Design, Synthesis, and Application of Chiral Nonracemic Lithium Amide Bases in Enantioselective Deprotonation of Epoxides†

Debnath Bhuniya, Arpita DattaGupta, and Vinod K. Singh*

Department of Chemistry, Indian Institute of Technology, Kanpur, India 208 016

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The reaction of epoxides with chiral nonracemic lithium amide bases, designed and prepared from (*R*)-phenylglycine, has been studied in detail. A maximum of 80% ee was obtained for conversion of cyclohexene oxide to (*S*)-2-cyclohexen-1-ol. Enantioselective deprotonation of a variety of other epoxides was studied. A cyclopentanoid core unit for prostaglandin synthesis was synthesized in 97% ee.

Introduction

An epoxide usually undergoes three kinds of transformations, viz. nucleophilic ring opening, isomerization under the influence of acidic reagents, and isomerization by non-nucleophilic strong bases such as lithium amides derived from organic amines. Since in the last category a proton is abstracted by a base, the process is also referred to as a deprotonation reaction. The asymmetric version of this reaction can be called an enantioselective deprotonation reaction.

Enantioselective deprotonation of symmetrical epoxides to optically active allylic alcohols using nonenzymatic methods, where enantiotopic proton selection takes place by chiral nonracemic lithium amide (CNLA) bases, is a very challenging area in asymmetric synthesis. Such a kind of conversion of cyclohexene oxide to (*S*)-2-cyclohexen-1-ol **1** was first reported by Whitesell and Felman in a maximum optical induction of 31% ee.[1,2] Later, Asami[3] and recently, we[4] extended the work further and reported a maximum of 82% ee for the same transformation using (*S*)-proline-based bases (Scheme 1).

High enantioselectivity in the above reaction has been ascribed to a chelated structure which indicates that in order to prepare (*R*)-cyclohexenol, one requires (*R*)-ligands.[4] Since (*R*)-proline is very expensive, it is not economically viable to use it as a precursor in the synthesis of ligands for deprotonation reactions. Efforts were made to prepare (*R*)-cyclohexenol using (*S*)-proline-based ligands but the enantioselectivity was moderate.[5] Recently, we discovered[6] that the chiral base (*S*)-**2** gave 77% ee in the conversion of cyclohexene oxide to (*R*)-2-cyclohexen-1-ol (*R*)-**1**. In this report, we deliniate full detail of our work. We also report synthesis of new chiral bases and their application in the synthesis of an enantiopure core unit for prostaglandins.

Scheme 1

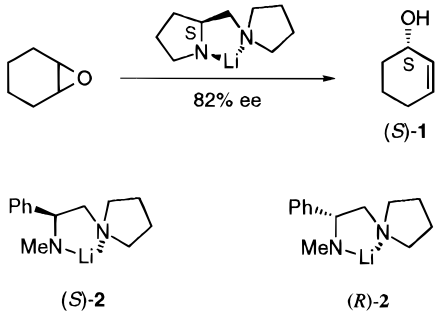


Figure 1.

Results and Discussions

It is well known that the deprotonation of cyclohexene oxide is highly selective for the syn proton that occupies the pseudoaxial orientation.[7,8] The cyclohexene oxide exists in two equilibrating conformations which must be differentiated by a CNLA base. The enantiotopic differentiation of these conformations with base of the type (*R*)-**2** can be rationalized by invoking cyclic six-membered transition state models $\mathbf{3T_f}$ (favored) and $\mathbf{3T_u}$ (unfavored). It is assumed that the orientation of R_1 and R_2 groups in these structures is *anti* to each other. In the case of the base (*R*)-**2** (R_1 = Ph, R_2 = Me), the transition state model $\mathbf{3T_u}$ is unfavorable due to two very strong nonbonding interactions of the epoxide's out-of-plane CH_2's with the phenyl group and pyrrolidine's CH_2. Although $\mathbf{3T_f}$ is also associated with one nonbonding interaction (Me with epoxide's CH_2), it is favored over $\mathbf{3T_u}$ because interaction is not severe.

In order to evaluate this model, and, with the aim of improving the enantioselectivity in the reaction, a variety of ligands were synthesized. Since a close scrutiny about the transition state using a molecular model indicated that a methyl group (R_2 = Me) on the nitrogen atom should be more effective, *N*-methyl ligands **6** were selected first for enantiotopic differentiation of protons in cyclohexene oxide. These ligands were synthesized from (*R*)-isomers of *N*-CBZ-phenylglycine, *N*-CBZ-valine, and *N*-CBZ-*tert*-leucine (Scheme 2).

The coupling reaction of *N*-CBZ-acids **4** with pyrrolidine was carried out with dicyclohexylcarbodiimide (DCC)

† The work was presented in the C.I.C. meeting, May 28−June 1, 1995, held at Guelf, Ontario, Canada, and NOST Symposium, December 2−4, 1995, held at Tirupati, India.

⊗ Abstract published in *Advance ACS Abstracts,* August 1, 1996.

(1) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755.

(2) For recent general reviews in this area, see: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron*: *Asymmetry* **1991**, *2*, 1 and references cited therein. (b) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (c). Simpkins, N. S. *Chem. Ind.* **1988**, 387.

(3) (a). Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 721. (b) Asami, M. *Chem. Lett.* **1984**, 829. (c) Asami, M.; Kirihara, H. *Chem. Lett.* **1987**, 389.

(4) Bhuniya, D.; Singh, V. K. *Synth. Commun.* **1994**, *24*, 375.

(5) Asami, M.; Kirihara, H. *Chem. Lett.* **1987**, 389.

(6) (a) Bhuniya, D.; DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1995**, *36*, 2847. (b) Bhuniya, D.; Singh, V. K. *Synth. Commun.* **1994**, *24*, 1475.

(7) (a) Rickborn, B.; Thummel, R. P. *J. Org. Chem.* **1969**, *34*, 3583. (b) Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064.

(8) For recent reviews, see: (a) Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345. (b) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semelhack, M. F., Eds.; Pergamon Press: Oxford; 1991; Vol. 1, p 733.

S0022-3263(96)00244-7 CCC: $12.00

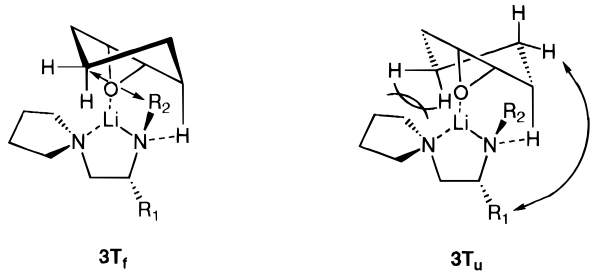
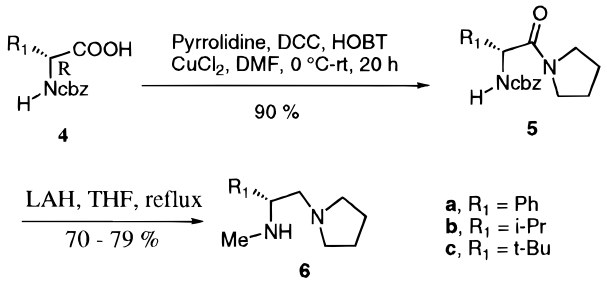


Figure 2.

Scheme 2



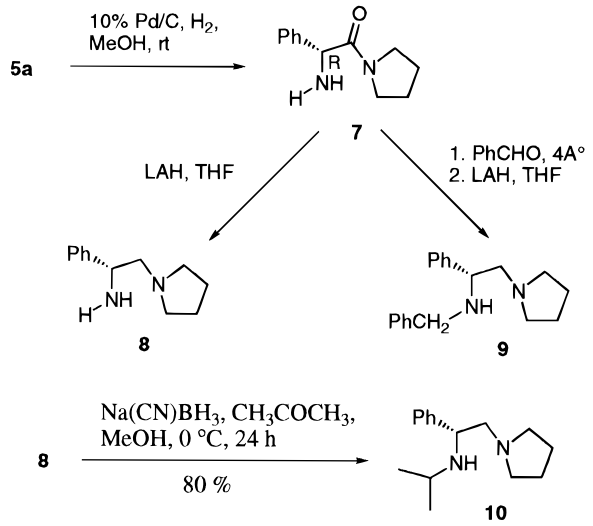
in the presence of 1-hydroxybenzotriazole (HOBT) and cupric chloride.[9] If both the latter reagents were not used, significant amount of racemization took place (*vide infra*). The (*R*)-*N*-CBZ-amides **5**, obtained in this way, were reduced to (*R*)-diamines **6** by using LAH. For initial studies, cyclohexene oxide was chosen as a model substrate, and its deprotonation with the bases derived from the diamines **6** was studied. Although the chemical yield of (*S*)-2-cyclohexen-1-ol obtained from the deprotonation reaction is similar (55−60%), the enantioselectivity is different (Table 1). Whereas phenylglycine-based ligand **6a** gave 77% ee, the valine and *tert*-leucine-based ligands **6b** and **6c** gave 60% ee and 58% ee, respectively.

From the above reactions it became clear that phenyl group as R_1 in the ligand **6** is better than isopropyl and *tert*-butyl groups. As per the proposed transition state model (Figure 2), the larger the size of the R_1 group, the higher should be the enantioselectivity. Since the phenyl group (*A* value 2.9) is bulkier than isopropyl (*A* value 2.1), the ligand **6a** gave better enantioselectivity than the **6b**. However, we are unable to give concrete explanation for the poor enantioselectivity with the *tert*-leucine-based ligand **6c** where R_1 is a *tert*-butyl group (*A* value >4). Perhaps, the basicity of the vicinal NHMe center in (*R*)-**6** is playing the role. With R_1 = Ph, the basicity of the vicinal NHMe center relatively decreases, so that the **3T** transition states may be late relative to those with alkyl R_1 groups, and therefore the repulsive effects unfavoring **3T$_u$** vs **3T$_f$** are relatively more pronounced.[10]

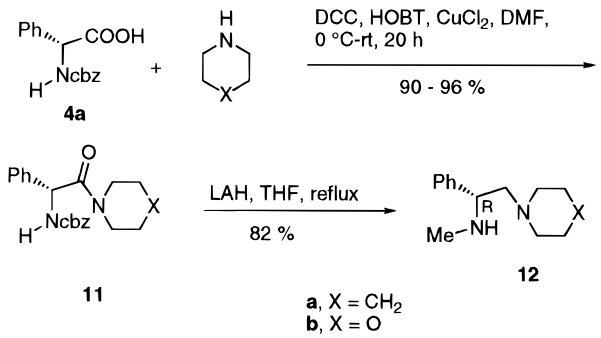
In order to study the effect of substituents (R_2) on the "N" in the ligand **6a**, three more diamines, which differ in relative size of R_2, were synthesized from a common phenylglycine-based intermediate **7** as indicated in Scheme 3.

The intermediate **7** was obtained by hydrogenolysis of the *N*-CBZ-amide **5a**. LAH reduction of the amide **7** gave a diamine **8** in 77% yield. In order to prepare *N*-benzylamine ligand **9**, the **7** was treated with benzaldehyde, and thus, the Schiff base obtained was reduced with LAH. *N*-Isopropyl ligand **10** was synthesized by reductive amination[11] of acetone with the diamine **8** in the presence of sodium cyanoborohydride. All three ligands were tested on cyclohexene oxide and results are summarized in Table 1. As expected from the model, the ligand **8** could not differentiate between the two rapidly equilibrating conformations of cyclohexene oxide and hence did not show any asymmetric induction in the reaction. The transition state model also indicated that an N-substituent larger than a methyl group might not be suitable, as its nonbonding interaction with the out-of-plane CH_2 of the epoxide would come into effect (cf. **3T$_f$** in Figure 2). In fact, this was indeed the case (Table 1).

Scheme 3



Scheme 4



So far we had kept the pyrrolidine unit constant in the above ligands. In order to see the effect of other cyclic amines, we synthesized two more diamine ligands in which the pyrrolidine part is replaced by piperidine and morpholine. These ligands were synthesized as shown in Scheme 4.

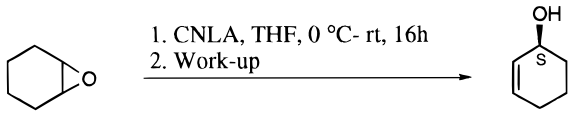
The choice of these amines was based on our reasoning that because of a little larger bond angle in the six-membered ring, the nonbonded interaction of its methylene with epoxide's CH_2 will be greater, and that will favor the required pathway. However, it was difficult to predict about the chelation effect on enantioselectivity because of the difference in pK_a values of the amines. The results of deprotonation of cyclohexene oxide from Table 1 are very close to our prediction. The ligand **12a** gave

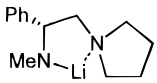
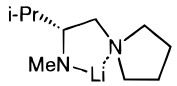
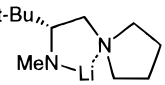
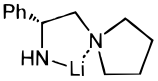
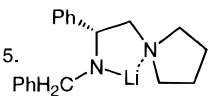
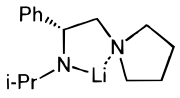
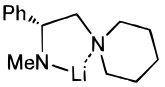
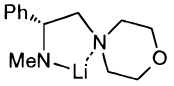
(9) Miyazawa, T.; Otomatsu, T.; Fukui, Y.; Yamada, T.; Kuwata, S. *Chem. Commun.* **1988**, 419.

(10) We thank one of the referees for this suggestion to explain the lower enantioselectivity with the ligand (*R*)-**6c**.

(11) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

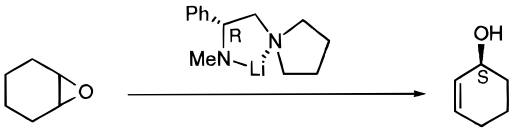
Table 1. Enantioselective Deprotonation of Cyclohexene Oxide



Entry	(*R*)- CNLA	Yield (%)	Config. (% ee)[a,b]
1.		60	S (77)
2.		58	S (60)
3.		55	S (58)
4.		60	RS (00)
5.		52	S (31)
6.		50	S (13)
7.		60	S (80)
8.		60	S (77)

[a]% ee was determined from the 400 MHz ^{1}H NMR spectrum of the corresponding Mosher ester. [b]The optical purity of Mosher acid used was 98% ee, and the results reported here are corrected to this value.

Table 2. Effect of Solvent and Additives on Enantioselective Deprotonation of Cyclohexene Oxide



Entry	Solvent	Additives	Yield (%)	%ee[a]
1.	THF	-	60	77
2.	Ether	-	55	65
3.	Benzene	-	50	63
4.	THF	LiCl	58	65
5.	THF	t-BuOLi	65	73

[a]Determined from the 400 MHz ^{1}H NMR spectrum of the MTPA-ester.

80% ee (entry 7) whereas the ligand **12b** gave 77% ee (entry 8). If the reaction was done at a temperature lower than 0 °C, isolated yield of the required product drops down and there was no effect on the enantioselectivity.

The enantioselective deprotonation of cyclohexene oxide with the ligand **6a** was studied in different solvents such as THF, ether, and benzene. THF turned out to be the suitable solvent for the reaction. Ether and benzene were not promising (Table 2). The effect of LiCl and t-BuOLi in the deprotonation reaction was also studied (Table 2). These additives lowered the enantioselectivity to 65% ee (with LiCl) and to 73% (with t-BuOLi). It is surprising that the effect of LiCl on deprotonation of epoxide was not in agreement with that of ketones.[12]

From the above results it is clear that the three ligands **6a**, **12a**, and **12b** are quite effective for the enantioselective deprotonation of cyclohexene oxide. Though the synthesis of the ligands was done in a mild way, it was imperative to know the effect of coupling reagents on the optical purity of the coupled products. Koga, during his work on deprotonation of ketones, had prepared the amide **5a**[13] having a specific rotation, $[\alpha]_D$ −123°, by using diethyl pyrocarbonate (DEPC) as a coupling reagent.[14] He had reported a maximum of 97% ee by using a ligand prepared through DEPC-induced coupling of **4a** and secondary amines.[15] It means that the coupled product **5a** with $[\alpha]_D$ −123° has at least 97% ee. In order to study the effect of coupling reagents on racemization, reaction of *N*-CBZ-phenylglycine (**4a**) with pyrrolidine was studied in the presence of several coupling reagents. The comparison of the specific rotations of the coupled product **5a** from our reactions with Koga's value indicated that an appreciable amount of racemization took place during the DCC and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[16] induced coupling reactions (Table 3). However, it was observed that when DCC was used in conjunction with 1-hydroxybenzotriazole (HOBT) and cupric chloride in DMF, the racemization was minimized to a great extent.[9]

In order to extend the scope of the CNLA base chemistry, deprotonation reaction of other epoxides was studied. The chiral allylic alcohols **14** are versatile intermediates[17] for cyclopentanoid natural products, especially in Noyori's three-component coupling process toward prostaglandin **13** (Scheme 5).[18] One of the efficient ways to **14** would be *via* enantioselective deprotonation of *meso*-epoxides of the type **15**. This kind of transformation has been studied in the past by others using proline-based ligands[19] and dilithiated chiral amino alcohols,[20] but the enantioselectivity remained only up to 90%.[21] We obtained a maximum of 88% ee in the deprotonation of *cis*-epoxides **15** with the ligand **6a**.[22] Solvent and R group in **15** had significant effect on the

(12) For the effect of LiCl on enantioselective deprotonation of cyclic ketones, see: (a) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533. (b) Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *36*, 5465.

(13) Koga, K. Asymmetric Synthesis using Chiral Bases. In *Organic Synthesis: Modern Trends*; Chizhov, O., Ed.; Blackwell Scientific Publication: London, 1987; p 285.

(14) We thank Professor Koga for providing specific rotation data of **5a**.

(15) Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543.

(16) Diago-Meseguer, J.; Palamo-Coll, A. L. *Synthesis* **1980**, 547.

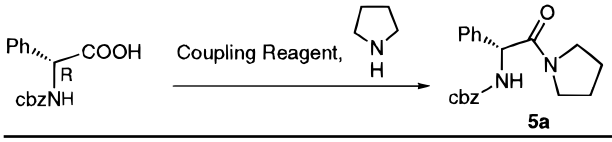
(17) For a review on 4-oxo-2-cyclopentenyl acetate, see: Harre, M.; Raddatz, P.; Walenta, R.; Winterfedt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480.

(18) Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809 and references cited therein.

(19) (a) Hendrie, S. K.; Leonard, J. *Tetrahedron* **1987**, *43*, 3289. (b) Asami, M. *Tetrahedron Lett.* **1985**, *26*, 5803. (c) Asami, M.; Takahashi, J.; Inoue, S.; *Tetrahedron: Asymmetry* **1994**, *5*, 1649. (d) Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1402.

(20) Milne, D.; Murphy, P. J. *Chem. Commun.* **1995**, 884.

Table 3. Effect of Coupling Reagents on the Formation of 5a



5a

Entry	Reagents and Conditions	Yield (%)	$[\alpha]_D$ (*c* 1.0, $CHCl_3$)	%ee[a]
1.	$(EtOCO)_2O$, Et_3N, DMF, 0 °C - rt, 3 h	95	-123°	97[b]
2.	DCC, CH_2Cl_2, 0 °C - rt, 24 h	63	-100°	82
3.	BOP-Cl, Et_3N 0 °C, 3 h	95	-85°	69
4.	DCC, HOBT, $CuCl_2$, DMF, 0 °C - rt, 20 h	90	-119°	96

[a]%ee for **5a** was determined based on $[\alpha]_D$ -123° (*c* 1, $CHCl_3$), a value provided by Professor Koga in a personal communication. [b]See reference 15.

Scheme 5

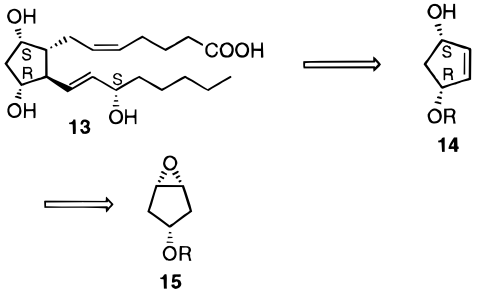
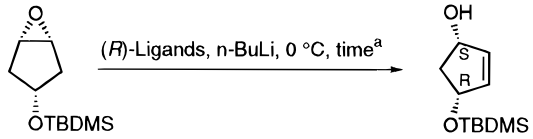


Table 4. Synthesis of Enantiopure Core Unit for Prostaglandins



15a 14a

Entry	Ligand	Solvent	Yield (%)	%ee[b]
1.	**6a**	THF	65	74
2.	**6a**	Benzene	40	88
3.	**6a**	Ether	65	82
4.	**12a**	Benzene	66	97
5.	**12b**	Benzene	60	94

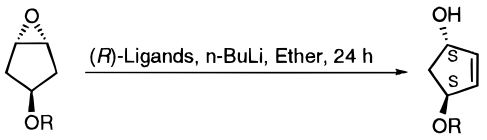
[a]With the ligands **6a** & **6b**, the reaction was run for 10 h, but for the ligands **12a** & **12b**, the time was 30 h. [b]%ee was determined from the 400 MHz ^{1}H NMR spectrum of the Mosher ester.

enantioselectivity of the reaction. The enantioselectivity is maximum when R is *tert*-butyldimethylsilyl (TBDMS) and the reaction is done in a noncoordinating solvent such as benzene. Coordinating solvent such as THF reduced the enantioselectivity (Table 4). If the R group

(21) Recently, Asami reconfirmed his previous results of 90% ee in the deprotonation of the epoxide **15a** with a proline-based base. For reference, see: Asami, M.; Inoue, S. *Tetrahedron* **1995**, *51*, 11725.

(22) The work has been communicated in preliminary form, see ref 6a.

Table 5. Enantioselective Deprotonation of 4-Substituted *trans*-Cyclopentene Oxide



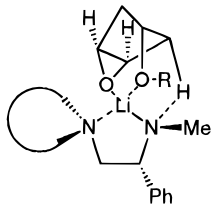
17 18

Entry	Ligand	R	Yield (%)	%ee[a]
1.	**6a**	TBDMS	38	55
4.	**12a**	TBDMS	35	68
3.	**6a**	THP	50	59
4.	**12a**	THP	52	21

[a]%ee was determined from the 400 MHz ^{1}H NMR spectrum of the Mosher ester.

is tetrahydropyranyl (THP) ether or benzyl group, enantioselectivity drops down drastically. In both these cases, the highest enantioselectivity (43−46% ee) was obtained when the reaction was done in THF and the lowest (25−29% ee) when benzene was used as a solvent in the reaction.

The reaction of *cis*-epoxide **15a** with the bases prepared from ligands **12** gave very high enantioselectivity in the deprotonation reaction. The ligand **12a** gave 97% ee whereas the ligand **12b** gave 94% ee in the reaction (Table 4). The enantioselectivity obtained from this reaction is the highest, to date, for this kind of transformation. Such a high level of optical induction in the above reaction indicates that the transition state of the reaction is highly ordered when R is a TBDMS group. Thus, a highly chelated transition state model **16** is proposed for the reaction.



16

Although, the effect of silicon protecting groups upon the coordinating ability of an oxygen has been much studied,[23,24] we propose that the TBDMS ether coordinates Li better than THP and benzyl ethers during the transition state of the reaction. The solvent effect is in accordance with the transition state model **16**. Partial support for this model also comes from the poor enantioselectivity during the deprotonation of *trans*-epoxides **17** (Table 5). This could be due to the absence of strong chelation by the ethereal groups because of their *trans* orientation.

The deprotonation reaction was also extended to other cyclic and acyclic epoxides. *cis*-Cyclooctene oxide on

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(24) (a) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778. (b) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. (c) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697. (d) For detailed calculations which suggest little difference in proton affinity between dialkyl ethers and sterically analogous alkyl silyl ethers, see: Blake, J. F.; Jorgensen, W. L. *J. Org. Chem.* **1991**, *56*, 6052.

reaction with the base prepared from the (*R*)-**6a** gave (*S*)-allylic alcohol in 51% ee. However, cyclopentene oxide and acyclic substrates failed to give any required product.

In conclusion we have designed new chiral nonracemic lithium amide bases which have been synthesized from the easily available precursor, phenylglycine. Since both enantiomers of the precursor are available at low cost, the versatility of the ligands will be greater. We have studied the deprotonation reaction of several epoxides. We have achieved a maximum of 80% ee in the conversion of cyclohexene oxide to 2-cyclohexen-1-ol. We have also synthesized an enantiopure core unit in 97% ee which is very useful for prostaglandin synthesis. The latter enantioselectivity is the highest, to date, for this kind of transformation.

Experimental Section

General. ^{1}H NMR spectra were recorded on 60, 300, and 400 MHz spectrometers. Chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in hertz. Routine monitoring of reactions was performed using silica gel-G obtained from Acme. All the column chromatographic separations were done by using silica gel (Acme's, 60−120 mesh). Petroleum ether used was of boiling range 60−80 °C. Reactions which needed anhydrous conditions were run under an atmosphere of dry nitrogen or argon using flame-dried glassware. The organic extracts were dried over *anhydrous* sodium sulfate. Evaporation of solvents was performed at reduced pressure. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen. Benzene and dichloromethane were distilled from CaH_2. N,N-Dimethylformamide (DMF) was distilled from CaH_2 at reduced pressure. Amines were distilled from CaH_2 at atmospheric pressure.

General Procedure for Coupling of Acid 4 with Amines. To a stirred solution of (*R*)-*N*-CBZ-acid **4** (10 mmol), *anhydrous* $CuCl_2$ (12 mmol), and 1-hydroxybenzotriazole (12 mmol) in dry DMF (50 mL) was added dropwise a solution of DCC (12 mmol) in 10 mL of DMF at 0 °C, and the mixture was stirred for 20 min. Amines (20 mmol) was added and the stirring continued for 20 h (0 °C to rt). The reaction mixture was diluted with EtOAc (100 mL) and washed with cold 0.1 N HCl, water, aqueous $NaHCO_3$. The organic layer was dried, and the solvent was evaporated in *vacuo*. Purification by column chromatography over silica gel gave pure coupled product **5** or **11**.

(*R*)-1-[*N*-(Benzyloxycarbonyl)phenylglycyl]-pyrrolidine (5a). The amide **5a**[13] is a viscous liquid; 90% yield; R_f 0.50 (1:2, EtOAc in petroleum ether); $[\alpha]^{25}_D$ −119.0° (*c* 1.0, $CHCl_3$) [lit.[14] maximum $[\alpha]^{25}_D$ −123.0° (*c* 1.06, $CHCl_3$)]; IR (film) 3410, 3300, 3040, 2980, 1700, 1630 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 1.5−1.95 (m, 4H), 2.8−3.7 (m, 4H), 4.95 (s, 2H), 5.23 (d, J = 9 Hz, 1H), 6.43 (d, J = 9 Hz, N*H*, 1H), 7.05−7.5 (aromatics, 10H). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 71.00; H, 6.51; N, 8.28. Found: C, 70.72; H, 6.64; N, 8.32.

(*R*)-1-[*N*-(Benzyloxycarbonyl)valyl]pyrrolidine (5b). The amide **5b**[6b] is a viscous liquid; 87% yield; R_f 0.65 (1:1, EtOAc in petroleum ether); $[\alpha]^{25}_D$ −85.0° (*c* 1.6, EtOH); IR (film) 3420, 3280, 3040, 2930, 1700, 1620 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 0.93 (d, J = 7 Hz, 6H), 1.5−2.2 (bm, 5H), 3.1−3.8 (m, 4H), 4.1 (dd, J = 9, 3 Hz, 1H), 4.95 (s, 2H), 6.16 (d, J = 9 Hz, N*H*, 1H), 7.2 (aromatics, 5H).

(*R*)-1-[*N*-(Benzyloxycarbonyl)-*tert*-leucyl]pyrrolidine (5c). The amide **5c** is a solid; 87% yield; mp 50 °C; $[\alpha]^{25}_D$ −87.0° (*c* 5, $CHCl_3$); IR (KBr) 3420, 3280, 1760, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.0 (s, 9H), 1.83 (m, 4H), 3.3−3.9 (m, 4H), 4.36 (d, J = 10 Hz, 1H), 5.1 (s, 2H), 6.03 (d, J = 10 Hz, N*H*, 1H), 7.36 (aromatics, 5H). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.92; H, 8.16; N, 8.79. Found: C, 67.80; H, 8.19; N, 8.82.

General Procedure for LAH Reduction of *N*-CBZ-Amides. The amide **5** or **11** (2 mmol) was dissolved in 30 mL of THF, treated with LAH (4 mmol), and stirred under reflux for 6 h. Excess of LAH was destroyed by addition of 2−3 drops of EtOAc. Water (100 μL) was added followed by the same amount of 4 N NaOH. After 5 min, 300 μL of water was again added and the mixture stirred for 15 min. A white precipitate was filtered off, the filtrate was dried, and solvent was evaporated. The diamines **6** or **12** were purified by distillation.

(*R*)-*N*-Methyl-1-phenyl-2-pyrrolidinoethanamine (6a): yield 79%; bp 100−120 °C (bath) at 0.2 mmHg; $[\alpha]^{25}_D$ −64.0° (*c* 1.4, EtOH); IR (film) 3380, 3060, 3030, 2960, 2880 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (m, 4H), 2.25 (d, J = 3.4Hz, 1H), 2.30 (s, 3H), 2.38, (s, N*H*, 1H), 2.45 (m, 2H), 2.62 (m, 2H), 2.84 (t, J = 11.2 Hz, 1H), 3.58 (dd, J = 9.6, 3.4 Hz, 1H), 7.18−7.4 (aromatics, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 34.7, 54.14, 63.8, 64.3, 127.0, 127.4, 128.3, 142.8; MS (CI, *m*/*z*): 206 (M^+ + 2), 205 (M^+ + 1), 203, 174 (base peak), 175, 134, 120. Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.47; H, 9.80; N, 13.72. Found: C, 76.38; H, 9.86, N, 13.74.

(*R*)-*N*-Methyl-1-isopropyl-2-pyrrolidinoethanamine (6b): yield 66%; bp 100 °C (bath) at 0.2 mmHg; $[\alpha]^{25}_D$ −51.5° (*c* 3.0, EtOH); IR (film) 3320, 2960, 2940, 2880, 960 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 0.83 (two doublets, J = 7 Hz, 6H), 1.0−2.7 (bm, 13H), 2.30 (s, 3H). Anal. Calcd for $C_{10}H_{22}N_2$: C, 70.59; H, 12.94; N, 16.47. Found: C, 70.46; H, 13.02; N, 16.48.

(*R*)-*N*-Methyl-1-*tert*-butyl-2-pyrrolidinoethanamine (6c): yield 70%; bp 100−120 °C (bath) at 0.2 mmHg; $[\alpha]^{25}_D$ −65.5° (*c* 2.0, EtOH); ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.90 (s, 9H), 1.60−2.80 (m, 12H), 2.50 (s, 3H); MS (CI, *m*/*z*): 184 (M^+), 128, 100 (base peak), 84. Anal. Calcd for $C_{11}H_{24}N_2$: C, 71.73; H, 13.04; N, 15.21. Found: C, 71.70; H, 13.11, N, 15.33.

(*R*)-1-(Phenylglycyl)pyrrolidine (7). A solution of the N-CBZ-amide **5a** (821 mg, 2.4 mmol) in methanol (10 mL) was hydrogenated (H_2 balloon) in the presence of a small amount of 10% Pd/C for 2 h. The solution was filtered, and the methanol was removed *in situ*. The crude material was used without further purification: yield 95%; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.68−2.0 (m, 4H), 2.10 (bs, 2H, NH), 2.90−3.7 (m, 4H), 4.57 (bs, 1H), 7.43 (aromatics, 5H).

(*R*)-1-Phenyl-2-pyrrolidinoethanamine (8). The crude (*R*)-**7** (735 mg, 3.6 mmol) was taken in THF (15 mL) and treated with LAH (140 mg, 3.6 mmol) under reflux for 6 h. Excess of LAH was destroyed by addition of 2−3 drops of EtOAc. Water (100 μL) was added followed by the same amount of 4 N NaOH. After 5 min, 300 μL of water was again added and the mixture stirred for 15 min. A white precipitate was filtered off, the filtrate was dried, and solvent was evaporated. The crude was distilled to afford **8** (527 mg, 77% yield): bp 110−120 °C at 0.2 mmHg; $[\alpha]^{25}_D$ −50.8° (*c* 3.0, EtOH); IR (film) 3300, 3080 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 1.50−2.9 (bm, 12H), 3.96 (dd, J = 10, 4 Hz, 1H), 7.2 (5H, aromatics). Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.78; H, 9.47, N, 14.73. Found: C, 75.69; H, 9.49, N, 14.78.

(*R*)-*N*-Benzyl-1-phenyl-2-pyrrolidinoethanamine (9). A solution of (*R*)-**7** (596 mg, 2.92 mmol) in benzene (3 mL) was treated with freshly distilled benzaldehyde (328 μL, 3.21 mmol) in the presence of 4 Å molecular sieves. The reaction mixture was kept at rt for 7 h, and after that it was decanted. The solvent was removed, and the crude was treated with LAH (245 mg, 6.4 mmol) in THF (10 mL) under reflux for 8 h. After usual workup as described earlier, **9** was obtained as a colorless liquid: yield 635 mg (77%); $[\alpha]^{25}_D$ −70.2° (*c* 1.2, EtOH); IR (film) 3300, 3080 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.8 (m, 4H), 2.1−2.9 (m, 7H), 3.7 (m, 3H), 7.2 (aromatics, 10H). Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.42; H, 8.57, N, 10.0. Found: C, 81.40; H, 8.61, N, 10.10.

(*R*)-*N*-Isopropyl-1-phenyl-2-pyrrolidinoethanamine (10). A solution of **8** (700 mg, 3.68 mmol) in acetone−methanol (1:3, 5 mL) was treated with 5−6 drops of 35% aqueous HCl at 0 °C. To this solution was added sodium cyanoborohydride (280 mg, 4.4 mmol), and the whole mixture was stirred at rt for 24 h. Evaporation of the solvent gave a residue which was mixed with 10 mL of ether. The mixture was extracted with aqueous HCl. The aqueous layer was washed with ether and basified with 4 N aqueous NaOH and extracted with CH_2Cl_2. The organic layer was dried and condensed. The crude material was distilled to give pure **10**[13] (682 mg, 80% yield) as a colourless liquid: bp 180 °C (bath) at 1 mmHg; $[\alpha]^{25}_D$ −66.0° (*c* 1.2, EtOH) [lit.[13] $[\alpha]^{25}_D$ −72.0° (*c* 1.1, EtOH)]; IR (film)

3300, 3080 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 0.97 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 1.6−3.0 (m, 12H), 3.80 (dd, J = 11.0, 4.0 Hz, 1H), 7.3 (aromatics, 5H). Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.58; H, 10.34, N, 12.06. Found: C, 77.39; H, 10.38, N, 12.12.

(*R*)-1-[*N*-(Benzyloxycarbonyl)phenylglycyl]-piperidine (11a). The **11a**[15] was prepared as a viscous liquid following the general procedure: yield 90%; R_f 0.70 (2:5, EtOAc in petroleum ether); $[\alpha]^{25}_D$ −100.0° (*c* 1.5, $CHCl_3$); IR (film) 3410, 3300, 3040, 1715, 1635 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 0.8−1.8 (m, 6H), 3.06−3.9 (m, 4H), 5.03 (s, 2H), 5.50 (d, J = 9 Hz, 1H), 6.40 (d, J = 9 Hz, NH, 1H), 7.15−7.63 (aromatics, 10H).

(*R*)-1-[*N*-(Benzyloxycarbonyl)phenylglycyl]-morpholine (11b). The *N*-CBZ-amide **11b** was obtained as a viscous liquid following the general procedure: yield 96%; R_f 0.53 (2:5, EtOAc in petroleum ether); $[\alpha]^{25}_D$ −104.6° (*c* 1.5, $CHCl_3$); IR (film) 3410, 3300, 1710, 1635 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 2.98−3.8 (m, 8H), 5.06 (s, 2H), 5.56 (d, J = 9 Hz, 1H), 6.46 (d, J = 9 Hz, NH, 1H), 7.16−7.50 (aromatics, 10H). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.79; H, 6.21, N, 7.90. Found: C, 66.90; H, 6.30, N, 8.01.

(*R*)-*N*-Methyl-1-phenyl-2-piperidinoethanamine (12a).[25] This was prepared as per the general procedure mentioned above: yield 83%; $[\alpha]^{25}_D$ −91.6° (*c* 1.8, $CHCl_3$); IR (film) 3330, 3020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (m, 2H), 1.56 (m, 4H), 2.20−2.33 (m, 4H), 2.30 (s, 3H), 2.46 (t, J = 11.0 Hz, 2H), 2.56 (bs, NH, 1H), 3.63 (dd, J = 9.0, 3.0 Hz, 1H), 7.20−7.40 (aromatics, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.4, 26.0, 34.6, 54.7, 62.3, 66.6, 126.9, 127.3, 128.2, 142.6; MS (CI, *m*/*z*): 220 (M^++ 2), 219 (M^++ 1), 217, 188, 134, 120, 98 (base peak). Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.06; H, 10.0, N, 12.80. Found: C, 77.34; H, 10.40, N, 12.72.

(*R*)-*N*-Methyl-1-phenyl-2-morpholinoethanamine (12b). This was prepared as per the general procedure mentioned above: yield 82%; $[\alpha]^{25}_D$ −92.0° (*c* 1.2, $CHCl_3$); IR (film) 3330, 3060, 3030 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 2.1−2.9 (m, 8H), 2.30 (s, 3H), 3.73 (m, 4H), 7.16−7.6 (aromatics, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.5, 53.7, 61.7, 66.2, 67.0, 127.1, 127.3, 128.3, 142.1; MS (CI, *m*/*z*): 222 (M^+ + 2), 221 (M^+ + 1), 219, 190, 134, 120, 100 (base peak). Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.90; H, 9.0, N, 12.70. Found: C, 71.32; H, 9.15, N, 12.9.

General Procedure for Enantioselective Deprotonation of Cyclohexene Oxide. n-BuLi (E. Merck, 1.48 M in hexane, 2.2 mmol) was added to a solution of (*R*)-diamine (2.2 mmol) in THF (10 mL) at 0 °C. After 15 min stirring, the cyclohexene oxide (2.0 mmol) was added and the mixture stirred for 16 h (0 °C to rt). Most of the THF was removed in *vacuo* at 0 °C, and the reaction mixture was taken up in ether (30 mL). It was washed with water and brine and dried. Solvent was removed in *vacuo* at 0 °C, and the crude was chromatographed to provide pure (*S*)-2-cyclohexen-1-ol **1**[6] as a colorless liquid. The spectral data for (*S*)-**1** from entry 1 of Table 1 is given as follows: $[\alpha]^{25}_D$ −117.0° (*c* 1.5, $CHCl_3$) [lit.[1] $[\alpha]^{25}_D$ +152.0° (*c* 5, $CHCl_3$) for *R*-isomer], [lit.[26] $[\alpha]^{25}_D$ +130.6° (*c* 5, $CHCl_3$) for *R*-isomer]; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60 (m, 2H), 1.75 (m, 1H), 1.85 (s, 1H, -OH), 1.90 (m, 1H), 2.0 (m, 2H), 4.2 (bs, 1H), 5.76 (m, 1H), 5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9, 25.0, 32.0, 65.4, 129.9, 130.4.

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Determination of Enantiomeric Purity of (*S*)-2-Cyclohexen-1-ol (Table 1; entry 1). The (*S*)-cyclohexenol **1** (5 mg), prepared by using the diamine ligand **6a**, was treated with 2 equiv of triethylamine and 1.5 equiv of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[27] (MTPA-Cl, 98% ee) in the presence of 1 crystal of DMAP in CH_2Cl_2 in a usual way to provide the (*SR*)-Mosher ester. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.5 (m, 2H), 1.75−2.1 (bm, 4H), 3.5 (bs, 3H), 5.45 (m, 1H), 5.72 (m, 0.88H, *SR*-diastereomer from major *S*-cyclohexenol), 5.81 (m, 0.12 H, *RR*-diastereomer from minor *R*-cyclohexenol), 5.85−6.0 (bm, 1H), 7.25−7.65 (bm, 5H, aromatics). Based on above NMR data, the enantiomeric excess of (*S*)-cyclohexenol for entry 1 of Table 1 is 77%.

General Procedure for Enantioselective Deprotonation of 3,4-Epoxycyclopentanol Derivatives 15 and 17. n-BuLi (E. Merck, 1.48 M in hexane, 2.0 mmol) was added to a solution of (*R*)-diamine (2.0 mmol) in the required solvent (10 mL) at 0 °C. After 15 min stirring, the epoxide **15** or **17** (2.0 mmol) was added and the mixture stirred (0 °C to rt) for the required period of time (see Tables 4 and 5). Most of the solvent was removed in *vacuo* at 0 °C, and the reaction mixture was taken up in ether (30 mL). The organic layer was washed with aqueous tartaric acid, water, and brine and dried. Solvent was removed in *vacuo*, and the crude was chromatographed to provide pure allylic alcohol **14** or **18** as a colorless liquid.

***cis*-(1*S*,4*R*)-4-(*tert*-Butyldimethylsiloxy)-2-cyclopenten-1-ol (14a).** The **14a**[19] was prepared as per the above general procedure. The spectral and physical data for the deprotonation reaction with the ligand **6a** (Table 4; entry 2) is given as follows: yield 40%; R_f 0.45 (1:10, EtOAc in petroleum ether); $[\alpha]^{25}_D$ +18.5° (*c* 0.75, $CHCl_3$); IR (film) 3350 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.50 (dt, J = 10.2, 5.7 Hz, 1H), 2.10 (s, 1H, OH), 2.68 (dt, J = 14.3, 5.7 Hz, 1H), 4.58 (bs, 1H), 4.65 (m, 1H), 5.50 (dd, J = 22.4, 5.6 Hz, 2H). ^1H NMR of its Mosher ester indicated the optical purity to be 88%. Similarly, the ligand **12a** gave the product in 97% ee.

***trans*-(1*S*,4*S*)-4-(*tert*-Butyldimethylsiloxy)-2-cyclopenten-1-ol (18) (Table 5: entry 1). 18** (R = TBDMS)[18] was prepared as per the above general procedure. The spectral and physical data for the deprotonation reaction with the ligand **6a** (Table 5; entry 1) is given as follows: yield 38%; R_f 0.25 (2:5, EtOAc in petroleum ether); $[\alpha]^{25}_D$ −65.0° (*c* 1, $CHCl_3$); IR (film) 3350 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.1 (s, 6H), 0.9 (s, 9H), 1.4−1.7 (bs, 1H, OH), 2.05 (m, 2H), 5.14 (bs, 1H), 5.1 (m, 1H), 5.95 (m, 2H). ^1H NMR of its Mosher ester indicated the optical purity to be 55%. Similarly, the ligand **12a** gave the product in 68% ee.

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