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Homochiral ligands derived from *cis*-1-phenylcyclohexane-1,2-diol and *cis*-2-azido-2-phenylcyclohexanol

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Abstract: Homochiral ligands (*R,R*)-**2**, (*R,R*)-**3a**, (*R,R*)-**3b**, (*S,S*)-**4a**, and (*S,S*)-**4b** were prepared from *cis*-1-phenylcyclohexane-1,2-diol or *cis*-2-azido-2-phenylcyclohexanol and were tested as ligands for the nucleophilic addition of alkyllithiums to benzaldehyde 4-anisidineimine. While moderate enantioselectivities (up to 43% e.e.) were observed with (*R,R*)-**3b** and (*S,S*)-**4a**, (*R,R*)-**2** and (*R,R*)-**3a** did not show enantioselectivities. Homochiral secondary amines (*S,S*)-**6a** and (*S,S*)-**6b** were also prepared from *cis*-2-azido-2-phenylcyclohexanol. Moderate enantioselectivities (up to 50%) were observed when they were used as chiral lithium amide base precursors for the deprotonation of 4-*t*-butylcyclohexanone. © 1997 Elsevier Science Ltd

Design and synthesis of chiral ligands play a crucial role in asymmetric syntheses using an external homochiral ligand. For asymmetric nucleophilic additions of organolithium, organomagnesium, and organozinc reagents to a C=X (X=O or N) double bond, a variety of chiral ligands, most of which are basically chiral derivatives of 2-alkoxy-1-aminoethane or 1,2-dialkoxyethane, has been developed.[1] Similarly, it has been demonstrated that the enantioselective deprotonation of prochiral carbonyl compounds can be achieved by homochiral lithium amides derived from chiral secondary amines bearing a 2-alkoxy-1-aminoethane or 1,2-diaminoethane backbone.[2]

We have synthesized homochiral 18-crown-6 ethers and azophenolic crown ethers derived from *cis*-1-phenyl-1,2-cyclohexanediol **1** and clarified their enantiomer recognition behavior in the transport of ammonium ions through bulk liquid membranes and complexation with amines in solution, respectively.[3] We found that the phenylcyclohexane unit exerted effective steric hindrance as a chiral barrier leading to moderate to substantial enantiomer recognition. Moreover, we also synthesized a 14-crown-4 derivative (±)-**2** from (±)-**1** and investigated its high lithium ion binding ability as well as excellent lithium/sodium selectivity, which were also ascribed to the steric bulkiness of the phenylcyclohexane unit.[4] These results, coupled with the fact that both enantiomers of **1** are readily available from kinetic resolution by the lipase-catalyzed acylation,[5] prompted us to examine the use of homochiral **2** as a chiral ligand for asymmetric nucleophilic addition of organolithium reagents to a C=X double bond.[6] For comparison, we also prepared the homochiral acyclic derivatives of **2**, dimethyl ether **3a** and bis(methoxyethyl) ether **3b**. Moreover, by analogy with the known chiral ligands having an alkoxyaminoethane backbone, we prepared the corresponding amino ether derivatives **4a** and **4b**, derived from *cis*-2-azido-2-phenylcyclohexanol **5c**. These compounds were examined as chiral ligands in the nucleophilic addition of alkyllithiums to benzaldehyde **9**[7] and its anisidineimine **12**.[8] In addition, we prepared the homochiral secondary amine derivatives **6a** and **6b** in order to use them as precursors of a homochiral lithium amide base in the deprotonation of a prochiral ketone, 4-*t*-butylcyclohexanone **14**.[9]

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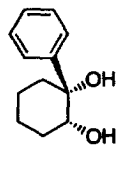
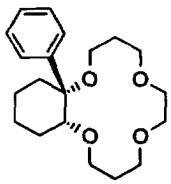


(*R,R*)-**1**



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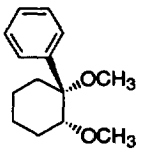

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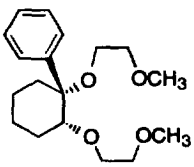

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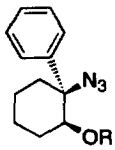
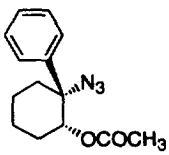
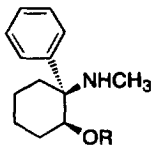


(*S,S*)-**5a**; R=CH_3
(*S,S*)-**5b**; R=$(CH_2)_2OCH_3$
(*S,S*)-**5c**; R=H;



(*R,R*)-**5d**

(*S,S*)-**4a**; R=CH_3
(*S,S*)-**4b**; R=$(CH_2)_2OCH_3$



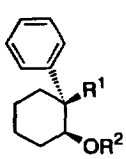
(*S,S*)-**6a**; R=CH_3
(*S,S*)-**6b**; R=$(CH_2)_2OCH_3$

Preparation of homochiral ligands

Homochiral crown ether (*R,R*)-**2** was prepared from *R,R*-diol **1**[3a,5] according to the manner described previously.[4] The acyclic ethers (*R,R*)-**3a** and (*R,R*)-**3b** were also prepared from diol (*R,R*)-**1** by alkylation with iodomethane and 2-methoxyethyl *p*-toluenesulfonate, respectively.

Azido alcohol (±)-**5c** was obtained from (±)-**1** as a major product (78% isolated yield) by the reaction with hydrogen azide in situ prepared from sodium azide and perchloric acid.[10] The *cis* stereochemistry of **5c** was assigned tenatively on the basis of the coupling constant of the tertiary proton adjacent to the hydroxy group. Namely, it appears as a double doublet with coupling constants of 4.0 and 10.3 Hz, indicating that it occupies an axial position. For comparison, the corresponding coupling constants of the *trans* isomer (not isolated in a pure form) are 3.4 and 4.2 Hz. Homochiral azido alcohols (*R,R*)-**5c** and (*S,S*)-**5c** can be prepared either by the transformation from homochiral diol **1** or by the kinetic resolution of (±)-**5c** by the lipase-catalyzed acetylation with isopropenyl acetate, the latter reaction gave (*S,S*)-**5c** (>99% e.e.) in 40% yield and (*R,R*)-**5c** (>99% e.e.) in 42% yield after hydrolysis of acetate (*R,R*)-**5d**. The resolution was thus carried out as effective as that of (±)-**1**.[5]

Homochiral azido alcohol (*S,S*)-**5c** was first converted to the ethers (*S,S*)-**5a** and (*S,S*)-**5b** as decribed above, which were then reduced to amino ethers (*S,S*)-**7a** and (*S,S*)-**7b**, respectively. The methylation of (*S,S*)-**7a** and (*S,S*)-**7b** with formaldehyde and formic acid[11] gave the tertiary amines (*S,S*)-**4a** and (*S,S*)-**4b**, respectively. Formylation of (*S,S*)-**7a** and (*S,S*)-**7b** to the corresponding formamides (*S,S*)-**8a** and (*S,S*)-**8b** and the subsequent LAH reduction afforded the secondary amines (*S,S*)-**6a** and (*S,S*)-**6b**, respectively.



(*S,S*)-**7a**; R^1=NH_2, R^2=CH_3
(*S,S*)-**7b**; R^1=NH_2, R^2=$(CH_2)_2OCH_3$
(*S,S*)-**8a**; R^1=NHCHO, R^2=CH_3
(*S,S*)-**8b**; R^1=NHCHO, R^2=$(CH_2)_2OCH_3$

Enantioselective addition of alkyllithiums to benzaldehyde and its anisidineimine

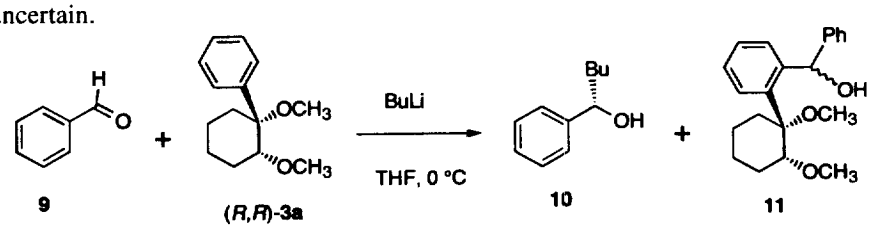
We examined first the nucleophilic addition of butyllithium to benzaldehyde **9**.[7] Preliminary experiments were undertaken using 1.5 equiv. each of butyllithium and (*R,R*)-**3a** (relative to **9**) in THF, ether, or toluene at 0°C. While no enantioselectivity was observed in toluene, *S*-alcohol **10** was

Table 1. Asymmetric 1,2-addition of organolithiums to imine **12**

		MeLi			BuLi		
Ligand	Equiv.	e.e. (%)[a]	Confn of **13**[b]	Yield (%)	e.e. (%)[a]	Confn of **13**[b]	Yield (%)
(*R*,*R*)-**2**	2.6	≈0	-	75	≈0	*S*	71
	0.3	≈0	-	53	≈0	*S*	63
(*R*,*R*)-**3a**	2.6	≈0	-	75	7	*S*	78
	0.3	≈0	-	87	7	*S*	97
(*R*,*R*)-**3b**	2.6	43	*S*	79	18	*S*	78
	0.3	35	*S*	53	≈0	*S*	97
(*S*,*S*)-**4a**	2.6	34	*R*	79	10	*R*	78
	0.3	33	*R*	84	≈0	*R*	97
(*S*,*S*)-**4b**	2.6	17	*R*	92	10	*R*	97
	0.3	11	*R*	66	7	*R*	85

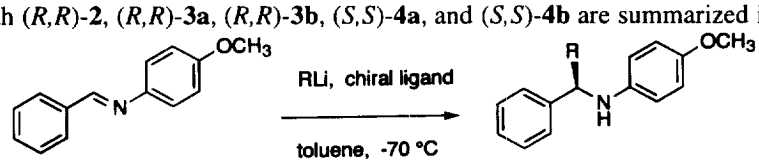
a) Determined by HPLC analysis using a chiral column.
b) Determined by the formally reported optical rotations.

obtained in moderate selectivity in THF (52% e.e.) and ether (14% e.e.). However, a closer look at the products from the reactions in THF or ether revealed that alcohol **11**, which was derived from (*R*,*R*)-**3a** through the ortholithiation[12] of the phenyl group followed by addition to **9**, was formed in about 10% yield. The ^{1}H and ^{13}C NMR spectra of **11** suggest that it is a single diastereomer, indicating that the nucleophilic attack of the lithiated (*R*,*R*)-**3a** to **9** took place enantioselectively, but the stereochemistry remains uncertain.



9 (*R*,*R*)-**3a** **10** **11**

Accordingly, we looked for a reaction that could be undertaken in hydrocarbon solvents. Tomioka *et al.* reported that the nucleophilic addition of alkyllithiums to benzaldehyde 4-anisidineimine **12** took place enantioselectively in toluene in the presence of chiral ligands to give the chiral amine derivatives.[8] We chose this reaction to test the performance of the ligands. The reaction was carried out using 2 equiv. of methyllithium or butyllithium and 2.6 equiv. of a ligand in toluene at −70°C. Since it has been reported that the asymmetric addition can also be carried out catalytically with less than 1 equiv. of a chiral ligand,[8b,d,e] the experiments using 0.3 equiv. of a ligand were also undertaken. The results with (*R*,*R*)-**2**, (*R*,*R*)-**3a**, (*R*,*R*)-**3b**, (*S*,*S*)-**4a**, and (*S*,*S*)-**4b** are summarized in Table 1.



12 **13**

In all cases, (*S*)-amine **10** was obtained when (*R*,*R*) ligands were used and vice versa. In general, the reactions with methyllithium gave better enantioselectivities than those with butyllithium. The highest enantioselectivity (43% e.e.) was obtained when acyclic ether (*R*,*R*)-**3b** was used. By contrast, 14-crown-4 ether (*R*,*R*)-**2** and dimethyl ether (*R*,*R*)-**3a** exhibited only negligible or no selectivities. The observed enantioselectivities with (*R*,*R*)-**3b** and amino ether (*S*,*S*)-**4a** are comparable to those reported for the related ligands having a 2-alkoxy-1-aminoethane or 1,2-dialkoxyethane unit.[8] However, the present results are inferior to those obtained using ligands having a 2-methoxyphenoxy group as a side

Table 2. Enantioselective deprotonation of 4-*t*-butylcyclohexanone **14**

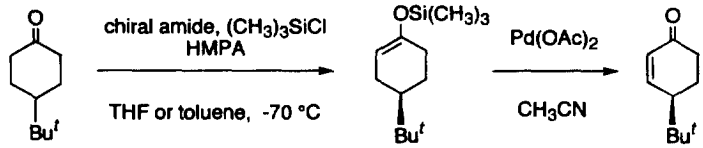
Ligand	Solvent	e.e. (%)[a]	Confn of **16**[b]	Yield of **15** (%)
(*S,S*)-**6a**	Toluene	39	*R*	77
	THF	50	*R*	70
(*S,S*)-**6b**	Toluene	34	*R*	37
	THF	34	*R*	51

a) Determined by HPLC analysis using a chiral column.
b) Determined by the formally reported optical rotation.

chain. With the ligands (*R,R*)-**3b**, (*S,S*)-**4a**, and (*S,S*)-**4b**, the reaction can be carried out catalytically, though the enantioselectivities are slightly lower than the corresponding reactions using an excess ligand.

Enantioselective deprotonation of 4-*t*-butylcyclohexanone

Koga *et al.* reported that the enantioselective deprotonation of prochiral cyclohexanone derivatives could be achieved by using chiral lithium amides derived from secondary amines having a 1,2-diaminoethane or 2-alkoxy-1-aminoethane unit.[9] In this context, we examined the use of secondary amines (*S,S*)-**6a** and (*S,S*)-**6b** as a source of homochiral lithium amide in the deprotonation of 4-*t*-butylcyclohexanone **14**. The reaction was carried out using 1.55 equiv. of (*S,S*)-**6a** or (*S,S*)-**6b**, 1.5 equiv. of butyllithium, 3.1 equiv. of HMPA, and 5.0 equiv. of chlorotrimethylsilane in toluene or THF at −70°C. The resultant silylenol ether **15** was converted to enone **16** by oxidation with $Pd(OAc)_2$ to determine its absolute configuration and enantiomeric excess.[13] The results are listed in Table 2.



14 **15** **16**

As shown in Table 2, (*R*)-enone **16** was obtained with moderate selectivity when (*S,S*)-amides were used. Methyl ether (*R,R*)-**6a** gave better results (up to 50% e.e.) than those with methoxymethyl ether (*R,R*)-**6b**. However, the selectivities are lower than those reported for the reactions using chiral 1,2-diaminoethane derivatives.[9]

In summary, homochiral ligands (*R,R*)-**2**, (*R,R*)-**3a**, (*R,R*)-**3b**, (*S,S*)-**4a**, and (*S,S*)-**4b**, (*S,S*)-**6a** and (*R,R*)-**6b** were prepared from the readily available chiral sources, *cis*-1-phenylcyclohexane-1,2-diol (*R,R*)-**1** and *cis*-2-azido-2-phenylcyclohexanol (*S,S*)-**5c**. Though the results presented in this paper for the enantioselective addition and deprotonation do not exceed those previously published, it is hoped that the enantioselectivity would be improved by further modification to the basic framework or adequate choice of reaction conditions.

Experimental section

General

^1H NMR spectra were recorded on a JEOL JNM-GX-270 spectrometer at 30°C. IR and mass spectra were taken with a Hitachi 260-10 and a JEOL LMS-DX-303-HF spectrometer, respectively. Elemental analyses were carried out with a Perkin–Elmer 2400II CHN-analyzer. Optical rotations were measured at ambient temperature with a JASCO DIP-40 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. HPLC analyses were carried out with a Shimadzu LC-6A chromatograph.

(2R,3R)-2-Phenylcyclohexano-14-crown-4 (R,R)-**2**

To a suspension of 2.4 g (60 mmol) of 60% NaH and 2.8 g (26 mmol) of $LiClO_4$ in 500 mL of THF heated under reflux was added a solution of a mixture of 2.60 g (13.5 mmol) of diol (*R,R*)-**1**[5] and 7.00

g (14.4 mmol) of 4,7-dioxadecane-1,10-diyl bis(*p*-toluenesulfonate)[14] in 500 mL of THF during a 10 h period. The mixture was heated for 3 days, while NaH (2.4 g, 60 mmol) and the ditosylate (2.8 g, 5.8 mmol) was added. The reaction was quenched by the addition of ice-water, and most of the THF was evaporated. The residue was extracted with ether and the extract was washed with brine and then dried ($MgSO_4$). Evaporation of the solvent and subsequent chromatography on silica gel (elution with hexane:ethyl acetate=9:1) gave 2.37 g (53%) of crown ether (*R,R*)-**2** as a colorless solid. The spectral data are reported elsewhere.[4] Mp 88–90°C; $[\alpha]_D^{22}$ −8.93 (*c* 1.03, $CHCl_3$).

*(1*R,2R*)-1,2-Dimethoxy-1-phenylcyclohexane* (R,R)-***3a***

A mixture of 2.00 g (10.4 mmol) of diol (*R,R*)-**1** and 1.7 g (42 mmol) of 60% NaH in 460 mL of THF was heated under reflux for 2 h. After being cooled, 5.90 g (41.6 mmol) of iodomethane was added and the mixture was heated again for 1.5 h. The reaction was quenched by the addition of ice-water and most of the THF was evaporated. The residue was extracted with ethyl acetate and the extract was washed with brine and dried ($MgSO_4$). Flash chromatography (elution with hexane:ethyl acetate=9:1) of the residue obtained by evaporation of the solvent afforded 2.07 g (90%) of (*R,R*)-**3a** as a colorless solid. Mp 91–92°C; IR (KBr) 1100, 1070, 955, 755, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (dd, *J*=1.5, 8.2 Hz, 2H), 7.33 (dd, *J*=7.2, 8.2 Hz, 2H), 7.24 (t, *J*=7.2 Hz, 1H), 3.15 (s, 3H), 3.05 (dd, *J*=4.7, 10.1 Hz, 1H), 2.98 (s, 3H), 2.1–2.2 (m, 1H), 1.7–2.0 (m, 4H), 1.2–1.6 (m, 3H); MS (EI) *m/z* 220 (M^+, 19), 84 (100); $[\alpha]_D^{24}$ −28.5 (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.60; H, 9.06.

*(1*R,2R*)-1,2-Bis(2-methoxyethoxy)-1-phenylcyclohexane* (R,R)-***3b***

The reaction of 3.00 g (15.6 mmol) of diol (*R,R*)-**1** with 7.90 g (34.3 mmol) of 2-methoxyethyl *p*-toluenesulfonate was carried out as described above. The product was isolated by chromatography on silica gel (hexane:ethyl acetate=7:3) and subsequent distillation (bp 124–126°C, 0.5 mmHg) gave 4.10 g (85%) of (*R,R*)-**3b** as a colorless oil. IR (neat) 1100, 760, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (dd, *J*=1.3, 8.3 Hz, 2H), 7.32 (dd, *J*=1.0, 7.7 Hz, 2H), 7.24 (t, *J*=7.3 Hz, 1H), 3.58 (ddd, *J*=2.0, 5.5, 7.7 Hz, 1H), 3.0–3.4 (m, 14H, containing s at 3.38 and 3.18), 1.2–2.2 (m, 8H); MS (EI) *m/z* 308 (M^+, 2), 128 (100); $[\alpha]_D^{23}$ −8.80 (*c* 1.52, $CHCl_3$). The high-resolution mass spectrum was not obtained because of low intensity of the parent peak.

*(±)-2-Azido-2-phenylcyclohexanol (±)-**5c***

To a solution of 10.0 g (52.0 mmol) of (±)-diol **1** in 200 mL of chloroform was added 11.3 g (156 mmol) of 90% sodium azide and the mixture was cooled to −5°C by an ice–salt bath. 70% Perchloric acid (18 mL) was added dropwise during 30 min and the mixture was stirred at room temperature for 5 days. During the reaction another sodium azide (6.76 g, 93.6 mmol) and 18 mL of 70% perchloric acid was added. Saturated $NaHCO_3$ solution was added to neutralize the acid, and the organic layer was separated. The aqueous layer was extracted with chloroform and the combined organic layer was washed with 10% HCl and water and dried over $MgSO_4$. After removal of the solvent, the product was purified by flash chromatography (elution with hexane:ether=85:15) to give 8.84 g (78%) of (±)-**5c** as a colorless solid. Mp 62–63°C; IR (KBr) 3350, 2080, 1265, 1080, 1065, 985, 750, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.5 (m, 5H), 3.94 (dd, *J*=4.0, 10.3 Hz, 1H), 1.4–2.1 (m, 9H); MS (EI) *m/z* 217 (M^+, 1), 119 (100), 104 (100). Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.43; H, 6.98; N, 19.32.

Small amounts of the *trans* isomer were detected by ^1H NMR spectra, but it was obtained as a mixture with *cis*-**5c** and was not isolated in a pure form. ^1H NMR ($CDCl_3$) for *trans* isomer: δ 3.84 (dd, *J*=3.4, 4.2 Hz, C*H*OH).

(1S,2S)- and (1R,2R)-2-Azido-2-phenylcyclohexanol (S,S)-***5c*** *and* (R,R)-***5c***

(A) Substitution of diol (S,S)-***1*** *by hydrogen azide*

Reaction of (*S,S*)-**1** (10.0 g, 52.0 mmol) was carried out in essentially the same manner as described above to give 8.61 g (76%) of (*S,S*)-**5c**: mp 64–65°C; $[\alpha]_D^{25}$ +59.2 (*c* 1.00, $CHCl_3$).

*(B) Kinetic resolution of (±)-**5c** by lipase-catalyzed acetylation*

A mixture of 8.91 g (41.0 mmol) of (±)-**5c**, 16.4 g (164 mmol) of isopropenyl acetate, and 4.1 g of Lipase P (from *Pseudomonas cepacia*) in 200 mL of diisopropyl ether was stirred at 30°C for 76 h. The mixture was filtered and the filtrate was concentrated. Flash chromatography of the residue on silica gel (elution with hexane:ethyl acetate=97:3–8:2) gave 5.52 g (52%) of (*R,R*)-acetate **5d** as a colorless oil and 3.55 g (40%) of (*S,S*)-**5c** [>99% e.e. by HPLC (Daisel CHIRALPAK AD, eluent; hexane:EtOH=8:1)]. (*R,R*)-Acetate **5c**; IR (neat) 2080, 1735, 1235, 1045, 755, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.5 (m, 5H), 5.31 (dd, *J*=5.7, 8.4 Hz, 1H), 1.4–2.1 (m, 11H, containing s at 1.88); MS (EI) *m/z* 259 (M^+, <1), 119 (100); $[\alpha]_D^{24}$ +64.7 (*c* 1.50, $CHCl_3$).

The above acetate (5.52 g, 21.3 mmol) was dissolved in 800 mL of 5% methanol solution of KOH and the solution was stirred at room temperature overnight. The mixture was neutralized with conc. HCl and most of the methanol was evaporated under reduced pressure. The residue was diluted with water and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and brine and then dried ($MgSO_4$). After removal of the solvent, the product was isolated by recrystallization from hexane to give 3.74 g (81%) of (*R,R*)-**5c**, which was >99% ee by HPLC: $[\alpha]_D^{22}$ −59.0 (*c* 0.99, $CHCl_3$).

(1S,2S)-2-Methoxy-1-phenylcyclohexyl azide (S,S)-***5a***

The reaction of 500 mg (2.30 mmol) of azido alcohol (*S,S*)-**5c** with 653 mg (4.60 mmol) of iodomethane was carried out as described for the preparation of (*R,R*)-**3a**. The product was isolated by flash chromatography on silica gel (hexane:ethyl acetate=98:2) to give 444 mg (84%) of (*S,S*)-**5a** as a colorless solid. Mp 46–47°C; IR (KBr) 2100, 1270, 1130, 1110, 980, 770, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4–7.5 (m, 4H), 7.29 (t, *J*=7.0 Hz, 1H), 3.57 (dd, *J*=4.1, 10.5 Hz, 1H), 3.16 (s, 3H), 1.2–2.1 (m, 8H); MS (EI) *m/z* 232 (M^++1, 2), 230 (M^+−1, 2), 189 (100); $[\alpha]_D^{22}$ −11.1 (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.33; H, 7.45; N, 18.19.

(1S,2S)-2-(2-Methoxyethoxy)-1-phenylcyclohexyl azide (S,S)-***5b***

The reaction of 5.00 g (23.0 mmol) of azido alcohol (*S,S*)-**5c** with 9.80 g (42.5 mmol) of 2-methoxyethyl *p*-toluenesulfonate was carried out as described for the preparation of (*R,R*)-**3b**. The product was isolated by flash chromatography on silica gel (hexane:ethyl acetate=9:1) to give 4.89 g (77%) of (*S,S*)-**5b** as a colorless oil. IR (neat) 2110, 1260, 1110, 750, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (dd, *J*=1.3, 8.4 Hz, 2H), 7.39 (dd, *J*=7.0, 8.0 Hz, 2H), 7.28 (tt, *J*=1.3, 7.1 Hz, 1H), 3.71 (dd, *J*=4.2, 10.6 Hz, 1H), 3.4–3.6 (m, 1H), 3.2–3.4 (m, 3H), 3.18 (s, 3H), 1.2–2.1 (m, 8H); MS (EI) *m/z* 232 (M^+−43, 5), 188 (90), 59 (100); $[\alpha]_D^{23}$ +1.48 (*c* 1.12, $CHCl_3$).

(1S,2S)-2-Methoxy-1-phenylcyclohexylamine (S,S)-***7a***

To an ice-cooled suspension of 121 mg (3.20 mmol) of $LiAlH_4$ in 2 mL of THF was added a solution of 360 mg (1.56 mmol) of azide (*S,S*)-**5a** in 2 mL of THF. The mixture was stirred at room temperature for 1 h, before the reaction was quenched by the addition of 0.5 mL of acetone followed by saturated NH_4Cl solution. The mixture was filtered through a pad of Celite and the solvent was evaporated. The product was isolated by flash chromatography on silica gel (hexane:ethyl acetate=8:2) to give 271 mg (85%) of (*S,S*)-**7a** as a colorless oil. IR (neat) 3380, 1200, 1100, 900, 750, 725, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (dd, *J*=1.3, 8.6 Hz, 2H), 7.33 (dd, *J*=7.2, 8.6 Hz, 2H), 7.21 (tt, *J*=1.3, 7.2 Hz, 1H), 3.53 (dd, *J*=4.4, 10.4 Hz, 1H), 3.09 (s, 3H), 1.2–2.0 (m, 10H); MS (EI) *m/z* 206 (M^++1, 65), 132 (100); HRMS Calcd for $C_{13}H_{19}NO$: 205.1467. Found: 205.1479; $[\alpha]_D^{22}$ +47.1 (*c* 1.02, $CHCl_3$).

(1S,2S)-2-(2-Methoxyethoxy)-1-phenylcyclohexylamine (S,S)-***7b***

The reduction of 11.8 g (42.9 mmol) of azide (*S,S*)-**5b** with 2.45 g (64.6 mmol) of $LiAlH_4$ was carried out as described above to give 8.54 g (80%) of (*S,S*)-**7b** as a colorless oil. Bp 118–120°C, 10 mmHg; IR (neat) 3350, 1190, 1100, 850, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (dd, *J*=1.3, 7.3 Hz, 2H), 7.34 (dd, *J*=7.2, 7.9 Hz, 2H), 7.20 (tt, *J*=1.3, 7.3 Hz, 1H), 3.62 (dd, *J*=4.1, 10.4 Hz, 1H), 3.45 (ddd, *J*=3.6, 5.3, 9.6 Hz, 1H), 3.1–3.3 (m, 6H, containing s at 3.17), 1.2–2.0 (m, 10H); MS (EI) *m/z* 249 (M^+, 31), 190 (98), 132 (100); HRMS Calcd for $C_{15}H_{23}NO_2$: 249.1729. Found: 249.1748; $[\alpha]_D^{21}$ +48.4 (*c* 0.99, $CHCl_3$).

(1S,2S)-2-Methoxy-N,N-*dimethyl-1-phenylcyclohexylamine* (S,S)-***4a***

To 2.3 mL (ca 61 mmol) of formic acid cooled in an ice bath was added dropwise 2.50 g (12.2 mmol) of amine (*S,S*)-**7a** followed by 2.74 mL (ca 37 mmol) of 37% formalin. The solution was heated under reflux for 2 h. After being cooled in an ice bath, 6 mL of 4 N HCl was added. The mixture was diluted with water (5 mL), its pH was adjusted to 9 by 18 N NaOH solution (ca 6 mL), and extracted with ether. The extract was dried over K_2CO_3 and the solvent was evaporated. The distillation under reduced pressure (bp 92–94°C, 0.25 mmHg) afforded 2.28 g (80%) of (*S,S*)-**4a** as a colorless oil. IR (neat) 1190, 1100, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (t, *J*=7.5 Hz, 2H), 7.2–7.3 (m, 3H), 4.17 (br t, *J*=2.3 Hz, 1H), 3.46 (s, 3H), 2.50 (m, 1H), 2.01 (s, 6H), 1.1–2.0 (m, 7H); MS (EI) *m/z* 233 (M^+, 54), 218 (98), 160 (100); HRMS Calcd for $C_{15}H_{23}NO$: 233.1780. Found: 233.1795; $[\alpha]_D^{21}$ −18.4 (*c* 1.05, $CHCl_3$).

(1S,2S)-2-(2-Methoxyethoxy)-N,N-*dimethyl-1-phenylcyclohexylamine* (S,S)-***4b***

The reaction of 2.00 g (8.02 mmol) of amine (*S,S*)-**7b** with 1.5 mL (ca 40 mmol) of formic acid and 1.8 mL (ca 24 mmol) of 37% formalin was carried out as described above to give 1.25 g (56%) of (*S,S*)-**4b** as a colorless oil. Bp 106°C, 0.2 mmHg; IR (neat) 1240, 1100, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (dd, *J*=7.3, 7.6 Hz, 2H), 7.2–7.3 (m, 3H), 4.34 (br t, *J*=2.3 Hz, 1H), 3.6–3.8 (m, 4H), 3.41 (s, 3H), 2.43 (m, 1H), 2.04 (s, 6H), 1.2–2.0 (m, 7H); MS (EI) *m/z* 277 (M^+, 34), 218 (100); HRMS Calcd for $C_{17}H_{27}NO_2$: 277.2042. Found: 277.2002; $[\alpha]_D^{23}$ +38.1 (*c* 1.05, $CHCl_3$).

(1S,2S)-2-Methoxy-1-phenylcyclohexyl formamide (S,S)-***8a***

A mixture of 3.00 g (29.4 mmol) of acetic anhydride and 1.28 mL (ca 34 mmol) of formic acid was heated at 50–60°C for 2 h. After being cooled to room temperature, the mixture was diluted with 2.5 mL of THF. A solution of 2.32 g (11.3 mmol) of amine (*S,S*)-**7a** in 5 mL of THF was added and the mixture was stirred at room temperature for 2 h. The mixture was diluted with water and extracted with ether. The extract was dried ($MgSO_4$) and the solvent was evaporated. The product was isolated by chromatography on silica gel (hexane:ethyl acetate=7:3) to give 2.29 g (87%) of (*S,S*)-**8a** as a colorless solid. Mp 74°C; IR (KBr) 3300, 1680, 1530, 1100, 1090, 760, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43 (d, *J*=2.2 Hz, 0.4H), 8.13 (d, *J*=12.6 Hz, 0.6H), 7.2–7.4 (m, 5H), 6.26 (br d, *J*=12.6 Hz, 0.6H), 6.04 (br s, 0.4H), 3.56 (dd, *J*=3.8, 10.0 Hz, 0.6H), 3.38 (dd, *J*=4.6, 10.5 Hz, 0.4H), 3.12 (s, 1.8H), 3.01 (s, 1.2H), 1.4–2.2 (m, 8H); MS (EI) *m/z* 233 (M^+, 33), 84 (100); $[\alpha]_D^{21}$ +72.8 (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.66; H, 8.02; N, 5.89.

(1S,2S)-2-(2-Methoxyethoxy)-1-phenylcyclohexyl formamide (S,S)-***8b***

The reaction of 1.00 g (4.01 mmol) of amine (*S,S*)-**7b** with 1.06 g (10.4 mmol) of acetic anhydride and 0.45 mL (ca 12 mmol) of formic acid was carried out as described above. The product was isolated by chromatography on silica gel (hexane:ethyl acetate=1:1) to give 931 mg (84%) of (*S,S*)-**8b** as a colorless solid. Mp 90°C; IR (KBr) 3260, 1670, 1530, 1140, 1110, 1100, 1030, 750, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41 (d, *J*=2.0 Hz, 0.5H), 8.13 (d, *J*=12.6 Hz, 0.5H), 7.2–7.5 (m, 5H), 6.38 (d, *J*=12.6 Hz, 0.5H), 6.17 (br s, 0.5H), 3.68 (dd, *J*=3.8, 10.0 Hz, 0.5H), 3.0–3.5 (m, 7.5H, containing s at 3.21), 1.4–2.2 (m, 8H); MS (EI) *m/z* 277 (M^+, 51), 128 (98), 59 (100); $[\alpha]_D^{21}$ +74.7 (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.26; H, 8.36; N, 5.10.

*(1S,2S)-2-Methoxy-*N*-methyl-1-phenylcyclohexylamine (*S,S*)-**6a***

To a suspension of 700 mg (18.4 mmol) of $LiAlH_4$ in 9 mL of THF was added a solution of 2.15 g (9.22 mmol) of amide (*S,S*)-**8a** in 9 mL of THF and the mixture was heated under reflux for 2 h. The mixture was cooled in an ice bath, saturated NH_4Cl solution was added, and was filtered through a pad of Celite. The filtrate was evaporated to dryness to leave 1.95 g (96%) of (*S,S*)-**6a** as a colorless solid. Mp 65–66°C; IR (KBr) 3400, 1190, 1100, 970, 770, 760, 710, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7.5 (m, 5H), 3.35 (dd, *J*=3.8, 8.2 Hz, 1H), 3.11 (s, 3H), 2.08 (s, 3H), 1.2–2.2 (m, 9H); MS (EI) *m/z* 219 (M^+, 73), 204 (86), 146 (100); $[\alpha]_D^{23}$ +46.7 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.83; H, 9.69; N, 6.41.

*(1S,2S)-2-(2-Methoxyethoxy)-*N*-methyl-1-phenylcyclohexylamine (*S,S*)-**6b***

The reduction of 3.36 g (12.1 mmol) of amide (*S,S*)-**8b** with 919 mg (24.2 mmol) of $LiAlH_4$ was carried out as described above. The product was isolated by distillation under reduced pressure (bp 102–104°C, 0.2 mmHg) to give 2.63 g (83%) of (*S,S*)-**6b** as a colorless oil. IR (neat) 3350, 1200, 1130, 1100, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44 (dd, *J*=1.3, 8.6 Hz, 2H), 7.33 (dd, *J*=7.3, 8.6 Hz, 2H), 7.21 (t, *J*=7.3 Hz, 1H), 3.3–3.5 (m, 4H), 3.17 (s, 3H), 3.1–3.2 (m, 1H), 2.08 (s, 3H), 1.2–2.1 (m, 9H); MS (EI) *m/z* 263 (M^+, 30), 204 (100); HRMS Calcd for $C_{16}H_{25}NO_2$: 263.1885. Found: 263.1866; $[\alpha]_D^{23}$ +52.4 (*c* 0.99, $CHCl_3$).

Asymmetric addition of butyllithium to benzaldehyde ***9***

To a solution of 33 mg (0.15 mmol) of (*R,R*)-**3b** in 0.45 mL of THF cooled in an ice bath was added 90 μL (0.15 mmol) of butyllithium solution (1.66 M) in hexane. The mixture was stirred at 0°C for 30 min, then a solution of 10.6 mg (0.10 mmol) of benzaldehyde **9** in 0.2 mL of THF was added. The mixture was stirred at 0°C for 1 h, before 0.4 mL of 3 N HCl was added. The mixture was extracted with ether and the extract was dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by preparative TLC separation gave 8 mg (49%) of (*S*)-1-phenyl-1-pentanol (*S*)-**10**, 19 mg (58% recovery) of (*R,R*)-**3b**, and 6 mg (12%) of alcohol **11**. The enantiomeric excess of **10** was determined to be 52% by HPLC equipped with a Waters OptiPak XC column (eluent; hexane:*i*-PrOH=99.5:0.5), and its absolute configuration was determined by the comparison of the specific rotation ($[\alpha]_D^{22}$ +24.7 (*c* 0.35, benzene), 69% e.e.) with the reported value.[7c–e] The reaction in ether or toluene gave (*S*)-**10** and **11** in the following yields: in ether; (*S*)-**10** (55%, 14% e.e.), **11** (10%): in toluene; (*S*)-**10** (73%, ~0% e.e.), **11** (not detected). **11** mp 85–86°C; IR (KBr) 3855, 1112, 1092, 1062, 1015, 963, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–7.4 (m, 9H), 7.03 (br d, 1H), 3.53 (dd, *J*=3.6, 10.3 Hz, 1H), 3.16 (s, 3H), 3.13 (s, 3H), 2.3–2.4 (m, 1H), 2.18 (br d, 1H), 1.3–1.9 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 145.2 (s), 144.2 (s), 140.6 (s), 130.8 (d), 128.2 (d), 127.7 (d), 127.5 (d), 127.4 (d), 127.3 (d), 126.6 (d), 84.7 (d), 82.4 (s), 71.5 (d), 56.3 (q), 52.1 (q), 35.8 (t), 25.4 (t), 24.1 (t), 21.6 (t); MS (CI) *m/z* 327 (M^++1, 8), 309 (71), 277 (100); HRMS Calcd for $C_{20}H_{22}O_2$ (M^+-CH_3OH): 294.1620. Found: 294.1588; $[\alpha]_D^{28}$ −8.07(*c* 0.58, $CHCl_3$).

Typical procedure for asymmetric 1,2-addition of an alkyllithium to N*-benzylidene-4-methoxyaniline* ***12***

To a solution of 21 mg (0.10 mmol) of imine **12** and 80 mg (0.26 mmol) of ligand (*R,R*)-**3b** in 2 mL of toluene, which was cooled in a dry ice–ethanol bath (−70°C), was added 143 μL (0.20 mmol) of methyllithium (1.4 M solution in ether) over a 5 min period. The mixture was stirred at −70°C for 1 h, before 1.5 mL of 3 N HCl was added. The mixture was washed with ether and the aqueous layer was made alkaline with a saturated $NaHCO_3$ solution (pH=8). The solution was extracted with ether and the extract was dried over K_2CO_3. Removal of the solvent under reduced pressure gave 18 mg (66% crude yield) of (*R*)-4-methoxy-*N*-(2-phenylethyl)aniline **13** as a red oil. The enantiomeric excess was determined by HPLC equipped with a Waters OptiPak XC column (eluent; hexane:*i*-PrOH=99:1). The

absolute configuration was determined by the comparison of the specific rotation ($[\alpha]_{365}^{24}$ +9.42 (*c* 1.21, EtOH), 22% e.e.) of a sample obtained from a large-scale run with the reported value.[8d,e]

The reaction with butyllithium was carried out in a similar manner using 1.66 M butyllithium solution in hexane. The enantiomeric excess was determined by HPLC under the same conditions as above and the absolute configuration was determined by the comparison of the specific rotation ($[\alpha]_{365}^{25}$ −20.0 (*c* 1.21, EtOH), 13% e.e.) of a sample obtained from a large-scale run with the reported value.[8d]

Typical procedure for asymmetric deprotonation of 4-t-butylcyclohexanone ***14***

To a solution of 340 mg (1.55 mmol) of amine (*S,S*)-**6a** in 25 mL of THF was added a solution of butyllithium in hexane (1.66 M, 93 μL, 1.5 mmol) at −70°C and the mixture was stirred for 30 min. After 555 mg (3.1 mmol) of HMPA was added, a solution of a mixture of 154 mg (1.0 mmol) 4-*t*-butylcyclohexanone **14** and 543 mg (5.0 mmol) of chlorotrimethylsilane in 2 mL of THF was added over a 5 min period. The mixture was stirred at −70°C for 1 h, 2 mL of triethylamine followed by 5 mL of saturated $NaHCO_3$ solution was added, and then warmed up to room temperature. The mixture was diluted with water and extracted with hexane. The extract was washed successively with water, 0.1 N aqueous solution of citric acid, water, saturated $NaHCO_3$ solution, and brine, and then dried (Na_2SO_4). After removal of the solvent, the products were separated by preparative TLC on silica gel (elution with hexane:ether=3:1) to give 158 mg (70%) of silylenol ether **15** and 211 mg (62% recovery) of (*S,S*)-**6a**.

A solution of the above product (158 mg, 0.70 mmol) in 0.7 mL of acetonitrile was added to a solution of 157 mg (0.70 mmol) of palladium (II) acetate in 6.7 mL of acetonitrile. The mixture was stirred at room temperature for 12 h and filtered through a column of silica gel (elution with ether). The solvent was evaporated and the products were purified by preparative TLC on silica gel (elution with hexane:ether=3:1) to afford 77 mg (73%) of enone **16**. The enantiomeric excess was determined by HPLC equipped with a Daisel CHIRALPAK AD column (eluent; hexane:*i*-PrOH=97:3). The absolute configuration was determined by the comparison of the specific rotation ($[\alpha]_D^{22}$ +30.1 (*c* 1.43, benzene), 54% e.e.) with the reported value.[13]

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