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# Stereoselective Reactions. 30.[1] Enantioselective Alkylation of the Lithium Enolates of Six-membered Cyclic Ketones Using Tetradentate Chiral Amines in the Presence of Lithium Bromide

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***Abstract:*** An efficient enantioselective alkylation of the lithium enolates of cyclohexanone and 1-tetralone with reactive alkyl halides was realized using a stoichiometric amount of a tetradentate chiral amine as a ligand for the lithium in the presence of lithium bromide in toluene.


## INTRODUCTION

Asymmetric synthesis has been the focus of studies in synthetic organic chemistry. Numerous methods have been developed up to the present time,[2] and are classified into two kinds of strategies. One is the so-called diastereoselective asymmetric synthesis, in which the substrate is first connected with the chiral auxiliary by a covalent bond, and then a new stereogenic center is introduced intramolecularly. The chiral product is isolated after cleavage of the covalent bond between the product and the chiral auxiliary. The other is the so-called enantioselective asymmetric synthesis, in which a new stereogenic center is introduced intermolecularly by converting the substrate directly to the chiral product in the presence of a chiral auxiliary, but without forming any covalent bond with the substrate at any stage of the whole process of the reaction. Owing mainly to the accumulation of knowledge on the conformation of organic molecules and ions in solution, diastereoselective asymmetric synthesis has become more reasonably understandable. On the other hand, novel designs and stereochemical explanation of enantioselective asymmetric synthesis still remain difficult, due to the shortage of precise knowledge on the interactions and associations of molecules and/or ions in solution. It should be mentioned that catalytic asymmetric synthesis is possible only by enantioselective method.

Lithium enolates play a central role in synthetic organic chemistry, because they can react with various electrophiles to undergo many synthetically important reactions, such as alkylation, acylation, aldolization halogenation, protonation, etc.[3] Examples are known in which the lithium enolate prepared from a carbonyl compound and lithium amide forms a complex in solution with the amine coming from the lithium amide used.[4] It is therefore reasonable to assume that the achiral lithium enolate prepared by using a chiral lithium amide forms a complex with the chiral amine coming from the chiral lithium amide used, where the symmetrical $\pi$-system of the enolate is expected to exist in a chiral environment, and possibly reacts with electrophiles enantioselectively. One of the first successful examples of enantioselective alkylation by this strategy was reported by Yamashita[5] in 1982, who carried out deprotonation of *N*-benzylidene-*dl*-phenylalanine methyl ester with chiral bidentate lithium amides followed by methylation with methyl iodide. The product was isolated as *N*-acetyl-α-methylphenylalanine in up to 31% ee. We have already reported enantioselective deprotonation of

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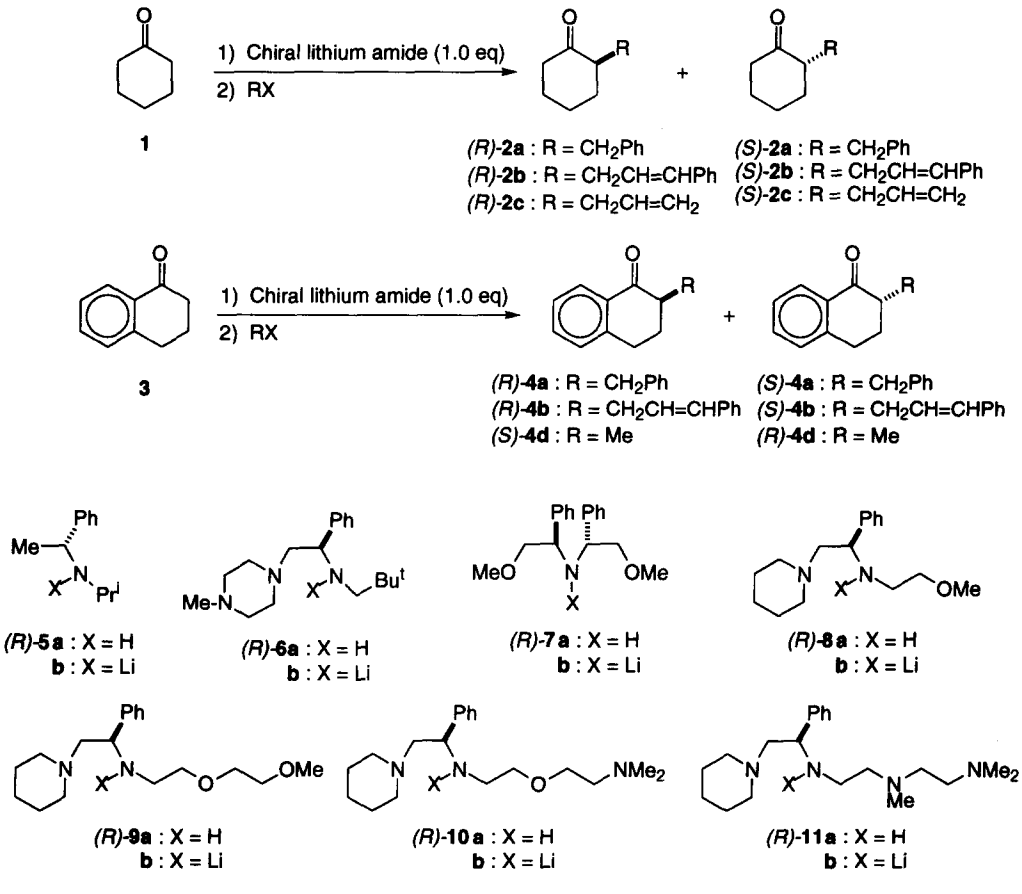
prochiral cyclic ketones using various chiral lithium amides.[6] The present paper describes an approach which uses chiral lithium amides for enantioselective alkylation at the α-position of cyclic ketones.[7]

## RESULTS AND DISCUSSION

***Enantioselective Alkylation of Cyclohexanone and 1-Tetralone via Deprotonation Using Chiral Lithium Amides*** An approach to enantioselective alkylation was examined first by the procedure shown in Scheme 1. Thus, cyclohexanone (**1**) and 1-tetralone (**3**) were treated with an equimolar amount of monodentate (*(R)*-**5b**[8]), bidentate (*(R)*-**6b**[9]), tridentate (*(R)*-**7b**,[10] *(R)*-**8b**), or tetradentate (*(R)*-**9b**[9]) chiral lithium amides, and the resulting lithium enolates containing the corresponding chiral amines were then treated with reactive alkyl halides in several solvents.

**Scheme 1**




Some results are summarized in Table 1. Among the reactions of **1** with benzyl bromide in toluene, chemical yields of the product (**2a**) are very low using *(R)*-**5b**, *(R)*-**6b**, and *(R)*-**7b** for deprotonation (runs 2~4), and are comparable to that using LDA (run 1). Ee's of **2a** are also very low. By using another tridentate

lithium amide ((*R*)-**8b**), chemical yield and ee of **2a** are somewhat improved (run 5). However, chemical yield and ee of **2a** increase greatly by using (*R*)-**9b**, a tetradentate chiral lithium amide (run 6). It is also shown that toluene is superior as a solvent to give **2a** in higher ee than ether, DME and THF (runs 7~10), indicating that (*R*)-**9a** coming from (*R*)-**9b** works as the ligand for the lithium of the lithium enolate, and that ether, DME, and THF compete with (*R*)-**9a** as a ligand. The reactions in the presence of HMPA (runs 11, 12) gave **2a** in very low ee, presumably for the same reason. Variations in the amount of (*R*)-**9b** (runs 13 and 15) and (*R*)-**9a** (run 14) do not improve the enantioselectivity of the reaction.

**Table 1**. Enantioselective Alkylation of **1** and **3** via Deprotonation Using Chiral Lithium Amides[a]

| | | | | | Alkylation step | | Product | | |
|---|---|---|---|---|---|---|---|---|---|
| Run | Ketone | Lithium amide (equiv.) | RX (equiv.) | Solvent | Additive (equiv.) | Temp. (°C) | Time (hr) | Compound | Chem. y. (%) | E. e. (%) |
| 1 | **1** | LDA | $PhCH_2Br$ (2.0) | toluene | - | -20 | 90 | **2a** | 5 | - |
| 2 | **1** | (*R*)-**5b** (1.0) | $PhCH_2Br$ (2.0) | toluene | - | -20 | 18 | **2a** | 1 | - |
| 3 | **1** | (*R*)-**6b** (1.0) | $PhCH_2Br$ (2.0) | toluene | - | -20 | 18 | (*S*)-**2a** | 7 | 1 |
| 4 | **1** | (*R*)-**7b** (1.0) | $PhCH_2Br$ (2.0) | toluene | - | -20 | 18 | (*S*)-**2a** | 7 | 6 |
| 5 | **1** | (*R*)-**8b** (1.0) | $PhCH_2Br$ (2.0) | toluene | - | -40 | 22 | (*R*)-**2a** | 15 | 27 |
| 6 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (2.0) | toluene | - | -20 | 18 | (*R*)-**2a** | 62 | 58 |
| 7 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (1.0) | toluene | - | -20 | 18 | (*R*)-**2a** | 47 | 53 |
| 8 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (1.0) | ether | - | -20 | 18 | (*R*)-**2a** | 14 | 25 |
| 9 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (1.0) | DME | - | -20 | 18 | (*R*)-**2a** | 69 | 30 |
| 10 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (1.0) | THF | - | -20 | 18 | **2a** | 42 | ~0 |
| 11 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (1.0) | toluene | HMPA (1.0) | -20 | 18 | (*R*)-**2a** | 67 | 8 |
| 12 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (1.0) | THF | HMPA (1.0) | -20 | 18 | **2a** | 69 | ~0 |
| 13 | **1** | (*R*)-**9b** (2.0) | $PhCH_2Br$ (1.0) | toluene | - | -20 | 18 | (*R*)-**2a** | 22 | 27 |
| 14 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (1.0) | toluene | (*R*)-**9a** (1.0) | -20 | 18 | (*R*)-**2a** | 48 | 45 |
| 15 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (1.0) | toluene | BuLi (1.0) | -20 | 18 | (*R*)-**2a** | 16 | 19 |
| 16 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (2.0) | toluene | - | -20 | 3 | (*R*)-**2a** | 29 | 36 |
| 17 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (2.0) | toluene | - | -20 | 180 | (*R*)-**2a** | 74 | 62 |
| 18 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (2.0) | toluene | LiBr (1.0) | -20 | 18 | (*R*)-**2a** | 60 | 83 |
| 19 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (10.0) | toluene | LiBr (1.0) | -45 | 18 | (*R*)-**2a** | 63 | 92 |
| 20 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (5.0) | toluene | LiBr (1.0) | -40 | 20 | (*R*)-**2a** | 58 | 90 |
| 21 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (5.0) | toluene | LiCl (1.0) | -40 | 24 | (*R*)-**2a** | 56 | 69 |
| 22 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (5.0) | toluene | LiI (1.0) | -40 | 19 | (*R*)-**2a** | 17 | 94 |
| 23 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (5.0) | toluene | LiF (1.25) | -40 | 20 | (*R*)-**2a** | 54 | 64 |
| 24 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (10.0) | ether | LiBr (1.0) | -45 | 18 | (*R*)-**2a** | 56 | 91 |
| 25 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (10.0) | DME | LiBr (1.0) | -45 | 18 | (*R*)-**2a** | 86 | 41 |
| 26 | **1** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (10.0) | THF | LiBr (1.0) | -45 | 18 | **2a** | 87 | ~0 |
| 27 | **1** | (*R*)-**9b** (1.0) | $PhCH{=}CHCH_2Br$ (10.0) | toluene | LiBr (1.0) | -45 | 18 | (*R*)-**2b** | 60 | 87 |
| 28 | **1** | (*R*)-**9b** (1.0) | $CH_2{=}CHCH_2Br$ (10.0) | toluene | LiBr (1.0) | -50 | 18 | (*R*)-**2c** | 41 | 80 |
| 29 | **3** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (10.0) | toluene | - | -45 | 18 | (*R*)-**4a** | 88 | 62 |
| 30 | **3** | (*R*)-**9b** (1.0) | $PhCH_2Br$ (10.0) | toluene | LiBr (1.0) | -45 | 18 | (*R*)-**4a** | 89 | 92 |
| 31 | **3** | (*R*)-**9b** (1.0) | $PhCH{=}CHCH_2Br$ (10.0) | toluene | LiBr (1.0) | -45 | 18 | (*R*)-**4b** | 93 | 88 |
| 32 | **3** | (*R*)-**9b** (1.0) | MeI (10.0) | toluene | LiBr (1.0) | -45 | 18 | (*S*)-**4d** | 71 | 88 |

[a] All reactions were carried out according to Scheme 1. For details, see experimental section.

We were afraid that **2a** might be partially racemized during the reaction, because **2a** formed is forced to exist in a strongly basic medium for a considerable time. Using the result of run 6 (reaction time: 18 hr) as reference, the reaction was carried out under the same conditions except that the reaction was stopped after 3 hr,

sacrificing the chemical yield on one hand (run 16), and the reaction was continued for 180 hr on the other hand (run 17). If partial racemization of **2a** occurs during the reaction, ee of **2a** should be higher after 3 hr, while lower after 180 hr. The results were contrary to our assumption. Thus, ee of *(R)*-**2a** was lower after 3 hr, while higher after 180 hr. This means that the reaction is less stereoselective at the early stage of the reaction, but becomes more stereoselective as the alkylation proceeds. This interesting phenomenon is parallel to the presence of LiBr, whose concentration is low at the early stage of the reaction, but increases as the alkylation proceeds. It is thus found that ee of *(R)*-**2a** is increased greatly by adding LiBr (1 equiv.) from the beginning (run 18). Among the lithium halides examined, LiBr was found to be the best (runs 20~23).[11] The ee of *(R)*-**2a** was further enhanced by increasing the amount of benzyl bromide and lowering the reaction temperature (runs 18~20). Under these optimized conditions, it is again shown that toluene is the solvent of choice (runs 19, 24~26). The reactions of cinnamyl bromide (run 27) and allyl bromide (run 28) occur similarly. It is also shown that alkylation of 1-tetralone (**3**) under the same conditions gave the corresponding products (*(R)*-**4a**, *(R)*-**4b**, and *(S)*-**4d**) in similar selectivity and in the same sense of asymmetric induction (runs 30~32).

It is thus shown that, as expected, enantioselective alkylation is realized efficiently by deprotonating cyclic ketones (**1**, **3**) with a tetradentate chiral lithium amide (*(R)*-**9b**), and then treating the resulting solution with reactive alkyl halides in toluene in the presence of LiBr. It is also shown that the yield of the benzylation reaction of lithium enolate is increased greatly in the presence of a tetradentate chiral amine (*(R)*-**9a**).[12]

***Enantioselective Alkylation of Cyclohexanone and 1-Tetralone via Their Silyl Enol Ethers*** The above results strongly suggest that the intermediate of the reaction should be a complex comprising a lithium enolate, a chiral tetradentate amine, and LiBr. This working hypothesis suggests that it should be possible to carry out the reactions more conveniently by the procedure shown in Scheme 2, since silyl enol ethers (**12** and **13**) are easily prepared from **1** and **3**, respectively, and an ethereal solution of MeLi-LiBr is commercially available. Thus, **12** and **13** were treated with an equimolar amount of MeLi-LiBr to give the corresponding lithium enolates containing LiBr. After addition of an equimolar amount of tridentate (*(R)*-**8a**) or tetradentate (*(R)*-**9a**, *(R)*-**10a**, *(R)*-**11a**) chiral amines, 10 equivalents of reactive alkyl halides were added. Some results are summarized in Table 2.

**Scheme 2**

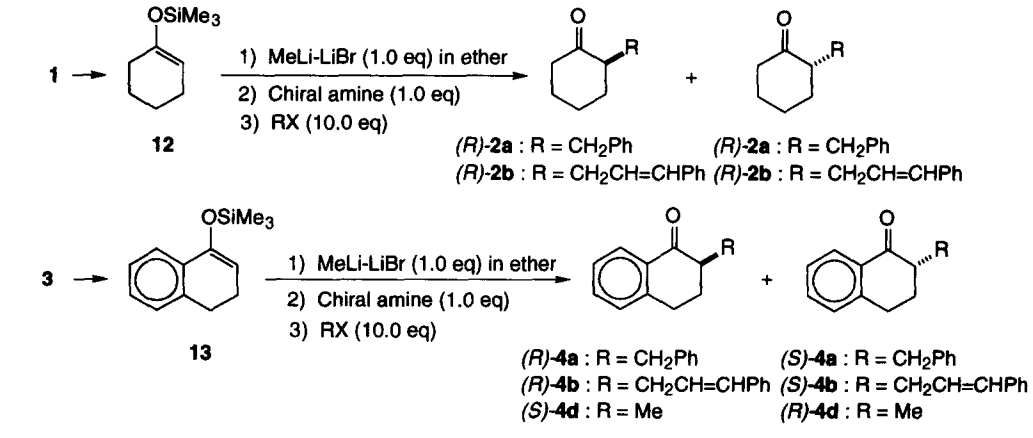


**Table 2.** Enantioselective Alkylation of **1** and **3** via Their Silyl Enol Ethers[a]

| Run | Silyl enol ether | Amine (1.0 equiv.) | RX (10.0 equiv.) | Solvent | Product: Compound | Product: Chem. y. (%) | Product: E. e. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **12** | *(R)*-**8a** | $PhCH_2Br$ | toluene | *(R)*-**2a** | 26 | 68 |
| 2 | **12** | *(R)*-**9a** | $PhCH_2Br$ | toluene | *(R)*-**2a** | 68 | 92 |
| 3 | **12** | *(R)*-**11a** | $PhCH_2Br$ | toluene | *(R)*-**2a** | 43 | 91 |
| 4 | **12** | *(R)*-**9a** | $PhCH{=}CHCH_2Br$ | toluene | *(R)*-**2b** | 75 | 87 |
| 5 | **13** | *(R)*-**9a** | $PhCH_2Br$ | toluene | *(R)*-**4a** | 81 | 92 |
| 6 | **13** | *(R)*-**11a** | $PhCH_2Br$ | toluene | *(R)*-**4a** | 56 | 97 |
| 7[b] | **13** | *(R)*-**11a** | $PhCH_2Br$ | toluene | *(R)*-**4a** | 86 | 96 |
| 8 | **13** | *(R)*-**11a** | $PhCH_2Br$ | cyclopentane | *(R)*-**4a** | 70 | 99 |
| 9 | **13** | *(R)*-**11a** | $PhCH_2Br$ | ether | *(R)*-**4a** | 42 | 97 |
| 10 | **13** | *(R)*-**11a** | $PhCH_2Br$ | DME | *(R)*-**4a** | 95 | 87 |
| 11 | **13** | *(R)*-**11a** | $PhCH_2Br$ | THF | *(R)*-**4a** | 39 | 77 |
| 12 | **13** | *(R)*-**9a** | $PhCH{=}CHCH_2Br$ | toluene | *(R)*-**4b** | 82 | 88 |
| 13 | **13** | *(R)*-**9a** | MeI | toluene | *(S)*-**4d** | 79 | 88 |
| 14 | **13** | *(R)*-**10a** | MeI | toluene | *(S)*-**4d** | 66 | 87 |
| 15 | **13** | *(R)*-**11a** | MeI | toluene | *(S)*-**4d** | 64 | 98 |
| 16 | **13** | *(R)*-**11a** | MeI | ether | *(S)*-**4d** | 20 | 86 |
| 17 | **13** | *(R)*-**11a** | MeI | DME | *(S)*-**4d** | 65 | 56 |
| 18 | **13** | *(R)*-**11a** | MeI | THF | *(S)*-**4d** | 44 | 14 |

[a] All reactions were carried out according to Scheme 2. Alkylation step was carried out at -45 °C for 18 hr. For details, see experimental section. [b] DME (8.0 equiv.) was added to complete the desilylation of **13** with MeLi-LiBr.

It is found that the results of the reactions by the procedure shown in Scheme 2 are almost comparable to those achieved by the procedure shown in Scheme 1. Thus, the products were obtained in reasonably good chemical and optical yields by using an equimolar amount of a tetradentate chiral amine (*(R)*-**9a**, *(R)*-**10a**, or *(R)*-**11a**) in toluene. These results strongly suggest that the formation of lithium enolate-tetradentate chiral amine-LiBr complex as an intermediate is responsible for the present enantioselective alkylation reaction. Studies on the structures of this type of complexes are under way.

## CONCLUSION

Enantioselective alkylation reaction of cyclohexanone and 1-tetralone by reactive alkyl halides was realized by treating the corresponding lithium enolates with an eqimolar amount of a tetradentate chiral amine such as *(R)*-**9a**, *(R)*-**10a**, or *(R)*-**11a** in the presence of LiBr in toluene. A ternary complex comprising lithium enolate, tetradentate chiral amine, and LiBr is proposed as an intermediate of the reaction.

## EXPERIMENTAL SECTION

**General** All melting and boiling points are uncorrected. IR spectra were recorded on a Jasco IRA-1 or a Jasco Report-100 spectrometer. $^1$H-NMR spectra were recorded on a JEOL JNX-FX 100 (100 MHz), a JEOL EX-270 (270 MHz), or a JEOL GSX-400 (400 MHz) spectrometer. Chemical shifts are given in δ

(ppm) using tetramethylsilane as an internal standard. Coupling constants($J$) are given in hertz. Mass spectra (MS) were recorded on a JEOL JMS-01 SG-Z or a JEOL JMX-DX-300 spectrometer. Optical rotations were measured by a Jasco DIP-370 polarimeter. For anhydrous solvents, toluene, ether, THF, DME, and cyclopentane were distilled from sodium/benzophenone ketyl under argon atmosphere. HMPA was distilled from $CaH_2$ under argon atmosphere. *(R)*-**5b**,[8] *(R)*-**6b**,[9] *(R)*-**7b**,[10] *(R)*-**9b**,[9] *(R)*-**10b**,[9] and *(R)*-**11b**[9] were prepared as reported. Absolute configurations of *(R)*-**2a**,[13a] *(R)*-**2b**,[7] *(R)*-**2c**,[13a,b] *(R)*-**4a**,[7] *(R)*-**4b**,[7] and *(R)*-**4d**[13a,c] are already reported. Ee's of the products were determined by HPLC using Waters Opti-Pak TA® as a chiral column and hexane-isopropanol (36:1) as an eluent for **2a**, **2b**, **4a**, and **4b**, or Waters Opti-Pak XC® as a chiral column and hexane-isopropanol (100:1) as an eluent for **4d**. Ee's of **2c** were determined by optical rotation, using a reported value of $[\alpha]_D^{20}$ +15.8 (c=3.00, MeOH) for *(S)*-**2c** of 99% ee.[13a] **12**[14] and **13**[15] were prepared as reported.

***(R)*-*N*-(2-Methoxyethyl)-1-phenyl-2-(1-piperidino)ethylamine (*(R)*-8a)** Triethylamine (1.87 g, 18.5 mmol) was added dropwise over 10 min to a mixture of *(R)*-1-phenyl-2-(1-piperidino)ethylamine[8] (3.43 g, 16.8 mmol), methoxyacetic acid (1.66 g, 18.4 mmol), and DEPC[16] (95%, 3.03 g, 17.7 mmol) in DMF (60 ml), and the whole was stirred at room temperature for 12 hr. The reaction mixture was diluted with ethyl acetate (400 ml) and benzene (50 ml), and the whole was washed with water (100 ml x 3), saturated aqueous $NaHCO_3$ (20 ml), and brine. The organic layer was dried over anhydrous $K_2CO_3$ and evaporated *in vacuo* to dryness. The residue was dissolved in ether, and the whole was extracted with 8% aqueous HCl (80 ml). The aqueous layer was washed with ether, made alkaline using conc. aqueous ammonia, and the whole was extracted with ether. The ethereal extracts were combined, washed with brine, dried over anhydrous $K_2CO_3$, and evaporated to dryness *in vacuo* to give the corresponding amide (3.61 g, 78%) as a colorless solid of mp 48-51 °C. Recrystallization from hexane gave colorless needles of mp 52-54 °C. IR (nujol) $cm^{-1}$: 1685. Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.82; H, 8.89; N, 10.28.

A solution of this amide (2.7 g, 9.8 mmol) in THF (10 ml) was added dropwise to a suspension of $LiAlH_4$ (1.0 g, 24.7 mmol) in THF (20 ml), and the whole was heated under reflux for 12 hr. Under ice-cooling, water (1 ml), 15% aqueous NaOH (1 ml), and water (3 ml) were added successively, and the whole was filtered. The filtrate and the THF washings were combined, and evaporated to dryness *in vacuo* to give a colorless oil (2.55 g). A solution of this oil in MeOH was mixed with a solution of excess picric acid in MeOH. Yellow precipitates were collected and recrystallized from MeOH to give *(R)*-**8a**·dipicrate (4.8 g, 67%) as yellow leaflets of mp 211 °C (dec.). Anal. Calcd for $C_{28}H_{32}N_8O_{16}$: C, 46.67; H, 4.48; N, 15.55. Found: C, 46.84; H, 4.44; N, 15.38. A suspension of *(R)*-**8a**·dipicrate in hexane was mixed with excess aqueous NaOH, and the whole was shaken vigorously. The organic layer was separated, and the aqueous layer was extracted again with hexane. The organic extracts were combined, washed with water and brine, dried over anhydrous $K_2CO_3$, and evaporated to dryness *in vacuo*. The residue was distilled under reduced pressure to give *(R)*-**8a** as a colorless oil of $bp_{0.2}$ 125-127 °C. $[\alpha]_D^{25}$ -83.2 (c=4.06, benzene). NMR (in $C_6D_6$): 1.04-1.81 (6H, m), 1.90-2.73 (8H, m), 3.10 (3H, s), 3.24-3.36 (2H, m), 3.82 (1H, dd, $J$=4 and 10), 7.0-7.7 (5H, m). MS *m/z*: 262 ($M^+$).

**Typical Procedures via Deprotonation Using Chiral Lithium Amides (Scheme 1, Table 1)** a) Run 6: Under argon atmosphere, a solution of *n*-BuLi (1.62 *N*, 0.62 ml, 1.0 mmol) in hexane was added to a solution of *(R)*-**9a** (306 mg, 1.0 mmol) in toluene (5 ml) at -20 °C under stirring, and the whole was

stirred for 30 min. A solution of **1** (98 mg, 1.0 mmol) in toluene (3 ml) was added, and the resulting solution was stirred at -20 °C for 30 min. A solution of benzyl bromide (0.24 ml, 2.0 mmol) in toluene (2 ml) was added, and the reaction mixture was stirred at -20 °C for 18 h. After addition of aqueous HCl (0.5 *N*, 10 ml) under vigorous stirring, the mixture was allowed to warm to room temperature, and was extracted with ether (20 ml x 3). The organic extracts were combined, washed successively with water (10 ml), saturated aqueous $NaHCO_3$ (10 ml), and brine (10 ml), and dried over $MgSO_4$. Evaporation of the solvent gave the crude product, which was purified by column chromatography (silica gel, hexane-ether (15:1)) followed by bulb-to-bulb distillation to give *(R)*-**2a** (117 mg, 62%, 58% ee by HPLC analysis) as a colorless oil of $bp_1$ 120 °C (bath temperature). $[\alpha]_D^{25}$ +27.1 (c=4.65, MeOH). Spectral data were identical to those described in b) below.

b) Run 19: Under argon atmosphere, LiBr (94.3 mg, 1.08 mmol) was dissolved in a solution of *(R)*-**9a** (306 mg, 1.0 mmol) in toluene (7 ml) with the aid of ultrasonic vibration at room temperature. The resulting solution was cooled to -20 °C, and was then mixed with a solution of *n*-BuLi in hexane (1.45 *N*, 0.69 ml, 1.0 mmol), and the whole was stirred for 30 min. A solution of **1** (98 mg, 1.0 mmol) in toluene (3 ml) was added, the whole was stirred at -20 °C for 30 min, and then cooled to -78 °C. A solution of benzyl bromide (1.2 ml, 10 mmol) in toluene (2 ml) was added. The reaction mixture was warmed to -45 °C, and was stirred at this temperature for 18 h. Work-up as described in a) above gave the crude product, which was purified by column chromatography (silica gel, hexane-ether (15:1)) followed by bulb-to-bulb distillation to give *(R)*-**2a** (118 mg, 63%, 92% ee by HPLC analysis) as a colorless oil of $bp_1$ 120 °C (bath temperature). $[\alpha]_D^{25}$ +43.1 (c=4.58, MeOH). IR (film) $cm^{-1}$: 1710. NMR (in $CDCl_3$): 1.2-2.1 (6H, m), 2.2-2.6 (4H, m), 3.23 (1H, dd, *J*=14 and 5), 7.1-7.3 (5H, m). MS *m/z*: 188 ($M^+$). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.64; H, 8.56.

c) Run 27: The reaction was carried out exactly by the same method described in b) above using **9a** (306 mg, 1.0 mmol), LiBr (98.2 mg, 1.13 mmol), **1** (98 mg, 1.0 mmol), *n*-BuLi in hexane (1.45 *N*, 0.69 ml, 1.0 mmol), and cinnamyl bromide (1.97g, 10 mmol) in toluene. The crude product obtained by working-up as described in a) above was purified by column chromatography (silica gel, hexane-ether (30:1)) followed by preparative TLC (silica gel plate, hexane-ether (4:1)) and then bulb-to-bulb distillation to give *(R)*-**2b** (129 mg, 60%, 87% ee by HPLC analysis) as a colorless oil of $bp_{0.2}$ 120 °C (bath temperature). $[\alpha]_D^{25}$ +30.4 (c=1.27, MeOH). IR (film) $cm^{-1}$: 1715. NMR (in $CDCl_3$): 1.3-2.7 (11H, m), 6.20 (1H, ddd, *J*=16, 8, 6.4), 6.39 (1H, d, *J*=16), 7.2-7.35 (5H, m). MS *m/z*: 214 ($M^+$).

d) Run 28: The reaction was carried out exactly by the same method described in b) above using **9a** (520 mg, 1.7 mmol), LiBr (164.5 mg, 1.89 mmol), **1** (166.6 mg, 1.7 mmol), *n*-BuLi in hexane (1.71 *N*, 0.99 ml, 1.7 mmol), and allyl bromide (1.5 ml, 17 mmol) in toluene. The crude product obtained by working-up as described in a) above was purified by column chromatography (silica gel, pentane-ether (15:1))followed by bulb-to-bulb distillation to give *(R)*-**2c** (95.9 mg, 41%) as a colorless oil of $bp_{12}$ 80 °C (bath temperature). $[\alpha]_D^{20}$ +12.5 (c=3.3 MeOH), corresponding to be 80% ee.[13a] IR (film) $cm^{-1}$: 1710. NMR (in $CDCl_3$): 1.20-2.68 (11H, m), 4.91-5.13 (2H, m), 5.58-5.99 (1H, m). MS *m/z*: 138 ($M^+$).

e) Run 30: The reaction was carried out exactly by the same method described in b) above using **9a** (306 mg, 1.0 mmol), LiBr (92.1 mg, 1.06 mmol), **3** (146 mg, 1.0 mmol), *n*-BuLi in hexane (1.71 *N*, 0.59 ml, 1.0 mmol), and benzyl bromide (1.2 ml, 10 mmol) in toluene. The crude product obtained by working-up as described in a) above was purified by column chromatography (silica gel, benzene) followed by bulb-to-bulb

distillation to give *(R)*-**4a** (210 mg, 89%, 92% ee by HPLC analysis) as a colorless oil of $bp_{0.3}$ 160 °C (bath temperature). $[\alpha]_D^{25}$ +17.8 (c=1.9, MeOH). IR (film) $cm^{-1}$: 1680. NMR (in $CDCl_3$): 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.6-2.8 (2H, m), 2.8-3.0 (2H, m), 3.49 (1H, dd, *J*=13, 3.3), 7.2-7.4 (7H, m), 7.45 (1H, dt, *J*=7.6, 1.3), 8.07 (1H, dd, *J*=8.6, 1.3). MS *m/z*: 236 ($M^+$). Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.13; H, 6.95.

f) Run 31: The reaction was carried out exactly by the same method described in b) above using **9a** (306 mg, 1.0 mmol), LiBr (98.9 mg, 1.14 mmol), **3** (146 mg, 1.0 mmol), *n*-BuLi in hexane (1.71 *N*, 0.59 ml, 1.0 mmol), and cinnamyl bromide (1.97 g, 10 mmol) in toluene. The crude product obtained by working-up as described in a) above was purified by column chromatography (silica gel, hexane-ether (15:1)) to give *(R)*-**4b** (243 mg, 93%, 88% ee by HPLC analysis) as a colorless oil.[17] $[\alpha]_D^{25}$ +16.0 (c=0.08, EtOH). IR (film) $cm^{-1}$: 1680. NMR (in $CDCl_3$): 1.8-2.0 (1H, m), 2.2-2.35 (1H, m), 2.4-2.5 (1H, m), 1.57-2.69 (1H, m), 2.85-2.95 (1H, m), 2.95-3.1 (2H, m), 6.27 (1H, dt, *J*=15.8, 7.6), 6.46 (1H, d, *J*=15.8), 7.16-7.38 (7H, m), 7.46 (1H, m), 8.06 (1H, d, *J*= 6.6). HRMS *m/z*: Calcd for $C_{19}H_{18}O$: 262.1358. Found: 262.1340.

g) Run 32: The reaction was carried out exactly by the same method described in b) above using **9a** (306 mg, 1.0 mmol), LiBr (98.7 mg, 1.13 mmol), **3** (146 mg, 1.0 mmol) *n*-BuLi in hexane (1.71 *N*, 0.59 ml, 1.0 mmol), and MeI (0.62 ml, 10 mmol) in toluene. The crude product obtained by working-up as described in a) above was purified by column chromatography (silica gel, hexane-ether (30:1)) followed by bulb-to-bulb distillation to give *(S)*-**4d** (113 mg, 71%, 88% ee by HPLC analysis) as a colorless oil of $bp_1$ 100 °C (bath temperature). $[\alpha]_D^{22}$ -45.2 (c=2.79, dioxane) (reported[13c] $[\alpha]_D^{22}$ -51.2 (c=2.5, dioxane) for *(S)*-**4d**). IR (film) $cm^{-1}$: 1680. NMR (in $CDCl_3$): 1.28 (3H, d, *J*=6.6), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 2.5-2.7 (1H, m), 2.9-3.1 (2H, m) 7.23 (1H, m), 7.30 (1H, m), 7.46 (1H, m), 8.04 (1H, m). MS *m/z*: 160 ($M^+$).

**Typical Procedures via Silyl Enol Ethers (Scheme 2, Table 2)** a) Run 5: Under argon atmosphere, MeLi-LiBr in ether (1.50*N* for MeLi, 0.67 ml, 1.0 mmol) was added to **13** (218 mg, 1.0 mmol) at room temperature and stirred for 1 h. Toluene (7 ml) was added, and the whole was cooled to -20 °C. After addition of a solution of *(R)*-**9a** (306 mg, 1.0 mmol) in toluene (3 ml), the whole was stirred at -20 °C for 0.5 h and then cooled to -78 °C. A solution of benzyl bromide (1.2 ml, 10 mmol) in toluene (2 ml) was added, and the whole was stirred at -45 °C for 18h. After addition of aqueous HCl (0.5 *N*, 10 ml) under vigorous stirring at -78 °C, the mixture was allowed to warm to room temperature, and was extracted with ether (20 ml x 3). The organic extracts were combined, washed successively with water (10 ml), saturated aqueous $NaHCO_3$ (10 ml) and brine (10 ml), and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a residue, which was purified by column chromatography (silica gel, hexane-ether (15:1)) followed by bulb-to-bulb distillation to give *(R)*-**4a** (191 mg, 81%, 92% ee by HPLC analysis) as a colorless oil of $bp_{0.3}$ 160 °C (bath temperature). $[\alpha]_D^{25}$ +17.7 (c=2.2, MeOH). Spectral data were identical to those described above.

b) Run 7: Under argon atmosphere, MeLi-LiBr in ether (1.55 *N* for MeLi, 0.72 ml, 1.12 mmol) was added to **13** (245 mg, 1.12 mmol) at room temperature and stirred for 1.5 h. After addition of a solution of DME (0.93 ml, 8.98 mmol) in toluene (7 ml), the whole was stirred at -20 °C for 10 min. A solution of *(R)*-**9a** (373 mg, 1.12 mmol) in toluene (5 ml) was added, and the resulting solution was stirred at -20 °C for 40 min, and then at -78 °C for 15 min. A solution of benzyl bromide (1.34 ml, 11.2 mmol) in toluene (5 ml) was added, and the reaction mixture was stirred at -45 °C for 18 h. Work-up as described in a) above gave the crude product, which was purified by column chromatography (silica gel, hexane-ether (50:1)) gave *(R)*-**4a**

(228mg, 86%, 96% ee by HPLC analysis) as a pale yellow oil. Spectral data were identical to those described above.

c) Run 15: The reaction was carried out exactly by the same method using **13** (201 mg, 0.84 mmol), MeLi-LiBr in ether (1.62 *N* for MeLi, 0.52 ml, 0.84 mmol), *(R)*-**11a** (288mg, 0.87 mmol), and MeI (0.53 ml, 8.5 mmol) in toluene. The crude product obtained by working-up as described in a) above was purified by column chromatography (silica gel, hexane-ether (30:1)) to give *(S)*-**4d** (86.4 mg, 64%, 98% ee by HPLC analysis) as a colorless oil. $[\alpha]_D^{22}$ -49.9 (c=3.14, dioxane). Spectral data were identical to those described above.

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