# Chiral Organolithium Complexes: The Effect of Ligand Structure on the Enantioselective Deprotonation of Boc-Pyrrolidine

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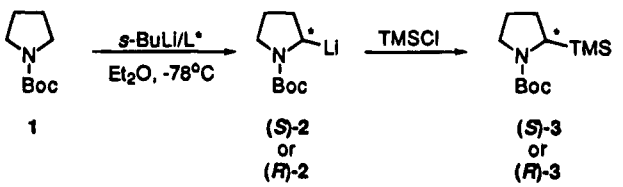
The efficacies of a number of *s*-BuLi/chiral ligand complexes as reagents for the asymmetric deprotonation of Boc-pyrrolidine (**1**) to provide enantioenriched 2-lithio-Boc-pyrrolidine (**2**) have been evaluated by the conversion of **2** to 2-(trimethylsilyl)-Boc-pyrrolidine (**3**). The syntheses of new enantioenriched proline-based and bispidine ligands are described. The most effective newly examined ligands are the diproline-based diamino alcohol **20** and the α-methylbenzylamine-derived bispidine **35**, which provided (*S*)-**3** and (*R*)-**3** with enantiomeric excesses of 72% and 75%, respectively. Use of the ligand (−)-isosparteine (**28**) resulted in lower conversions and enantioselectivities than (−)-sparteine (**27**). A rationale is proposed to explain the relative rates of the lithiation of **1** by *s*-BuLi/TMEDA, **27**, or **28** complexes and the remarkable effectiveness of (−)-sparteine as the best chiral ligand examined to date.

## Introduction

The asymmetric chemistry available from complexes formed between organolithium reagents and enantioenriched ligands offers convenient approaches to syntheses of enantioenriched compounds. Of particular interest has been the complex of *sec*-butyllithium (*s*-BuLi) and (−)-sparteine, which Hoppe first showed could induce high enantioenrichments in lithiation reactions to provide α-oxygen-substituted dipole-stabilized carbanions.[1] We subsequently established that *s*-BuLi/(−)-sparteine is effective in producing (*S*)-2-lithio-Boc-pyrrolidine ((*S*)-**2**) in high enantioenrichment from Boc-pyrrolidine (**1**). The organolithium **2** was shown to be configurationally stable at −78 °C and to react with electrophiles with retention of configuration.[2] Our further work established that *i*-PrLi/(−)-sparteine is also an effective asymmetric base and that it exists as an unsymmetrical dimer (*i*-PrLi)$_2$/(−)-sparteine/(Et$_2$O)$_n$ in solution.[3] We have recently reported the full details of our studies on the use of *s*-BuLi/(−)-sparteine to carry out the asymmetric deprotonation of **1** and electrophilic substitution of (*S*)-**2** to give highly enantioenriched products such as the TMS-substituted pyrrolidine **3**.[4–6]

In order to gain further understanding of the asymmetric deprotonation reaction, we have evaluated the effect of selected ligands on the enantioselective conversion of **1** to the lithiated species **2** by trapping with TMSCl and evaluating the enantiomeric excess of **3**. In this sequence, the use of (−)-sparteine (**27**) as the ligand provided **3** in 87% yield with 96% ee.[2,4] The goals of this work were to provide new synthetically useful ligands which would be available in both enantiomeric forms and to determine the structural features of the ligands that induce enantioselectivity in the asymmetric deprotonation pathway.




## Results and Discussion

**Proline-Based Chiral Ligands.** Pyrrolidine ring-based ligands are an attractive class of ligands. They are ultimately derived from proline, which is available as the (*S*)-isomer from natural sources, while (*R*)-proline derivatives are available from the (−)-sparteine-mediated asymmetric deprotonation methodology.[4] Since both antipodes of these ligands would then be available, access to both enantiomeric products of an asymmetric deprotonation would follow. Structural variations in this well-studied ligand series are either known compounds or could be synthesized using established methodology.[7]

The syntheses of new proline-based ligands are shown in Scheme 1, and full details and yields are given in the Experimental Section. The DCC/HOBT coupling of the protected amino acids **5** and **6** with either the methyl or ethyl esters of proline (**4a,b**) provided the amides **10** and **11**, which were reduced with LiAlH$_4$/THF to the diamino alcohols **15** and **16**. In a similar manner, coupling of

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1995.

(1) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69. Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422. Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. For a recent summary, see Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1454.

(2) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.

(3) Gallagher, D. J.; Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 5872.

(4) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

(5) It has been established that a mechanism of asymmetric substitution, in which the chiral ligand influences the reaction of the lithiated intermediate with the electrophile, can also produce high enantioselectivities. Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516. Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755.

(6) For leading references regarding enantioselective trapping of configurationally labile organolithium species in the presence of (−)-sparteine, see; Kaiser, B.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323. Asymmetric additions to imines; Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797. Asymmetric ring openings: Lautens, M.; Gajda, C.; Chiu, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1193.

(7) For a review with leading references on the synthesis and utility of chiral pyrrolidine-based ligands, see: Mukaiyama, T.; Asami, M. *Top. Curr. Chem.* **1985**, *127*, 133.

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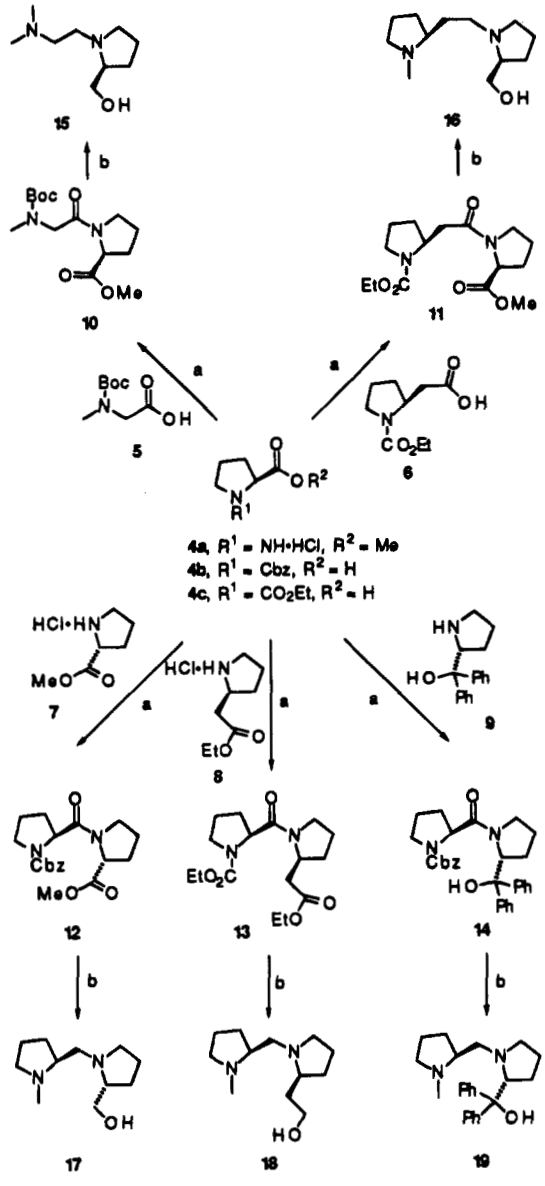
**Scheme 1**[a]




[a] Conditions: (a) DCC, HOBT; (b) $LiAlH_4$, Δ, THF.

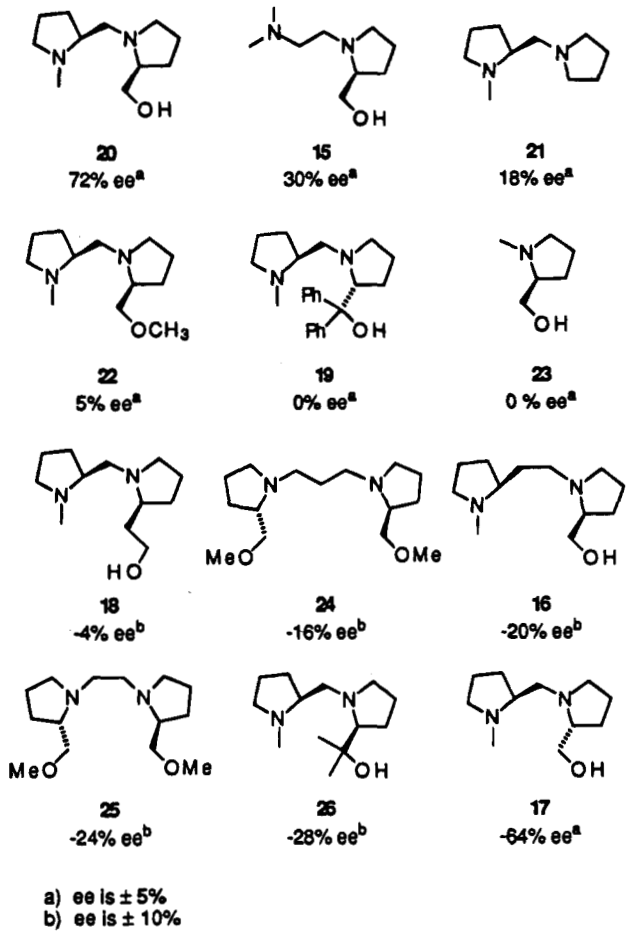
*N*-protected L-proline with amino esters **7** and **8**, followed by $LiAlH_4$ reduction, provided diamino alcohols **17** and **18**. Coupling of **4c** with the diphenylamino alcohol **9** and reduction provided **19**.[8] Ligands **20**–**26** are previously reported compounds and were synthesized using reported methods.[7]

In order to determine ligand structure–enantioselectivity relationships, each ligand was assayed for the reaction sequence **1** to **2** to **3**. A 1:1 *s*-BuLi/ligand complex was formed at −78 °C, and then a solution of **1** was transferred into the reaction by cannula.[9] The reaction was stirred at −78 °C for 5–8 h before TMSCl was added. The enantiomeric excess of **3** was determined either directly by chiral stationary phase (CSP) GC or by hydrolysis and conversion to the dinitrobenzamide derivative, which was analyzed by CSP HPLC.

(8) Amino alcohol **9** was synthesized optically pure using a scaled-up version of the procedure reported previously.[4] Nikolic, N. A.; Beak, P. *Org. Synth.*, submitted for publication.

(9) If the ligand was an alcohol, 2.2–2.4 equiv of *s*-BuLi was used. In the cases where there were no acidic protons in the ligand 1.2–1.4 equiv of *s*-BuLi was used.

The structures of the proline-based ligands assayed and the enantiomeric excesses obtained are shown below.




a) ee is ± 5%
b) ee is ± 10%

Isolated yields and conversions determined by GC are listed in the Experimental Section.[10] In this paper, we use the convention of positive ee indicating enrichment in (*S*)-**3**, the stereoisomer obtained using sparteine. A negative ee value indicates that the product was found to be enriched in (*R*)-**3**. The results are shown in order from the highest positive ee to the most negative ee.

As can be seen from the data, the diamino alcohol **20** provided the highest enantioselectivity (72% ee).[11] Modification of the structure of **20** at both stereogenic and nonstereogenic centers provided marked changes in the sense and level of asymmetric induction. Insertion of a methylene group between the amino groups for ligand **16** changes the sense of asymmetric induction, although the enantioselectivity is low. Use of ligand **18**, in which a methylene group has been inserted between the alkoxide and amine moieties, provides essentially racemic **3**. Use of the two $C_2$-symmetric ethers **24** and **25** provided low levels of enantioselective deprotonation, as did the dipyrrolidine ligand **21**, in which there is an alkoxide group.

Interesting trends are observed for the substituent and stereochemical changes on the carbon skeleton of **20**. Use

(10) In all cases except those indicated in the text, the conversions to products were greater than 42%. Isolated yields tended to be variable. Since reaction times did vary slightly for different ligands (5–8 h), we do not consider comparisons between conversions to be as quantitative as comparisons between enantiomeric excess values.

(11) We had reported 84% ee when using this ligand previously.[4] We have found 72% ee to be a reproducible value using the general lithiation procedures reported in this paper.

of the methyl ether **22** reduces asymmetric induction to a negligible value. Insertion of *gem*-dimethyl groups next to the alkoxide for **26** reverses the sense of asymmetric deprotonation, although the ee is only 28%. The presence of the larger *gem*-diphenyl groups in **19** provides 0% ee, suggesting that steric bulk around the alkoxide interferes with the asymmetric induction in the reaction.

The above comparisons suggest that changes near the alkoxide group have a profound effect on the enantioselectivity of the reaction. Use of diamino alcohol **17**, in which the stereocenter next to the alkoxide group has been inverted relative to **20**, provides **3** in −64% ee. This suggests that the primary stereodetermining feature is the stereocenter adjacent to the alkoxide functionality. This indication is supported by the 30% ee obtained with ligand **15**, in which the only stereocenter has the same absolute stereochemistry as **20**. We speculate that the lowering of enantiomeric excess in going from the diproline-based ligand **20** to **15** probably results from the loss of rigidity provided by the second pyrrolidine ring in **20**, rather than loss of the second stereocenter. The observation that a stereocenter next to an alkoxide is important for asymmetric induction has been reported previously by Jackman and co-workers for the addition of organolithium/aminoalkoxide complexes to aldehydes.[12]

Another interesting observation is that the alkoxide of *N*-methylprolinol (**23**) produces only 5% conversion to product in 0% ee. This seems to indicate that although the center next to the alkoxide can influence the stereochemistry for the asymmetric deprotonation, the diamino functionality is necessary to promote the lithiation reaction. The fact that **1** is lithiated only to an extent of about 5% after 4 h upon treatment with *s*-BuLi in the absence of any ligand supports that assessment.[13] The failure of the *s*-BuLi/**23** complex to effect the lithiation of **2** could be a result either of the failure of the alkoxide of **23** to bind with the organolithium or the necessity of having a diamino functionality present to stabilize the transition state for the lithiation. We suggest the latter is the more likely since the results of addition of RLi/aminoalkoxide mixtures to aldehydes with enantioselectivity suggest that organolithium/aminoalkoxide complexes do influence reactions.[12]

We are not able to offer a monomeric transition state model which convincingly rationalizes the observed stereoselectivities in these asymmetric deprotonations. The presence of stereogenic centers at carbon, invertomeric centers at nitrogen, and the possibility of complex aggregates involving alkoxides makes consideration of higher-order aggregates problematic.[14] It is also possible that the extent of enantioselective deprotonation using many of these ligands may be lowered due to multiple conformations of the complexing ligand which result in competing transition states that produce both enantiomers of **2**.

**Evaluation of (−)-Isosparteine.** Since (−)-sparteine (**27**) is the most effective ligand we have found for the asymmetric deprotonation of **1**, we investigated the use of a structural analog of **27**, the $C_2$-symmetric diamine

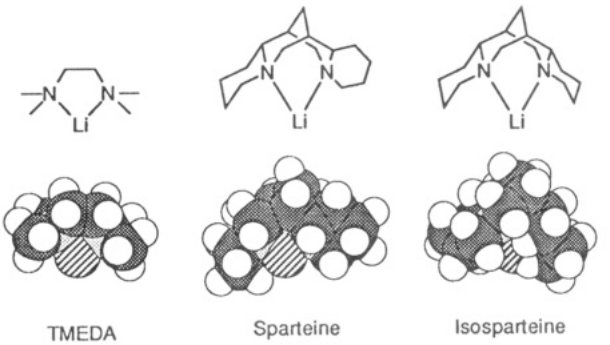



**Figure 1.** Space-filling diagrams of lithium atoms complexed by TMEDA, **27**, and **28**.

(−)-isosparteine (**28**).[15] Use of **28** in the standard asymmetric deprotonation protocol provided very low conversion of **1** to **3** (~10% by GC) and an enantiomeric excess of 61%. The use of (−)-isosparteine in the asymmetric deprotonation reaction appears to slow down the reaction significantly and provides lower enantioselectivity.


The relative reactivity of organolithium complexes with TMEDA, **27**, and **28** in the lithiation of **1** suggests that steric effects in the diamine/organolithium complex are important. Shown below are space-filling diagrams of a lithium atom complexed to TMEDA, **27**, and **28**. An organolithium complex with TMEDA would be expected to have the least steric hindrance for association with **1**. As shown qualitatively in Figure 1, the left peripheral ring of sparteine would extend closest toward a complexed organolithium, but the right peripheral ring would be expected to have a smaller steric effect. However, an organolithium complex with isosparteine would be expected to be much more sterically hindered since both peripheral rings would extend toward the organolithium. These speculative comparisons of steric effects parallel the observed reactivity of these complexes. Boc-pyrrolidine is lithiated by *s*-BuLi/TMEDA completely in 30 min at −78 °C, while the asymmetric deprotonation with *s*-BuLi/sparteine requires 4 h for substantial reaction and the complex of *s*-BuLi/isosparteine only lithiates **1** to a small extent even after 4 h. The low ee with **28** could be attributable either to the incursion of reaction by a small amount of free *s*-BuLi or to a lower extent of asymmetric deprotonation by the *s*-BuLi/**28** complex.

**Bispidine Ligands.** A class of ligands which contains the core diaza[3.3.1] ring system of sparteine and isosparteine is the bispidines.[16] The [3.3.1] ring system incorporated into a chiral complex should provide useful rigidity and reduce conformational variability in the asymmetric deprotonation transition state. In our initial work, chirality has been incorporated by the use of chiral amines in the synthetic sequence.

(12) Ye, M.; Logaraj, S.; Jackman, L. M.; Hillegass, K.; Hirsh, K. A.; Bollinger, A. M.; Grosz, A. L.; Mani, V. *Tetrahedron* **1994**, *50*, 6109.

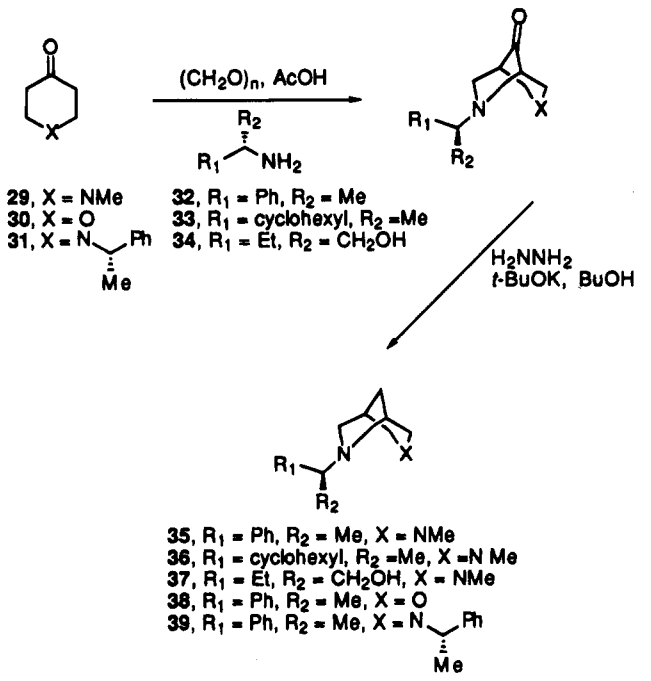
(13) For the achiral lithiation of **1**, the presence of TMEDA was needed. Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

(14) Jackman, L. M.; Rakiewicz, E. F.; Benesi, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 4101. McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805. See also ref 12.

(15) Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1316. For uses of (−)-isosparteine see: Kang, J.; Cho, W. O.; Cho, H. G. *Tetrahedron Asymmetry* **1994**, *5*, 1347.

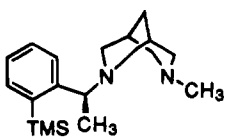
(16) Zefirov, N. S.; Palyulin, V. A. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley and Sons, Inc.: New York, 1991; Vol. 20.

**Scheme 2**

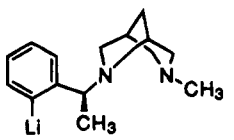



The synthesis of the bispidine ligands **35**–**39** that we have studied is shown in Scheme 2. The diaza[3.3.1] skeleton was constructed using a double Mannich reaction with chiral amines **32**–**34**.[17] The ketobispidine intermediates were reduced using Wolff–Kishner conditions[18] to provide the chiral bispidine ligands **35**–**39**. Yields of **35**–**39** from **29**–**31** ranged from 18 to 53%.

Use of the bispidine **35**, derived from α-methylbenzylamine, as a ligand in the asymmetric deprotonation reaction of **1** in $Et_2O$ provided a 55% yield of **3** in −75% enantiomeric excess (enrichment in (*R*)-**3**). The *s*-BuLi/**35** reaction with **1** gave a heterogeneous mixture in $Et_2O$, but when *s*-BuLi/**35** was used in either *t*-BuOMe or toluene the reaction mixtures were homogeneous. However, only ~20–25% conversions of **1** to **3** were indicated by GC analysis, and CSP GC of the crude solutions indicated enantiomeric excesses of only ~30% ee. Reisolation of the ligand provided **35** along with another compound, tentatively assigned structure **40**. The structural assignment of **40** is based on a GCMS analysis and is consistent with the known ability of benzylamines to act as good ortho-directing groups.[19] Thus, when the reaction is homogeneous, lithiation to form **41** and TMS trapping to provide **40** putatively occurs. The heterogeneous reaction conditions using $Et_2O$ as the solvent apparently minimizes this side reaction.

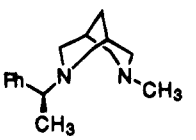



**40**

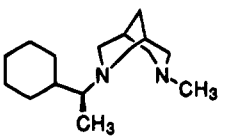



**41**

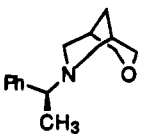
The structures of the bispidine ligands assayed in the asymmetric deprotonation reaction are shown below with the enantiomeric excesses obtained. As can be seen, none of the ligands other than **35** provided useful enantiomeric excesses in a variety of solvents.[20] Replacement of the phenyl group of **35** with a cyclohexyl ring as for **36** lowered the enantiomeric excess to −34% ee. Use of the amino alcohol **37** as a ligand provided low enantioselectivity, as did the amino ether **38**. The dibenzylbispidine **39** provided no enantioselectivity and only 20% conversion to product. This is consistent with the steric effect of diamine ligands complexed to lithium discussed above, since the steric bulk on both sides of bispidine **39** would be expected to slow the lithiation reaction. Interestingly, the benzylamine-containing ligands **38** and **39** were not lithiated under the reaction conditions.



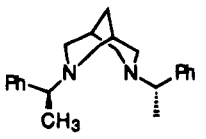
**35**
-75% ee ($Et_2O$)
-28% ee (*t*-BuOMe)
-35% ee (toluene)



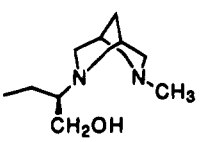
**36**
-34% ee (t-BuOMe)
-34% ee (toluene)
-34% ee (pentane)



**38**
-16% ee ($Et_2O$)
-20% ee (toluene)

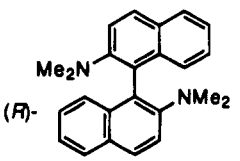


**39**
-1% ee ($Et_2O$)

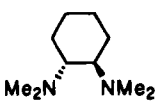


**37**
+27% ee ($Et_2O$)

**Other Ligand Systems.** Other ligand systems we have investigated are the binaphthyldiamine (**42**)[21] and *trans*-cyclohexanediamine derivative (**43**).[22] The binaphthyl ligand itself and its complex with *s*-BuLi were insoluble in *t*-BuOMe. Very low (<10%) conversion to product was observed with no enantioselectivity as shown by CSP GC. Use of *s*-BuLi/**43** in the asymmetric deprotonation provided good conversion to product (~90%), but no enantioselectivity in the product **3** was observed.




**42**




**43**

An effective chiral ligand for highly enantioselective deprotonation reactions must have balanced dynamic properties. It must bind the organolithium species strongly enough to keep the concentration of reactive racemic organolithium species low.[23] Ideally, the chiral ligand should also accelerate the lithiation reaction compared to a ligand-free reaction. For the asymmetric deprotonation of **1**, (−)-sparteine and some of the other diamines in this study fulfill these requirements. It is

(17) For previous applications of this methodology, see: Douglass, J. E.; Ratliff, T. B. *J. Org. Chem.* **1968**, *33*, 353.
(18) Todd, D. *Org. React.* **1948**, *4*, 378.
(19) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1984**, *26*, 48.
(20) In other systems we have observed enhancement of enantioselectivity when other solvents were assayed, particularly toluene. Wu, S.; Lee, S. P.; Beak, P. *J. Org. Chem.*, submitted for publication.
(21) Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335.
(22) Galsbøl, F.; Steenbøl, P.; Sørenson, B. S. *Acta. Chem. Scand.* **1972**, *26*, 3605.
(23) For a study of (−)-sparteine complexation with organomagnesium compounds, see: Fraenkel, G.; Appleman, B.; Ray, J. G. *J. Am. Chem. Soc.* **1974**, *96*, 5113.

also necessary that proper steric interactions be present in the diastereomeric transition structure which introduces enantioselectivity. These interactions are clearly present in (−)-sparteine and to a slightly lesser extent in **17**, **20**, **35**, and (−)-isosparteine. However, the chiral ligand/organolithium complex must have sufficient flexibility to allow incorporation of the reaction substrate into the diastereomeric transition state of the reaction. Although the dibenzylbispidine **39** and (−)-isosparteine possess chiral steric interactions similar to **35** and (−)-sparteine, they fail in this requirement because their steric bulk does not allow conversion to lithiated product to proceed efficiently.

In conclusion, although some of the ligand systems we examined do provide substantial enantioselectivities in the asymmetric deprotonation of **1**, none provided enantioselectivities as high as (−)-sparteine. The most successful ligands assayed were the diproline-based ligand **20** and the bispidine **35**. However, the utility of **35** is limited since it is competitively lithiated in solution. We believe that a combination of binding, rigidity, and the specific steric features of (−)-sparteine contribute to its effectiveness as a chiral ligand. For the purposes of mechanistic analysis and rational design, it would be desirable to assay ligands that possess a limited number of binding modes in order to understand the critical features of the enantiodetermining transition structure. Our initial bispidine ligands possess the binding modes and some of the rigidity of sparteine but do not contain substitution that provides a suitable steric environment for effective asymmetric deprotonation. Synthesis and evaluation of ligands that more closely emulate the steric interactions of (−)-sparteine should be informative.

## Experimental Section

**General.** $^1$H NMR and $^{13}$C NMR spectra were recorded using tetramethylsilane (TMS) or residual solvent as an internal standard. Chiral stationary phase (CSP) gas chromatography was performed on a Hewlett-Packard 5790 gas chromatograph equipped with a Cyclodex cyclodextrin column (J & W Scientific). CSP HPLC of dinitrobenzamide derivatives was performed using a Pirkle Covalent S-N1N-naphthylleucine column produced by Regis Chemical Co. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Microanalyses were obtained from the University of Illinois Microanalytical Service Laboratory. Compounds which were not analyzed were judged to be >95% pure based on the $^1$H and $^{13}$C NMR spectra which are provided as supporting information. Kugelrohr bulb to bulb distillation temperatures refer to air-bath temperatures and are not necessarily an accurate measure of boiling points.

All reactions involving organolithium reagents were carried out under a dry nitrogen atmosphere unless otherwise noted. Diethyl ether ($Et_2O$) and *tert*-butyl methyl ether (MTBE) were distilled over sodium/ benzophenone. Toluene was distilled over $CaH_2$. *sec*-Butyllithium in cyclohexane (*s*-BuLi) was obtained from Lithium Corp. and filtered through Celite, and stock solutions were titered prior to use by the method of Suffert.[24] All other reagents were obtained from commercial sources and used without purification unless otherwise noted.

**Synthesis of (2*S*)-2-(Hydroxymethyl)-1-[2-(dimethylamino)ethyl]pyrrolidine (15).** To a solution of *N*-Boc-sarcosine (**5**) (5.36 g, 28.4 mmol) in $CHCl_3$ (30 mL) was added solid DCC (5.85 g, 28.4 mmol) and HOBT (3.83 g, 28.4 mmol). The suspension was stirred for 10 min, and then a solution of **4a** (1.95 g, 7.71 mmol) and 7 mL of triethylamine in 50 mL of $CHCl_3$ was added and the reaction mixture stirred for 18 h. The solvents were removed in vacuo, EtOAc (300 mL) was added, and the mixture was stirred. The solids were filtered, and the EtOAc solution was washed with 10% citric acid (100 mL) and 10% $NaHCO_3$ (100 mL) and dried over $Na_2SO_4$. The solvents were removed in vacuo to provide a brown oil which was filtered through a short pad of silica to provide the amide **10** as a pale yellow oil (6.24 g, 20.8 mmol, 77% crude yield) which was used immediately in the next step.

To a stirred suspension of excess $LiAlH_4$ (2.9 g) cooled to 0 °C in 50 mL of THF was added dropwise a solution of **10** in 50 mL of THF. The reaction mixture was stirred for 10 min at room temperature and then was heated at reflux for 6 h. The reaction mixture was cooled to 0 °C and carefully quenched by addition of EtOAc (10 mL). A slurry of $Na_2SO_4/H_2O$ was added while the reaction mixture was vigorously mixed until all the salts appeared white. The solvent was decanted, and the remaining white solid was washed several times with $Et_2O$. The $Et_2O$ layers were concentrated in vacuo to provide a yellow oil which was purified by Kugelrohr distillation (0.2 torr, 80−90 °C) to provide **15** as a clear oil (2.34 g, 13.6 mmol, 65%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.47−1.88 (m, 4 H), 2.19 (m, 4 H), 2.19 (s, 6 H), 2.20−2.79 (overlapping m, 6 H), 3.12 (m, 1 H), 3.23 (m, 1 H), 3.44 (m, 1 H), 4.60 (bs, 1 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 24.36, 28.24, 45.39, 53.35, 56.10, 59.29, 64.71, 65.26. Anal. Calcd for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26. Found: C, 63.02; H, 12.08; N, 16.58.

**Synthesis of (2*S*,2′*S*)-2-(Hydroxymethyl)-1-[2-(1-methylpyrrolidin-2′-yl)ethyl]pyrrolidine (16).** To a solution of the carboxylic acid **6** (1.60 g, 7.96 mmol) in chloroform (24 mL) was added DCC (1.60 g, 7.80 mmol) and 1-hydroxybenzotriazole (HOBT) (1.08 g, 7.80 mmol). The mixture was stirred for 5 min, and then L-proline methyl ester hydrochloride (**4a**) (1.32 g, 7.98 mmol) and triethylamine (1.1 mL) were added and stirring continued for 18 h until the starting material had been consumed. The insoluble solid formed was removed by filtration, and the filtrate was washed with water (3 × 20 mL) and evaporated in vacuo. The residue was dissolved in ether (30 mL), and additional insoluble material was removed. The filtrate was dried over $MgSO_4$ and filtered, and the solvents were removed in vacuo to provide the crude product, which was purified by chromatography (1:9 methanol:methylene chloride) to give **11** as a clear oil (1.58 g, 4.85 mmol, 61% yield): $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.20 (t, 3 H), 1.81−2.16 (m, 10 H), 2.85, 3.15 (m, 2 H), 3.34−3.73 (m, 5 H), 3.68 (s, 3 H), 4.10 (bs, 3 H), 4.40 (m, 1 H).

A THF (10 mL) solution of **11** (1.20 g, 3.68 mmol) was added to a stirred suspension of $LiAlH_4$ (0.6 g) in THF (20 mL) at 0 °C, and the reaction mixture was heated to reflux for 5 h. The reaction was cooled to room temperature, and aqueous sodium sulfate was added dropwise to the reaction mixture. The resulting precipitate was removed by filtration, and the filtrate was dried over anhydrous $MgSO_4$ and concentrated to give a crude oil. The ligand **16** was obtained as a clear oil by Kugelrohr distillation (0.58 g, 2.74 mmol, 75% yield): $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.30−1.88 (m, 10 H), 2.00−2.20 (m, 4 H), 2.23 (s, 3 H), 2.48 (m, 1 H), 2.74 (q, 1 H), 3.02 (t, 1 H), 3.11 (m, 1 H), 3.35 (q, 1 H), 3.55 (q, 1 H), 3.50 (bs, 1 H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 21.72, 23.42, 27.59, 30.51, 32.46, 40.28, 51.63, 54.02, 57.12, 62.38, 64.24, 64.86. Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.92; H, 11.32; N, 13.20. Found: C, 67.56; H, 11.42; N, 13.16.

**Synthesis of (2*R*,2′*S*)-2-(Hydroxymethyl)-1-[(1-methylpyrrolidin-2′-yl)methyl]pyrrolidine (17).** To a solution of **4b** (1.79 g, 11.2 mmol) in $CHCl_3$ (30 mL) were added solid DCC (2.31 g, 11.2 mmol) and HOBT (1.51 g, 11.2 mmol). The suspension was stirred for 10 min, and then a solution of **7** (1.85 g, 11.2 mmol) and triethylamine (3 mL) in 20 mL of $CHCl_3$ was added and the mixture stirred for 10 h. The solvents were removed in vacuo, 100 mL of EtOAc was added, and the mixture was stirred. The solids were removed by filtration, and the EtOAc solution was washed with 10% citric acid (50 mL) and 10% $NaHCO_3$ (50 mL) and was dried over $Na_2SO_4$. The solvents were removed in vacuo to provide the amide **12** as a pale yellow oil (2.60 g, 63% crude yield) which was used immediately in the next step.

To a stirred suspension of excess $LiAlH_4$ (2.0 g) cooled to 0 °C in 30 mL of THF was added dropwise a solution of **12** in 10

(24) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.

mL of THF. The reaction mixture was stirred for 10 min at room temperature and then was heated at reflux for 3 h. The mixture was cooled to 0 °C and was carefully quenched by slow addition of EtOAc (10 mL). A slurry of $Na_2SO_4/H_2O$ was added while the reaction mixture was vigorously mixed until all the salts appeared white. The solvent was decanted, and the remaining white solid was washed several times with $Et_2O$. The $Et_2O$ layers were concentrated to 100 mL and were extracted with 2 N HCl (100 mL). The water layers were washed once with $Et_2O$ and then basified with NaOH and extracted with $Et_2O$. Removal of solvent in vacuo provided a pale yellow oil which was purified by two Kugelrohr distillations (95 °C, 0.4 torr) to provide **17** as a clear oil (0.7986 g, 4.03 mmol, 57%): $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.30–1.51 (m, 2 H), 1.65–1.95 (m, 6 H), 2.18–2.53 (m, 4 H), overlapping with 2.46 (s, 3 H), 2.72 (m, 1 H), 2.84 (m, 1 H), 3.02 (m, 1 H), 3.15 (m, 1 H0, 3.53 (m, 1 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 23.8, 24.5, 27.6, 29.7, 43.4, 55,5, 57.4, 61.9, 64.9, 65.7, 66.2. Anal. Calcd for $C_{11}H_{22}N_2O$: C, 66.63; H, 11.18; N, 14.13. Found: C, 66.78; H, 11.42; N, 14.12.

**Synthesis of (2*S*,2′*S*)-2-(2-Hydroxyethyl)-1-[(1-methylpyrrolidin-2′-yl)methyl]pyrrolidine (18).** *N*-(Ethoxycarbonyl)-L-proline (**4c**) (0.748 g, 4.00 mmol) was dissolved in chloroform (24 mL). Dicyclohexylcarbodiimide (DCC) (0.824 g, 4.00 mmol) and 1-hydroxybenzotriazole (HOBT) (0.540 g, 4.00 mmol) were added, and the mixture was stirred for 5 min. Then **8** (0.772 g, 4.00 mmol)) and triethylamine (0.55 mL) were added, and stirring was continued for 18 h until the starting material was consumed. The insoluble solids were removed by filtration, the filtrate was washed with water (2 × 10 mL), and the organic solvents were evaporated in vacuo. The residue was dissolved in ether (30 mL), and additional insoluble material was removed. The filtrate was dried over $MgSO_4$, and the solvents were removed in vacuo to provide a yellow-brown oil, which was purified by chromatography (silica, 1:9 methanol:methylene chloride) to provide the amide **13** as a pale yellow oil which was used in the next step. (0.857 g, 2.62 mmol, 62% yield): $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.17 (m, 6 H), 1.82–2.04 (m, 8 H), 2.40, 2.70 (m, 2 H), 3.40 (m, 4 H), 4.08 (m, 4 H), 4.20 (m, 2 H).

A THF (10 mL) solution of **13** (0.857 g, 2.62 mmol) was added to a stirred suspension of $LiAlH_4$ (0.6 g) in THF (30 mL) at 0 °C, and then the reaction mixture was heated to reflux for 5 h. The reaction was cooled to room temperature, and aqueous sodium sulfate was carefully added dropwise to the reaction mixture. The resulting precipitate was removed by filtration, and the filtrate was dried over $MgSO_4$ and concentrated. The product **18** was obtained as a clear oil by Kugelrohr distillation (0.460 g, 2.16 mmol, 86% yield): $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 1.32 (m, 1 H), 1.52–1.82 (m, 5 H), 2.05 (m, 2 H), 2.20 (s, 3 H), 2.58 (m, 2 H), 2.92 (t, 1 H), 3.03 (m, 1 H), 3.53 (m, 1 H), 3.82 (t, 1 H), 5.70 (bs, 1 H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 22.21, 23.56, 27.66, 30.06, 31.87, 41.13, 54.17, 57.42, 59.76, 59.87, 64.54, 64.67. Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.92; H, 11.32; N, 13.20. Found: C, 67.90; H, 11.39; N, 13.09.

**Synthesis of (2*R*,2′*S*)-2-(Diphenylhydroxymethyl)-1-[(1-methylpyrrolidin-2′-yl)methyl]pyrrolidine (19).** To a solution of **4b** (1.92 g, 7.71 mmol) in $CHCl_3$ (15 mL) were added solid DCC (1.58 g, 7.71 mmol) and HOBT (1.04 g, 7.71 mmol). The suspension was stirred for 10 min, and then a solution of **9** (1.95 g, 7.71 mmol) in 20 mL $CHCl_3$ was added and the reaction stirred overnight. The solvents were removed in vacuo, 100 mL of EtOAc was added, and the mixture was stirred. The solids were filtered, and the EtOAc solution was washed with 10% citric acid (50 mL) and 10% $NaHCO_3$ (50 mL) and dried over $Na_2SO_4$. The solvents were removed in vacuo to provide the amide **14** as a pale yellow oil (2.43 g, 5.03 mmol, 65% crude yield) which was used immediately in the next step.

To a stirred suspension of excess $LiAlH_4$ (1.1 g) cooled to 0 °C in 30 mL THF was added dropwise a solution of **14** in 10 mL of THF. The reaction mixture was stirred for 10 min at room temperature and then was heated at reflux for 3 h. The mixture was cooled to 0 °C and was carefully quenched by slow addition of EtOAc (10 mL). A slurry of $Na_2SO_4/H_2O$ was added while the reaction mixture was vigorously mixed until all the salts appeared white. The solvent was decanted, and the remaining white solid was washed several times with $Et_2O$. The $Et_2O$ layers were concentrated to 100 mL and were extracted with 2 N HCl (100 mL). The water layers were washed once with $Et_2O$ and then basified with NaOH and extracted with $Et_2O$. Removal of the solvents in vacuo provided a pale yellow solid which was purified by recrystallization from a minimal amount of hexanes to provide **19** as a white solid: mp 76–78 °C (1.11 g, 3.17 mmol, 63%); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.5–2.1 (several m, 11 H), overlapping with 1.74 (s, 3 H), 2.43–2.59 (m, 2 H), 2.88 (m, 1 H), 3.28 (m, 1 H), 3.95 (m, 1 H), 5.09 (s, 1 H), 7.17–7.14 (m, 1 H), 7.22–7.27 (m, 4 H), 7.51 (d, $J$ = 7.6 Hz, 2 H), 7.66 (d, $J$ = 7.7 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 22.4, 24.8, 29.4, 31.0, 40.9, 56.8, 57.3, 61.5, 66.4, 72.1, 77.8, 125.5, 125.87, 125.98, 126.2, 127.9, 128.2, 147.0, 148.2. Anal. Calcd for $C_{23}H_{30}N_2O$: C, 78.82; H, 8.63; N, 7.99. Found: C, 78.80; H, 8.45; N, 8.14.

**Representative Preparation of Bispidine Ligands 35–39: Preparation of (*S*)-3-Methyl-7-(1′-cyclohexylethyl)-3,7-diazabicyclo[3.3.1]nonane (36).** A mixture of (*S*)-cyclohexylethyl-amine (**32**) (1.60 g, 12.6 mmol), paraformaldehyde (1.13 g, 37.7 mmol), acetic acid (0.75 mL, 12.6 mmol), and 1-methyl-4-piperidone (**29**) (1.42 g, 12.6 mmol) in EtOH (20 mL) was heated at reflux overnight. Upon cooling to room temperature the solvents were removed in vacuo. A solution of 50% KOH (20 mL) was added, and the mixture was extracted with 3 × 50 mL of *t*-BuOMe. The ether layers were dried ($Na_2SO_4$) and filtered, and the solvent was removed in vacuo. The brown oil obtained was purified by Kugelrohr distillation (180–200 °C, 0.25 Torr) to provide a crude yellow oil (1.62 g, 6.41 mmol, 50%).

The yellow oil obtained in the previous step was dissolved in BuOH (15 mL) and heated to 180 °C in a sealed glass tube for 12 h. The reaction mixture was cooled to room temperature, and the mixture was rinsed into a separatory funnel with *t*-BuOMe (~100 mL) and washed with brine. The organic layer was dried ($K_2CO_3$) and filtered, and the solvent was removed in vacuo to provide a yellow oil which was purified by Kugelrohr distillation (120–130 °C, 0.25 Torr) to provide **36** as a clear oil (0.7387 g, 3.10 mmol, 48%): $^1$H NMR ($CD_2Cl_2$, 300 MHz) $\delta$ 0.85 (d, $J$ = 6.6 Hz, 3 H, overlapping with multiplet, 2 H), 1.1–1.35 (overlapping m, 5 H total), 1.45–1.74 (overlapping m, 6 H total), 1.82 (m, 2 H), 2.13 (s, 3 H, with overlapping m, 1 H), 2.25–2.65 (overlapping m, 8 H); $^{13}$C NMR ($CD_2Cl_2$) $\delta$ 9.93, 26.89, 26.95, 27.36, 29.33, 29.49, 29.98, 30.84, 31.50, 41.20, 46.16, 51.31, 56.09, 59.47, 59.53, 64.04.

**(*S*)-3-Methyl-7-(1′-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane (35)** was prepared as a clear oil in 40% overall yield from **29** and **31**: $^1$H NMR ($CD_2Cl_2$, 300 MHz) $\delta$ 1.31 (d, $J$ = 6.9 Hz, 3 H), overlapping with 1.32–1.55 (m, 2 H), 1.87 (m, 2 H), 2.20 (s, 3 H), 2.26–2.38 (m, 4 H), 2.61–2.83 (m, 4 H), 3.35 (q, $J$ = 6.7 Hz, 1 H), 7.22 (m, 1 H), 7.32 (m, 2 H), 7.40 (m, 2 H); $^{13}$C NMR ($CD_2Cl_2$, 75 MHz) $\delta$ 19.34, 30.02, 30.10, 46.49, 54.66, 55.94, 59.81, 59.90, 64.97, 126.63, 128.05, 128.29, 145.75.

**(*S*)-3-Methyl-7-(1′-(hydroxymethyl)propyl)-3,7-diazabicyclo[3.3.1]nonane (37)** was prepared as a clear oil in 19% overall yield from **29** and **34**: $^1$H NMR ($CD_2Cl_2$) $\delta$ 0.92 (m, 3 H), 1.05 (m, 1 H), 1.41 (m, 1 H), 1.55 (m, 2 H), 1.72 (m, 2 H), 2.05 (2 overlapping singlets, total 3 H), 2.15 (m, 3 H), 2.49–2.95 (overlapping m, total 6 H), 3.10–3.31 (m, 3 H). Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.83; H, 11.65; N, 13.13.

**(*S*)-7-(1′-Phenylethyl)-3-oxa-7-azabicyclo[3.3.1]nonane (38)** was prepared as a clear oil in 18% overall yield from **30** and **32**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.37 (d, $J$ = 6.7 Hz, 3 H), 1.54–1.83 (m, 4 H), 2.26 (d, $J$ = 10.9 Hz, 1 H), 2.37 (d, $J$ = 10.8 Hz, 1 H), 2.87 (d, $J$ = 10.8 Hz, 1 H), 3.13 (d, $J$ = 10.6 Hz, 1 H), 3.34 (q, $J$ = 6.71 Hz, 1 H), 3.76–3.98 (m, 4 H), 7.27–7.42 (overlapping m, 5 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 19.69, 30.28, 30.44, 30.49, 54.54, 56.03, 65.30, 70.87, 71.02, 126.48, 127.59, 128.10, 145.17.

**(*S*, *S*)-3,7-Bis(1′-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane (39)** was prepared as a clear oil (solidified over time)

in 53% overall yield from **31**[25] and **32**: $^1$H NMR ($CDCl_3$) $\delta$ 1.33 (d, $J$ = 6.8 Hz, 6 H), 1.48 (broad peak, 2 H), 1.83 (broad peak, 2 H), 2.22 (m, 2 H), 2.32 (m, 2 H), 2.72 (d, $J$ = 10.5 Hz, 2 H), 2.95 (d, $J$ = 9.5 Hz, 2 H), 3.24 (q, $J$ = 6.6 Hz, 2 H), 7.21 (m, 2 H), 7.31 (m, 4 H), 7.49 (m, 4 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.98, 30.66, 31.61, 54.36, 65.76, 126.55, 127.93, 128.35, 147.02.

**General Procedure for the Screening of Chiral Ligands in the Asymmetric Deprotonation Reaction.** To an approximately 0.1 M solution of the ligand (1.25 equiv) in the appropriate solvent cooled to −78 °C in a dry ice/2-propanol bath was added *s*-BuLi in cyclohexane (1.25 equiv or 2.25 equiv if the ligand contained an acidic proton). The reaction mixture was stirred for 5−10 min, and then a solution of Boc-pyrrolidine (**1**) (1.0 equiv) in a minimal amount of $Et_2O$ was added by cannula. The reaction was allowed to stir for 4−6 h, and then TMSCl (1.5 equiv) was added and the reaction was allowed to warm slowly to room temperature overnight. The reaction was quenched by addition of 5% $H_3PO_4$, additional $Et_2O$ was added, and the layers were extracted. The $Et_2O$ layer was dried over $MgSO_4$ and filtered, and the solvents were removed in vacuo to provide a clear oil which was a mixture of starting material and product **3** by NMR spectral and gas chromatographic criteria. The yield was determined by isolation of product by flash chromatography (5−10% EtOAc/hexane). In cases where GC indicated only starting material or product present the approximate yield was estimated from the mass of the mixture of starting material and product and the GC ratio. The enantiomeric excess was determined either directly by CSP gas chromatography of **3** or by hydrolysis of **3** and conversion to the dinitrobenzamide (DNB) derivative. The enantiomeric excess of the DNB derivative was then determined by HPLC analysis of the derivative using a CSP HPLC column (S-N1N-naphthylleucine, 2.5% IPA/hexane, 1.0 mL/min). The results from the ligand screening reactions are summarized in Table 1. The reaction solvent was $Et_2O$ unless otherwise specified.

**Table 1**

| compd no. | % ee | GC conversn | % yield |
|---|---|---|---|
| **15** | 30 | 73 | |
| **16** | −20 | 48 | 47 |
| **17** | −64 | 83 | 55 |
| **18** | −4 | 69 | 56 |
| **19** | 0 | 42 | 26 |
| **20** | 72 | | 63 |
| **21** | 18 | 96 | 73 |
| **22** | 5 | 45 | 37 |
| **23** | 0 | 5 | |
| **24** | −16 | 96 | 86 |
| **25** | −24 | 84 | 68 |
| **26** | −28 | 70 | 50 |
| **28** | 61 | 10 | |
| **28** (*t*-BuOMe) | 55 | 5 | |
| **35** | −75 | | 51 |
| **35** (*t*-BuOMe) | −28 | 20 | |
| **35** (toluene) | −34 | 25 | |
| **36** (*t*-BuOMe) | −34 | 80 | |
| **37** | 27 | 16 | |
| **38** | −16 | 80 | |
| **38** (toluene) | −20 | 85 | |
| **39** | −1 | 20 | |
| **42** (*t*-BuOMe) | 0 | 8 | |
| **43** | −1 | 89 | |

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**Supporting Information Available:** Copies of the $^1$H NMR and $^{13}$C NMR spectra of compounds **35**, **36**, **38**, and **39** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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