little turnover of *(R)*-**3b** in the absence of HMPA. In the presence of HMPA (2 equivalents to **5a** used), however, *(R)*-**4a** was obtained in 53% ee, indicating some turnover of *(R)*-**3b** during

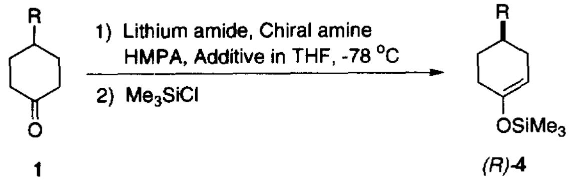


Table 2. Stoichiometric and Catalytic Asymmetric Deprotonation of **1** to Give *(R)*-**4** by External Quench Method [a]

Run	**1**	Lithium amide (eq.) Achiral	Lithium amide (eq.) Chiral	Chiral amine (eq.)	HMPA (eq.)	Additive (eq.)	Time (hr)	Product *(R)*-**4**	Product Chem. y. (%)	Product E. e. (%)
1	**1a**	-	*(R)*-**2b** (1.2)	-	0	-	1	**4a**	83	79
2	**1a**	**5a** (3.6)	-	*(R)*-**3b** (0.3)	0	-	3	**4a**	57	31
3	**1a**	-	*(R)*-**2b** (1.2)	-	2.4	-	1	**4a**	85	81
4	**1a**	**5a** (3.6)	-	*(R)*-**3b** (0.3)	7.2	-	3	**4a**	61	53
5	**1a**	**5a** (3.6)	-	*(R)*-**3b** (0.3)	0.9	-	3	**4a**	74	61
6	**1a**	**5a** (3.6)	-	*(R)*-**3b** (0.3)	1.8	-	3	**4a**	78	70
7	**1a**	**5a** (3.6)	-	*(R)*-**3b** (0.3)	3.6	-	3	**4a**	70	70
8	**1a**	**5a** (3.6)	-	*(R)*-**3b** (0.3)	5.4	-	3	**4a**	69	55
9	**1a**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	2.4	-	3	**4a**	74	72
10	**1a**	**5a** (2.0)	-	*(R)*-**3b** (0.3)	2.0	-	3	**4a**	73	69
11	**1a**	**5a** (1.5)	-	*(R)*-**3b** (0.3)	1.5	-	3	**4a**	59	47
12	**1a**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	2.4	LiBr (2.4)	1.5	**4a**	63	28
13	**1a**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	2.4	**6a** (1.2)	1.5	**4a**	75	73
14	**1a**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	2.4	TMEDA (2.4)	1.5	**4a**	77	71
15	**1a**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.2)	1.5	**4a**	83	78
16	**1a**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	0	DABCO (1.2)	1.5	**4a**	61	27
17	**1a**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.5)	1.5	**4a**	83	79
18	**1a**	**5a** (2.4)	-	*(R)*-**3b** (0.2)	2.4	DABCO (1.2)	1.5	**4a**	75	69
19	**1a**	**5b** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.2)	1.5	**4a**	43	26
20	**1a**	**5c** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.2)	1.5	**4a**	8	5
21	**1a**	**5d** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.2)	1.5	**4a**	30	27
22	**1a**	**5e** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.2)	1.5	**4a**	78	76
23	**1a**	**5f** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.2)	1.5	**4a**	71	71
24	**1a**	**5g** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.2)	1.5	**4a**	53	14
25	**1a**	**5h** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.2)	1.5	**4a**	43	9
26	**1a**	-	*(R)*-**2c** (1.2)	-	2.4	-	1	**4a**	83	77
27	**1a**	**5a** (2.4)	-	*(R)*-**3c** (0.3)	2.4	DABCO (1.5)	1.5	**4a**	82	76
28	**1a**	-	*(R)*-**2d** (1.2)	-	2.4	-	1	**4a**	49	47
29	**1a**	**5a** (2.4)	-	*(R)*-**3d** (0.3)	2.4	DABCO (1.5)	1.5	**4a**	50	12
30	**1a**	-	*(R)*-**2e** (1.2)	-	2.4	-	1	**4a**	64	68
31	**1a**	**5a** (2.4)	-	*(R)*-**3e** (0.3)	2.4	DABCO (1.5)	1.5	**4a**	78	69
32	**1b**		*(R)*-**2b** (1.2)	-	2.4	-	1	**4b**	77	80
33	**1b**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.5)	1.5	**4b**	77	76
34	**1c**	-	*(R)*-**2b** (1.2)	-	2.4	-	1	**4c**	75	79
35	**1c**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.5)	1.5	**4c**	80	76
36	**1d**	-	*(R)*-**2b** (1.2)	-	2.4	-	1	**4d**	82	78
37	**1d**	**5a** (2.4)	-	*(R)*-**3b** (0.3)	2.4	DABCO (1.5)	1.5	**4d**	70	75

[a] For the procedure, see text and experimental section.

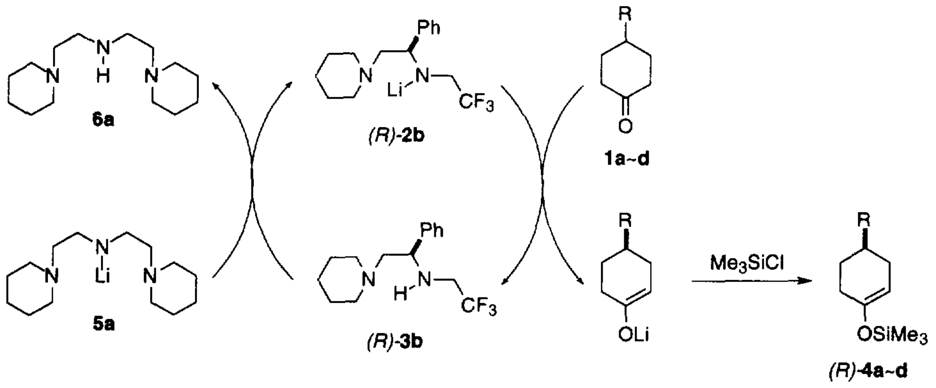
the reaction (run 4).[14] Based on this experimental fact, better conditions were sought as to the amounts of **5a** and HMPA relative to 0.3 equivalent of *(R)*-**3b** (runs 5~11). It is shown that ee of *(R)*-**4a** depends upon the amount of HMPA. By using 2.4 equivalents of **5a**, 2.4 equivalents of HMPA, and 0.3 equivalent of *(R)*-**3b**, *(R)*-**4a** was obtained in 74% (72% ee) (run 9). Using the conditions in run 9, the effects of other additives were also examined (runs 12~18). The best result was obtained by addition of DABCO in the presence of HMPA as shown in runs 15 and 17, where chemical and optical yields of *(R)*-**4a** were quite close to those obtained under stoichiometric conditions (runs 1 and 3). It should be noted by the data of runs 16 and 18 that the presence of HMPA and the use of at least 0.3 equivalent of *(R)*-**3b** are necessary.

It is shown that changes in the structure of achiral lithium amides (**5b~h**) (runs 19~25) and chiral amines (*(R)*-**3c~e**) (runs 27, 29, and 31) also affect the reactions . Thus, the result using **5e** (run 22) was almost comparable to that using **5a** (run 17), while other tridentate and tetradentate lithium amides gave poor results. As to the chiral amines, the results using *(R)*-**3c** (run 27) and *(R)*-**3e** (run 31) were almost comparable to those (runs 26 and 30, respectively) obtained under stoichiometric conditions, while turnover of *(R)*-**3d** was not observed under catalytic conditions (run 29).

It is thus concluded that the best conditions for the present catalytic asymmetric deprotonation of **1a** should be to use **5a** (2.4 equivalents) and *(R)*-**3b** (0.3 equivalents) in THF in the presence of HMPA (2.4 equivalents) and DABCO (1.5 equivalents) at -78 °C by the EQ method.

Catalytic asymmetric deprotonation of other 4-substituted cyclohexanones (**1b~d**) were examined under these conditions (runs 33, 35, and 37). It is shown that the results were almost comparable to those obtained under stoichiometric conditions (runs 32, 34, and 36, respectively).

The catalytic cycle of the present asymmetric deprotonation should be as shown below.



CONCLUSION

Lithium-hydrogen interchange between an achiral lithium amide (**5a**) and a chiral bidentate amine (*(R)*-**3b**) was successfully applied to the catalytic asymmetric deprotonation of 4-substituted cyclohexanones (**1a~d**). Using 2.4 equivalents of **5a** and 0.3 equivalent of *(R)*-**3b** in THF in the presence of 2.4 equivalents of HMPA and 1.5 equivalents of DABCO for deprotonation of **1a~d** followed by treatment with TMSCl (the EQ method), chemical and optical yields of the products (*(R)*-**4a**~**d**) were almost comparable to those obtained by using a stoichiometric amount of *(R)*-**2b**.

EXPERIMENTAL SECTION

General All melting and boiling points are uncorrected. IR spectra were recorded on an Analect FX-6200 FT-IR spectrometer. The NMR spectra were recorded on a JEOL JNM-FX 200, a JEOL JNM-EX 270, a Varian Gemini-300, or a JEOL JNM-GSX 400 spectrometer, using tetramethylsilane as an internal standard. The chemical shifts are given in δ (ppm). Coupling constants (*J*) are given in hertz. Mass spectra (MS) were recorded on a Finigan MAT Incos 50 or a JEOL JMS-HX 100 spectrometer. Optical rotations were measured by a JASCO DIP-370 or a Horiba SEPA-200 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. *(R)*-**3a**,[15a] *(R)*-**3b**~**e**,[1] *(R)*-**3f**~**h**,[5i] **6a**,[15b] **6b**,[15c] **6c**,[15d] **6d**,[15c] and **6e**[15e] were prepared by the reported methods. Maximum rotational values[16] of *(R)*-**4a**, *(R)*-**4b**, *(R)*-**4c**, and *(R)*-**4d** used in the present study are $[\alpha]_{365}^{25}$ +237 (benzene), $[\alpha]_{365}^{25}$ +146 (benzene), $[\alpha]_{365}^{25}$ +228 (benzene),and $[\alpha]_{365}^{25}$ +238 (benzene), respectively.

2,2'-Bis(2,2,6,6-tetramethyl-1-piperidino)diethylamine (6f) A mixture of 1-(2-aminoethyl)-2,2,6,6-tetramethylpiperidine dihydrochlordie[17] (10.3 g, 40 mmol), 1-carboxymethyl-2,2,6,6-tetramethylpiperidine hydrochloride (prepared from the corresponding ethyl ester[18]) (9.43 g, 40 mmol), DEPC[19] (7.97 g, 44 mmol) and triethylamine (16.9 g, 167 mmol) in DMF (300 mL) was stirred at room temperature for 18 hr. Evaporation of the solvent gave a residue, which was mixed with 10% aq. NaOH, and the whole was extracted with toluene three times. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and evaporated to dryness *in vacuo* to give a pale yellow solid. Recrystallization from hexane gave the corresponding amide (11.2 g, 77%) as colorless needles of mp 185.5-186.5 °C. MS *m/z*: 365 (M^+). IR (nujol) cm^{-1}: 3320, 1650. A solution of this amide (10.7 g, 29 mmol) in THF (90 mL) and a solution of BH_3·THF in THF (1 *M*, 175 mL, 175 mmol) were mixed and the whole was heated under reflux for 16 hr. A solution of BH_3·THF in THF (1 *M*, 90 mL, 90 mmol) was again added and the whole was heated under reflux for 40 hr. MeOH (50 mL) was added to the reaction mixture under ice-cooling, and the whole was evaporated to dryness *in vacuo*. The residue was dissolved in EtOH, and was mixed with 14% HCl-EtOH (56 mL, 170 mmol). The whole was heated under reflux for 4 hr. Evaporation of the solvent to dryness *in vacuo* gave a residue, which was mixed with 10% aq. NaOH, and the whole was extracted with hexane three times. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and evaporated to dryness *in vacuo* to give crude **6f** (7.16 g, 70%) as an oil. Purification by column chromatography (silica gel, 5% MeOH-$CHCl_3$) followed by bulb-to-bulb distillation gave a pale yellow oil of bp_1 240-250 °C (bath temperature), mp 74-75 °C. ^{1}H-NMR: 1.03 (24H, s), 1.35-1.6 (12H, m), 2.45-2.65 (8H, m). MS *m/z*: 352 (M^++1). Anal. Calcd for $C_{22}H_{45}N_3$: C, 75.15; H, 12.90; N, 11.95. Found: C, 75.32; H, 12.87; N, 11.91.

***N*-(2-Dimethylaminoethyl)-*N*-methyl-*N'*-[2-(1-piperidino)ethyl]ethylenediamine (6g)** Prepared from 2-aminoethylpiperidine, sarcosine, and *N,N*-dimethyl-β-alanine in a similar way as described above as a colorless oil of bp $_{0.8}$ 205-210 °C (bath temperature). MS *m/z*: 257 (M^++1), 255 (M^+-1). ^{1}H-NMR (in $CDCl_3$): 1.4-1.6 (6H, m), 2.25 (9H, s), 2.3-2.5 (12H, m), 2.7-2.8 (4H, m). ^{13}C-NMR (in $CDCl_3$): 24.5, 25.9, 42.6, 45.8, 46.9, 47.4, 54.7, 55.9, 57.4, 57.6, 58.7. **6g**·4HCl: colorless crystals of mp 216-220 °C (decomp.) (from MeOH). Anal. Calcd for $C_{14}H_{32}N_4 \cdot 4HCl$: C, 40.00; H, 9.11; N, 13.33. Found: C, 40.01; H, 9.12; N, 13.39.

***N*-Methyl-*N*,*N'*-bis[2-(1-piperidino)ethyl]ethylenediamine (6h)** Prepared from 1-(2-aminoethylpiperidine, sarcosine, and 1-carboxymethylpiperidine in a similar way as described above as a colorless oil of $bp_{0.8}$ 205-210 °C (bath temperature). MS *m/z*: 297 (M^{+}+1). ^{1}H-NMR (in $CDCl_3$): 1.35-1.65 (12H, m), 2.23)3H, s), 2.3-2.5 (16H, m), 2.65-2.75 (4H, m). **6h**·4HCl: colorless prisms of mp 276-280 °C (decomp.). Anal. Calcd for $C_{17}H_{36}N_4 \cdot 4HCl \cdot H_2O$: C, 44.35; H, 9.20; N, 12.17; Cl, 30.80. Found: C, 44.50; H, 9.26; N, 12.04; Cl, 30.90.

A Typical Procedure for Deprotonation Reactions under External Quench Method (Table 1) a) Run 2: A solution of *n*-butyllithium in hexane (1.58 *N*, 1.08 mL, 1.71 mmol) was added to a solution of *(R)*-**3b** (510 mg, 1.78 mmol) in THF (36 mL) at -78 °C under argon atmosphere. The resulting solution was stirred for 30 min. After addition of HMPA (0.60 mL, 3.45 mmol), the whole was stirred at -78 °C for 30 min. A solution of **1a** (220 mg, 1.43 mmol) in THF (5 mL) was added dropwise, and the whole was stirred at -78 °C for 1 hr. TMSCl (0.91 mL, 7.2 mmol) was added, and the whole was stirred at -78 °C for 15 min. The reaction mixture was quenched by addition of triethylamine (3 mL) and saturated aq. $NaHCO_3$ (5 mL), and the whole was allowed to warm to room temperature. After addition of water (15 mL), the whole was extracted with hexane (50 mL x 3). The organic extracts were combined, washed successively with water, 0.1 *N* aq. citric acid, water, saturated aq. $NaHCO_3$, and brine, and dried over 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 *(R)*-**4a** (275.5 mg, 85%) as a colorless oil of $bp_{0.8}$ 160 °C (bath temperature). $[\alpha]_{365}^{25}$ +191 (*c* 2.00, benzene), corresponding to 81% ee.

b) Run 6: A solution of *n*-butyllithium in hexane (1.37 *N*, 2.10 mL, 2.88 mmol) was added to a solution of **6a** (708 mg, 2.9 mmol) in THF (36 mL) at -78 °C under argon atmosphere. The resulting solution was stirred for 30 min. After addition of HMPA (1.00 mL, 5.76 mmol), the whole was stirred at -78 °C for 1 hr. A solution of **1a** (220 mg, 1.43 mmol) in THF (5 mL) was added dropwise, and the whole was stirred at -78 °C for 1 hr. TMSCl (0.91 mL, 7.2 mmol) was added, and the whole was stirred at -78 °C for 15 min. The reaction mixture was quenched by addition of triethylamine (3 mL) and saturated aq. $NaHCO_3$ (5 mL), and was then worked up as described in a) above to give **4a** (120 mg, 37%) as a colorless oil of $bp_{0.3}$ 150 °C (bath temperature).

Rotational Values of *(R)*-4a Obtained by the Reactions (Table 1) run 1: $[\alpha]_{405}^{25}$ +139 (*c* 2.15, benzene)[20]; run 3: $[\alpha]_{405}^{25}$ +140 (*c* 2.06, benzene)[20]; run 4: $[\alpha]_{405}^{25}$ +84 (*c* 2.00, benzene)[20]; run 5: $[\alpha]_{405}^{25}$ +122 (*c* 2.02, benzene).[20]

A Typical Procedure for Catalytic Asymmetric Deprotonation under External Quench Method (Table 2) a) Run 15: A solution of *n*-butyllithium in hexane (1.53 *N*, 2.25 mL, 3.40 mmol) was added to a solution of **6a** (855 mg, 3.57 mmol) in THF (18 mL) at -78 °C under argon atmosphere. After stirring for 40 min, a solution of *(R)*-**3b** (123 mg, 0.43 mmol) in THF (9 mL) was added, and the whole was stirred for 20 min. After addition of a solution of HMPA (0.60 mL, 3.40 mmol) and DABCO (192 mg, 1.70 mmol) in THF (9 mL) followed by stirring for 20 min, a solution of **1a** (220 mg, 1.43 mmol) in THF (5 mL) was added, and the whole was stirred at -78 °C for 1.5 hr. TMSCl (0.91 mL, 7.20 mmol) was added, and the whole was stirred for 15 min. The reaction mixture was quenched by addition of triethylamine (3 mL) and saturated aq. $NaHCO_3$ (5 mL), and the whole was allowed to warm to room temperature. After addition of water (15 mL), the whole was extracted with hexane (50 mL x 3). The organic extracts were combined, washed successively with water, 0.1 *N* aq. citric acid, water, saturated aq. $NaHCO_3$, and brine, and dried over 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 *(R)*-**4a** (268.3 mg, 83%) as a colorless oil of bp$_{0.7}$ 160 °C (bath temperature). $[\alpha]_{365}^{25}$ +186 (*c* 2.06, benzene), corresponding to 78% ee.

b) Run 37: A solution of *n*-butyllithium in hexane (1.50 *N*, 2.30 mL, 3.40 mmol) was added to a solution of **6a** (855 mg, 3.57 mmol) in THF (18 mL) at -78 °C under argon atmosphere. After stirring for 40 min, a solution of *(R)*-**3b** (123 mg, 0.43 mmol) in THF (9 mL) was added, and the whole was stirred for 20 min. After addition of a solution of HMPA (0.60 mL, 3.40 mmol) and DABCO (240 mg, 2.10 mmol) in THF (9 mL) followed by stirring for 20 min, a solution of **1d** (160 mg, 1.43 mmol) in THF (5 mL) was added and the whole was stirred at -78 °C for 1.5 hr. TMSCl (0.91 mL, 7.20 mmol) was added, and the whole was stirred for 15 min. The reaction mixture was quenched by addition of triethylamine (3 mL) and saturated aq. $NaHCO_3$ (5 mL), and was then worked up as described in a) above to give *(R)*-**4d** (183.5 mg, 70%) as a colorless oil of bp$_{40}$ 150 °C (bath temperature). $[\alpha]_{365}^{25}$ +178 (*c* 2.08, benzene), corresponding to 75% ee.

Rotational Values of *(R)*-4a~d Obtained by Catalytic Asymmetric Deprotonation (Table 2) For *(R)*-**4a**, run 2: $[\alpha]_{365}^{25}$ +73 (*c* 2.08, benzene); run 4: $[\alpha]_{365}^{25}$ +126 (*c* 1.25, benzene); run 5: $[\alpha]_{365}^{25}$ +144 (*c* 2.25, benzene); run 6: $[\alpha]_{365}^{25}$ +165 (*c* 2.72, benzene); run 7: $[\alpha]_{365}^{25}$ +165 (*c* 2.06, benzene); run 8: $[\alpha]_{365}^{25}$ +131 (*c* 2.10, benzene); run 9: $[\alpha]_{365}^{25}$ +171 (*c* 2.06, benzene); run 10: $[\alpha]_{365}^{25}$ +164 (*c* 2.20, benzene); run 11: $[\alpha]_{365}^{25}$ +110 (*c* 2.56, benzene); run 12: $[\alpha]_{365}^{25}$ +66 (*c* 2.02, benzene); run 13: $[\alpha]_{365}^{25}$ +173 (*c* 1.96, benzene); run 14: $[\alpha]_{365}^{25}$ +168 (*c* 2.62, benzene); run 16: $[\alpha]_{365}^{25}$ +65 (*c* 2.13, benzene); run 17: $[\alpha]_{365}^{25}$ +186 (*c* 2.20, benzene); run 18: $[\alpha]_{365}^{25}$ +163 (*c* 2.33, benzene); run 19: $[\alpha]_{365}^{25}$ +61 (*c* 1.95, benzene); run 20: $[\alpha]_{365}^{25}$ +13 (*c* 0.55, benzene); run 21: $[\alpha]_{365}^{25}$ +63 (*c* 1.11, benzene); run 22: $[\alpha]_{365}^{25}$ +179 (*c* 2.45, benzene); run 23: $[\alpha]_{405}^{25}$ +128 (*c* 1.01, benzene)[20]; run 24: $[\alpha]_{365}^{25}$ +33 (*c* 2.18, benzene); run 25: $[\alpha]_{405}^{25}$ +17 (*c* 2.19, benzene)[20]; run 27: $[\alpha]_{405}^{25}$ +137 (*c* 2.06, benzene)[20]; run 29: $[\alpha]_{405}^{25}$ +22 (*c* 2.15, benzene)[20]; run 31: $[\alpha]_{405}^{25}$ +127 (*c* 2.06, benzene).[20] For *(R)*-**4b**, run 33: $[\alpha]_{365}^{25}$ +111 (*c* 2.11, benzene). For *(R)*-**4c**, run 35: $[\alpha]_{365}^{25}$ +172 (*c* 2.19, benzene).

^{1}H-NMR Spectral Data (at -80 °C) of *(R)*-2a, *(R)*-2b, *(R)*-3a, *(R)*-3b, 5a, and 6a in THF-d_8 in the Presence of HMPA-d_{18} a) *(R)*-**2a**: *(R)*-**3a** (18.6 mg, 67.8 μmol) was put in a dried NMR sample tube. The tube was provided with a septum, and the inside of the tube was flushed with argon. THF-d_8 (0.3 mL) was added in the tube to get a clear solution. At -78 °C, a solution of *n*-butyllithium in hexane (7.0 *N*, 9.9 μL, 69 μmol) was added in the tube, and the solution adhering to the inside wall of the tube was washed down with THF-d_8 (0.2 mL). HMPA-d_{18} (23.2 μL, 133 μmol) was then put in the tube, and the inside wall of the tube was washed down with THF-d_8 (0.1 mL). The tube was then sealed with a flame. The benzylic proton signal appeared at δ 4.18 (almost doublet-like q, J = 11.3 and ~0).

b) *(R)*-**2b**: Using *(R)*-**3b** (14.9 mg, 52.0 μmol), *n*-butyllithium in hexane (7.0 *N*, 8.0 μL, 56 μmol), HMPA-d_{18} (18.0 μL, 103 μmol), and THF-d_{18} (0.6 mL), an NMR sample of *(R)*-**2b** was prepared as in a) above. The benzylic proton signal appeared at δ 4.17 (almost doublet-like q, J = 10.6 and ~0).

c) *(R)*-**3a**: NMR sample was prepared from *(R)*-**3a** (14.1 mg, 51 μmol) and HMPA-d_{18} (17.7 μL, 101 μmol) in THF-d_8 (0.6 mL). The benzylic proton signal appeared at δ 3.71 (q, J = 11.0 and 3.8).

d) *(R)*-**3b**: NMR sample was prepared from *(R)*-**3b** (15.4 mg, 53.8 μmol) and HMPA-d_{18} (18.7 μL, 107 μmol) in THF-d_8 (0.6 mL). The benzylic proton signal appeared at δ 4.00 (almost doublet-like q, *J* = 8.7 and ~0).

e) **5a**: Using **6a** (16.35 mg, 68.3 μmol), *n*-butyllithium in hexane (7.0 *N*, 10.0 μL, 70 μmol), HMPA-d_{18} (23.8 μL, 136 μmol), and THF-d_{18} (0.6 mL), an NMR sample of **5a** was prepared as in a) above. Except the signal of non-deuterated THF at δ 3.56, no signals appeared in a range of δ 3.2-6.

f) **6a**: NMR sample was prepared from **6a** (15.9 mg, 66.4 μmol) and HMPA-d_{18} (23.1μL, 132 μmol) in THF-d_6 (0.6 mL). Except the signal of non-deuterated THF at δ 3.56, no signals appeared in a range of δ 3.2-6.

g) A mixture of *(R)*-**3a** and **5a**: **6a** (25.8 mg, 108 μmol) was put in a dried NMR sample tube. The tube was provided with a septum, and the inside of the tube was flushed with argon. THF-d_8 (0.1 mL) was added in the tube to get a clear solution. At -78 °C, a solution of *n*-butyllithium in hexane (8.0 *N*, 13.8 μL, 110 μmol) was added in the tube, and the solution adhering to the inside wall of the tube was washed down with THF-d_8 (0.2 mL). HMPA-d_{18} (37.0 μL, 211 μmol) was then put in the tube, and the inside wall of the tube was washed down with THF-d_6 (0.1 mL). A solution of *(R)*-**3a** (14.8 mg, 54 μmol) in THF-d_8 (0.3 mL) was put in the tube, and the tube was sealed with a flame. The NMR spectrum showed a signal at δ 3.71, while no signal appeared around δ 4.18.

h) A mixture of *(R)*-**2a** and **6a**: *(R)*-**3a** (26.4 mg, 103 μmol) was put in a dried NMR sample tube. The tube was provided with a septum, and the inside of the tube was flushed with argon. THF-d_8 (0.1 mL) was added in the tube to get a clear solution. At -78 °C, a solution of *n*-butyllithium in hexane (8.0 *N*, 13.1 μL, 105 μmol) was added in the tube, and the solution adhering to the inside wall of the tube was washed down with THF-d_8 (0.2 mL). HMPA-d_{18} (35.0 μL, 200 μmol) was then put in the tube, and the inside wall of the tube was washed down with THF-d_6 (0.1 mL). A solution of **6a** (12.4 mg, 52 μmol) in THF-d_8 (0.3 mL) was put in the tube, and the tube was sealed with a flame. The NMR spectrum showed two signals at δ 3.71 and at δ 4.18 in almost the same intensity.

i) A mixture of **5a** and *(R)*-**3b**: **6a** (25.4 mg, 106 μmol) was put in a dried NMR sample tube. The tube was provided with a septum, and the inside of the tube was flushed with argon. THF-d_8 (0.1 mL) was added in the tube to get a clear solution. At -78 °C, a solution of *n*-butyllithium in hexane (8.0 *N*, 13.8 μL, 110 μmol) was added in the tube, and the solution adhering to the inside wall of the tube was washed down with THF-d_8 (0.2 mL). HMPA-d_{18} (36.2 μL, 207 μmol) was then put in the tube, and the inside wall of the tube was washed down with THF-d_6 (0.1 mL). A solution of *(R)*-**3b** (15.2 mg, 53 μmol) in THF-d_8 (0.3 mL) was put in the tube, and the tube was sealed with a flame. The NMR spectrum showed a signal at δ 4.17, while no signal appeared around δ 4.0.

j) A mixture of *(R)*-**2b** and **6a**: *(R)*-**3b** (30.1 mg, 105 μmol) was put in a dried NMR sample tube. The tube was provided with a septum, and the inside of the tube was flushed with argon. THF-d_8 (0.1 mL) was added in the tube to get a clear solution. At -78 °C, a solution of *n*-butyllithium in hexane (8.0 *N*, 13.1 μL, 105 μmol) was added in the tube, and the solution adhering to the inside wall of the tube was washed down with THF-d_8 (0.2 mL). HMPA-d_{18} (36.0 μL, 206 μmol) was then put in the tube, and the inside wall of the tube was washed down with THF-d_6 (0.1 mL). A solution of **6a** (15.6 mg, 53 μmol) in THF-d_8 (0.3 mL) was put in the tube, and the tube was sealed with a flame. The NMR spectrum showed a signal at δ 4.17, while no signal appeared around δ 4.0.

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REFERENCES AND NOTES

1. Part 28: Aoki, K.; Tomioka, K.; Noguchi, H.; Koga, K. *Tetrahedron,* in press.
2. a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*; Plenum Press: New York, 1990; Chapters 1 and 2. b) Mekelburger, H, B.; Wilcox, C. S. *Comprehensive Organic Synthesis;* Vol. 2, Trost, B. M.; Fleming, I., Ed.; Pergamon Press, Oxford, 1991, Chapter 1.4. c) Caine, D. *Comprehensive Organic Synthesis;* Vol. 3, Trost, B. M.; Fleming, I., Ed.; Pergamon Press, Oxford, 1991, Chapter 1.1.
3. For reviews: a) Koga, K. *J. Synth. Org. Chem., Jpn.* **1990**, *48*, 463-475. b) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1-26. c) Waldmann, H. *Nachr. Chem. Tech. Lab.* **1991**, *39*, 413-418. d) Koga, K. *Pure Appl. Chem.* **1994**, *66*, 1487-1492. e) Koga, K.; Shindo, M. *J. Synth. Org. Chem., Jpn.* **1995**, *52*, 1021-1032. f) Simpkins, N. S. *Pure Appl. Chem.* **1996**, *68*, 691-694. g) Simpkins, N. S. *Advanced Asymmetric Synthesis*; Stephenson, G. R. Ed.; Chapman & Hall: London, 1996; pp. 111-125.
4. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495-498.
5. a) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543-545. b) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761-763. c) Aoki, K.; Noguchi, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 5105-5108. d) Sugasawa, K.; Shindo, M.; Noguchi, H.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 7377-7380. e) Toriyama, M.; Sugasawa, K.; Shindo, M.; Tokutake, N.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 567-570. f) Aoki, K.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 2505-2506. g) Shirai, R.; Sato, D.; Aoki, K.; Tanaka, M.; Kawasaki, H.; Koga, K. *Tetrahedron,* **1997**, *53*, 5963-5972. h) Sato, D,; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *Tetrahedron* **1997**, *53*, 7191-7200. i) Sato, D.; Kawasaki, H.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 1399-1402. j) Chatani, H.; Nakajima, M.; Kawasaki, H.; Koga, K. *Heterocycles*, in press.
6. A part of this paper is reported as a communication: Yamashita, T.; Sato, D.; Kiyoto, T.; Kumar, A.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 8195-8198.
7. EQ method was employed because deprotonation of **1** by fluorine-containing chiral lithium amides under IQ method gave **4** in lower chemical yields due to the formation of *N*-silylated chiral amines to some extent.
8. It is conceivable that the tetramethylpiperidino group in **5f** is too bulky to work efficiently as an internal ligation site for the lithium.
9. a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877. b) Evans, D. A. In *Asymmetric Synthesis;* Vol. 3, Morrison, J. D. Ed,; Academic Press: Orlando, 1984; pp. 1-110.
10. Detailed examinations on lithium-hydrogen interchange between lithium dialkylamides and secondary amines in solution are reported. Fraser, R. R.; Baignée, A.; Bresse, M.; Hata, K. *Tetrahedron Lett.* **1982**, *23*, 4195-4198.
11. For example, *pKa* values of the conjugate acids of ethylamine and trifluoroethylamine are reported to be 10.97 and 5.84, respectively. Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622-2637.

12. A similar phenomenon was observed in THF-d_8 in the absence of HMPA-d_{18}.
13. In the present paper, the reaction conditions using 1.2 equivalents of *(R)*-**2b** are called stoichiometric conditions, while those using a combination of 0.3 equivalent (or less) of *(R)*-**2b~e** in the presence of excess **5a~h** are called catalytic conditions.
14. Since we have no data on the relative rates of deprotonation vs. lithium-hydrogen interchange, it is not possible to explain this difference at present.
15. a) Shirai, R.; Aoki, K.; Sato, D.; Kim, H.-D.; Murakata, M.; Yasukata, T.; Koga, K. *Chem. Pharm. Bull.* **1994**, *42*, 690-693. b) Hoover, J. R. *Diss. Abstr. Univ. Oklahoma* (*Chem. Abstr.* **1977**, *86*, *132704t*. c) Najer, H.; Giudicelli, R.; Sette, J. *Bull. Soc. Chim. Fr.* 556-559 (1962). d) Sacco, Jr., L. J.; Anthony, P. Z.; Borgen, D. R.; Ginger, L. G.; *J. Am. Chem. Soc.* **1954**, *76*, 303-305. e) Ger. Pat. 823451 (*Chem. Abstr.* **1955**, *49*, 3272b.)
16. Aoki, K.; Nakajima, M.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1993**, *41*, 994-996.
17. Gadekar, S. M.; Nibi, S.; Cohen, E. *J. Med. Chem.* **1868**, *11*, 811-814.
18. Robertson, J. E.; Biel, J. H.; DiPierro, F. *J. Med. Chem.* **1963**, *6*, 381-384.
19. Shioiri, T.; Yokoyama, Y.; Kasai, Y.; Yamada, S. *Tetrahedron* **1976**, *32*, 2211-2217.
20. Since a sample of *(R)*-**4a** ($[\alpha]_{365}^{25}$ +185.7 (benzene), corresponding to 78% ee) showed $[\alpha]_{405}^{25}$ +141.5 (benzene), and a sample of *(R)*-**4a** ($[\alpha]_{365}^{25}$ +176.5 (benzene), corresponding to 74% ee) showed $[\alpha]_{405}^{25}$ +132.4 (benzene), maximum rotation of *(R)*-**4a** was calculated to be $[\alpha]_{405}^{25}$ +180 (benzene).

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