Complex Induced Proximity Effects: Enantioselective Syntheses Based on Asymmetric Deprotonations of *N*-Boc-pyrrolidines

Peter Beak,* Shawn T. Kerrick, Shengde Wu, and Jingxi Chu

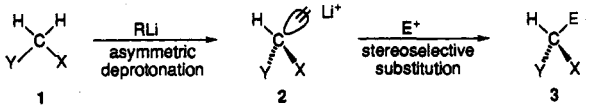
Contribution from the Department of Chemistry, University of Illinois at Urbana Champaign, Urbana, Illinois 61801

*Received October 20, 1993**

Abstract: Lithiation of *N*-Boc-pyrrolidine (**6**) with *sec*-butyllithium (*s*-BuLi)/(−)-sparteine (**14**) effects an asymmetric deprotonation to give (*S*)-2-lithio-*N*-Boc-pyrrolidine ((*S*)-**22**), which reacts with electrophiles to provide the 2-substituted *N*-Boc-pyrrolidines **7–11** and **13** in enantiomeric excesses which generally are >90%. In the lithiation–silylation of **6** the chiral ligand **15** gives **7** with a lower enantiomeric excess and chiral ligands **16** and **17** give **7** with lower and opposite enantiomeric excesses than that obtained with **14**. Diastereoselective amplification operates in a sequential lithiation–substitution sequence to provide the conversion of (*S*)-2-methyl-*N*-Boc-pyrrolidine ((*S*)-**10**) of 95% enantiomeric excess with *s*-BuLi/**14** to (*S*,*S*)-2,5-dimethyl-*N*-Boc-pyrrolidine ((*S*,*S*)-**19**) with >99% enantiomeric excess. Synthetic preparations of a useful chiral ligand, (*R*)-α,α-diphenyl-2-pyrrolidine ((*R*)-**20**), and a useful chiral auxillary, (*S*,*S*)-2,5-dimethylpyrrolidine hydrochloride ((*S*,*S*)-**21**), are reported. Reactions of racemic and enantioenriched 2-lithio-*N*-Boc-pyrrolidine and investigation of sequential lithiations–deuterations of **6** establish the reaction pathway to be asymmetric deprotonation rather than asymmetric substitution. A rationalization for the enantioselective deprotonation is provided.

Introduction

An attractive formal sequence for asymmetric synthesis is asymmetric deprotonation of a methylene group to give a configurationally stable carbanion which reacts stereoselectively with an electrophile.[1] The sequence is illustrated for the conversion of **1** to the enantioenriched organolithium intermediate **2** and the subsequent enantioenriched product **3**. With carbon electrophiles, convenient enantioselective carbon–carbon bond formations can be provided by this approach.



4, X = $OCONR_2$, Y = R
5, X = $NRCO_2t$-Bu, Y = R

Sparteine has been known to be an effective external chiral ligand for asymmetric induction for some time although the pathways for those reactions have been investigated only in recent years. Early work by Noyori established that *n*-butyllithium/(−)-sparteine gave an enantioselectivity of 30% in the conversion of **1** to **3** for a benzylic carbon (X = C_6H_5, Y = CH_3).[2] Raston has used this combination for asymmetric syntheses in his studies of metalations and structures of organolithium compounds.[3] Hoppe was the first to show that the use of *s*-butyllithium (*sec*-BuLi)/(−)-sparteine could provide products with very high enantioenrichments in a lithiation–substitution sequence.[4] Hoppe investigated the lithio oxygen dipole stabilized carbanions, generalized as **4**, and has developed elegant approaches for highly enantioselective preparations of a number of α-substituted alcohols and, by γ-substitution of allyl alcohol derivatives, β-substituted aldehydes.[4b,d] The initial cases involved deprotonations at sites additionally activated by adjacent unsaturation (e.g., **4**, X = $OCONR_2$, Y = $CH{=}CH_2$), but Hoppe has shown derivatives with single activation (e.g., **4**, X = $OCONR_2$, Y = CH_3) are reactive in the sequence.[4a] An X-ray structure for a derivative of **4** with (−)-sparteine has been determined by Hoppe and Boche.[4c] Quast had shown earlier that, with *s*-BuLi/(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane, *N*-methylmethyleneaziridine could be lithiated and silylated to give the trimethylsilyl product with 12% enantiomeric excess.[2,5]

We have communicated our observation that *s*-BuLi/(−)-sparteine can be used with *N*-Boc-pyrrolidine in an asymmetric deprotonation–electrophilic substitution sequence to provide highly enantioenriched 2-substituted *N*-Boc-pyrrolidines.[6,7] The intermediate in the sequence is considered to be an enantioenriched lithio nitrogen dipole stabilized carbanion represented as **5**. Acyclic examples of **5** have been reported from enantioenriched tin precursors by Pearson and by Chong, who have studied the configurational labilities of these systems.[8] In this report we detail our work on the use of the sequence of **1** to **3** for asymmetric syntheses of 2-substituted and 2,5-disubstituted *N*-Boc-pyrrolidines and support our claim that the pathway of the reaction

* Abstract published in *Advance ACS Abstracts,* March 15, 1994.

(1) For reviews and discussions of asymmetric deprotonations and of enantioselective carbon–carbon bond formation, see: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1. (b) Tomioka, K. *Synthesis* **1990**, 541. (c) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. For an early discussion of asymmetric inductions involving organolithium chelates, see: Whitney, T. P.; Langer, A. W. J. *ACS Advances in Chemistry Series*; American Chemical Society: Washington, DC, 1974; 270.

(2) Nozaki, H.; Aratani, T.; Torayta, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905.

(3) Papasergio, R. I.; Skelton, B. W.; Twiss, P.; White, A. H.; Raston, C. L. *J. Chem. Soc., Dalton Trans.* **1990**, 1161 and references cited therein.

(4) (a) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69. (b) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed.. Engl.* **1990**, *29*, 1422. (c) Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 321. (d) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394 and references cited therein.

(5) Quast, H.; Weise Velez, C. A. *Angew. Chem., Intl. Ed. Engl.* **1978**, *17*, 213.

(6) (−)-Sparteine has been investigated often as a chiral ligand. For examples see: (a) Kretchmer, R. A. *J. Org. Chem.* **1972**, *37*, 2744. (b) Okamoto, Y.; Suzuki, K.; Kitayama, T.; Yuki, H.; Kageyama, H.; Miki, K.; Tanaka, N.; Kasai, N. *J. Am. Chem. Soc.* **1982**, *104*, 4618. (c) Soai, K.; Machida, H.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1985**, 469. (d) Harvey, S.; Junk, P. C.; Raston, C. L.; Salem, G. *J. Org. Chem.* **1988**, *53*, 3134.

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

(8) (a) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546. (b) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. (c) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220.

0002-7863/94/1516-3231$04.50/0

Table 1. Enantioselective Substitutions of *N*-Boc-pyrrolidine (**6**) with *s*-BuLi/(−)-Sparteine

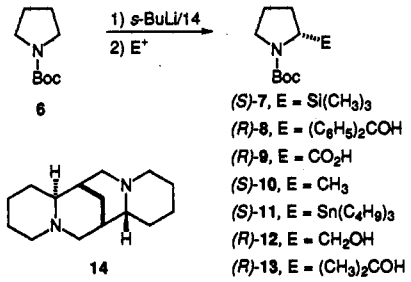
entry	product	E	procedure[a]	yield[b] (%)	ee[c] (%)
1	(*S*)-**7**	$Si(CH_3)_3$	A	71	94
2	(*S*)-**7**	$Si(CH_3)_3$	B	87	96
3	(*R*)-**8**	$(C_6H_5)_2COH$	A	45	83
4	(*R*)-**8**	$(C_6H_5)_2COH$	B	75	90
5	(*R*)-**9**	CO_2H	A	55	88
6	(*S*)-**10**	CH_3[d]	A	35	79
7	(*S*)-**10**	CH_3[e]	B	88	94
8	(*S*)-**11**	$Sn(n\text{-}C_4H_9)_3$	A	70	94
9	(*S*)-**11**	$Sn(n\text{-}C_4H_9)_3$	B	83	96
10	(*R*)-**12**	CH_2OH[f]	A	60	59
11	(*R*)-**13**	$(CH_3)_2COH$	A	12[g]	91
12	(*S*)-**6**-*d*	D	B	>99	*h*

[a] In procedure A *s*-BuLi is added to **6** and **14**. In procedure B a premixed and precooled mixture of *s*-BuLi/**14** is added to **6**. [b] The yields for entries 1, 3–6, 8, and 10–12 have not been optimized. [c] The error for the enantiomeric excess (ee) is judged to be ±5% unless otherwise noted. The methods for analyzing each substrate are described in the Experimental Section. [d] Methyl iodide was the electrophile. [e] Dimethyl sulfate was the electrophile. [f] Dimethylformamide was used as the electrophile, and the intermediate aldehyde was reduced, *in situ*, to the alcohol with sodium borohydride. [g] The low yield is attributed to competing enolization. [h] The enantiomeric excess of **6**-*d* was not determined and is estimated as 94% (*vide infra*).

provides enantioenriched **2** as an intermediate by an asymmetric deprotonation.[7,9,10]

Results and Discussion

Enantioselective Substitutions of *N*-Boc-pyrrolidine (6). Treatment of *N*-Boc-pyrrolidine (**6**) with *s*-BuLi/(−)-sparteine (**14**) at −78 °C for 4–6 h in diethyl ether followed by addition of an electrophile gives the enantioenriched 2-substituted pyrrolidines **7–13** generally in good yields and with high enantiomeric excesses



(*S*)-**7**, E = $Si(CH_3)_3$
(*R*)-**8**, E = $(C_6H_5)_2COH$
(*R*)-**9**, E = CO_2H
(*S*)-**10**, E = CH_3
(*S*)-**11**, E = $Sn(C_4H_9)_3$
(*R*)-**12**, E = CH_2OH
(*R*)-**13**, E = $(CH_3)_2COH$
(*S*)-**6**d, E = D

as shown in Table 1.[7,11-13] It is not necessary that the *s*-BuLi/(−)-sparteine be premixed. As shown in Table 1, addition of (−)-sparteine to the *N*-Boc-pyrrolidine prior to addition of the *s*-BuLi gives products with enantiomeric excesses only slightly degraded. The absolute configurations of (*R*)-**8**, (*R*)-**9**, and (*R*)-**12** were determined by comparison to authentic compounds. The absolute configuration of (*S*)-**10** was established by conversion to (*S*,*S*)-**19** (*vide infra*). The other assignments of configuration in the table are based on analogy to those secure assignments.

The enantiomeric excesses for the substitutions of **6** shown in Table 1 are high with the exception of entry 10. For that reaction the sequence of formylation and reduction to give (*R*)-**12** may allow epimerization of the intermediate aldehyde.[14] Low yields in substitutions of lithio nitrogen dipole stabilized carbanions on reactions with methyl iodide as shown in entry 6 are known and resolved by use of dimethyl sulfate as shown for (*S*)-**10** in entry 7. The low yield on reaction with deuterioacetone is provisionally attributed to competing enolization.[15]

A variety of methods were used to determine enantioenrichment, generally by comparisons of racemic and enantioenriched products.[11] Polarimetry was used for the characterization of all samples, but only for (*R*)-**12** was the enantiomeric excess assigned solely by optical rotation. Chiral stationary phase (CSP) GC was used for (*S*)-**7** and (*R*)-**13**. The (*S*)-2-methyl-Boc-pyrrolidine ((*S*)-**10**) was converted to the corresponding 3,5-dinitrobenzamide, and (*R*)-Boc-proline ((*R*)-**9**) was converted to the corresponding dimethylanilide according to the procedure of Pirkle and McCune and analyzed by CSP HPLC.[12] The enantiomeric excesses of (*R*)-**8**, (*S*)-**10**, and (*S*)-**11** were analyzed by cleavage of the Boc group with acid, base, or a bromoborane and conversion of the resulting secondary amines to the corresponding Mosher amides.[13]

The effect of variation of temperature, solvent, and equivalents of sparteine on the enantioselective substitution of **6** was investigated as shown in Table 2. The silyl adduct (*S*)-**7** was chosen as the product for this analysis because of good yield and ease of purification and determination of enantiomeric excess. The best conditions we have found for the preparation of (*S*)-**7** are listed in entry 1 of Table 2.

The lithiation reaction is not rapid and the enantioenrichment is not dependent on the lithiation time under these conditions, as shown by entry 2. An *in situ* lithiation with TMSCl did not proceed in useful yield. Warming the reaction mixture to −40 °C for 2 h decreases both the yield and enantiomeric excess, as shown in entries 3 and 4. Entry 5 shows that *i*-PrLi and *s*-BuLi behave similarly in effecting high enantiomeric excesses in the presence of (−)-sparteine. The observation that *i*-PrLi is as effective as *s*-BuLi in the sequence shows that an asymmetric carbon in the organolithium reagent is not required for the high enantioselectivity. The reactions in cyclopentane in entries 6 and 7 were partially heterogeneous and may indicate that hydrocarbon solvents give slightly higher yields at the expense of lower enantioenrichments. It is interesting to note that *n*-BuLi/**14** does not lithiate **6** and that *t*-BuLi/**14** in both Et_2O and cyclopentane gives a product with essentially no enantiomeric excess and somewhat lower yield, as shown in entries 8–10. Entries 8–13 can be taken to indicate that the combination of a secondary organolithium with Et_2O gives the highest yields and enantioenrichments. As shown in entry 11, lithiation in THF gave a number of compounds of which (*S*)-**7** was only a minor component. Entry 12 shows that *t*-BuOMe is effective as the solvent while entry 13 shows that reaction at −40 °C in pentane gives (*S*)-**7** in acceptable yield but with an eroded enantiomeric excess. The

(9) The chiral auxiliary approach has been developed for lithio nitrogen dipole stabilized carbanions from formamidines by Meyers and by Gawley: (a) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974. (b) Gawley, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265. (c) Gawley, R. E.; Rein, K.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002 and references cited therein.

(10) (a) For summaries of this methodology in racemic syntheses, see: (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. (b) Gawley, R. E.; Rein, K. In *Comprehensive Organic Chemistry*; Trost, B., Ed.; Pergamon Press: Oxford, England, 1991; Vol. 1, p 459, Vol. 3, p 65. (c) Hart, D. J. In *Alkaloids; Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1988: Vol. 6, p 227. (d) Highsmith, T. K.; Meyers, A. I. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1990; Vol. I, p 94.

(11) The racemic products were prepared using *s*-BuLi/TMEDA as the base, as previously described. Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

(12) Pirkle, W. H.; McCune, J. E. *J. Chromatogr.* **1989**, *479*, 419.

(13) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549. The enantiomeric purity of the Mosher acid chloride was determined by reaction of a small sample with enantiomerically pure (*S*)-2-methylbenzylamine and subsequent GC analysis of the resulting Mosher amide, which gave a de of 99.6%. Since the same amide, synthesized from a racemic sample of 2-methylbenzylamine, showed a 0% de by the same method of analysis, the ee of the Mosher acid chloride was assigned as 99.6%. (*S*)-2-Methylbenzylamine (Aldrich) was purified to constant optical rotation according to the method of Ault: Ault, A. *Org. Synth.* **1973**, *5*, 932.

(14) Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016.

(15) Reaction with acetone-d_6 gave (R)-**13**-d_6 in 12% yield with an ee of 96% along with (*S*)-**6**-*d* in 74% yield, which was 94% d_1. While the formation of **6**-*d* is consistent with enolization, the yield of **13**-d_6 should have been higher. The acetone-d_6 was not dried and may contain deuterium oxide, a possibility which compromises these results.

Table 2. Effect of Experimental Conditions on the Yields and Enantioselectivities of Formation of (*S*)-2-(Trimethylsilyl)-*N*-Boc-pyrrolidine ((*S*)-**7**) from *N*-Boc-pyrrolidine (**6**) with RLi/(−)-Sparteine

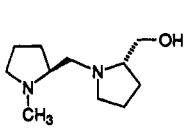
entry	RLi	solvent	conditions[a]	yield (%)	ee[b] (%)
1	*s*-BuLi	Et_2O		87	96
2	*s*-BuLi	Et_2O	−78 °C, 1 h	40	94
3	*s*-BuLi	Et_2O	*in situ* TMSCl[c]	17	84
4	*s*-BuLi	Et_2O	−40 °C, 2 h	54	63
5	*i*-PrLi	Et_2O		60	96
6	*i*-PrLi	cyclopentane		86	79
7	*i*-PrLi	cyclopentane	normal + 2 equiv of Et_2O	77	76
8	*n*-BuLi	Et_2O	−40 °C, 4 h	0	
9	*t*-BuLi	Et_2O		52	−6
10	*t*-BuLi	cyclopentane		32	0
11	*s*-BuLi	THF		<10[d]	
12	*s*-BuLi	*t*-BuOMe		56[e]	>90[f]
13	*s*-BuLi	pentane	−40 °C, 4 h	85[e]	65[f]
14	*s*-BuLi	Et_2O	0.25 equiv of **14**	33	64
15	*s*-BuLi	Et_2O	0.50 equiv of **14**	48	78
16	*s*-BuLi	Et_2O	0.1 equiv of **14**, 0.9 equiv of TMEDA	65	−3
17	*s*-BuLi	Et_2O	2.0 equiv of *s*-BuLi/**14**	60[g]	88
18	*s*-BuLi	Et_2O	3.0 equiv of *s*-BuLi/**14**	62[g]	89
19	*s*-BuLi	Et_2O	2.0 equiv of *s*-BuLi/**15**	51	84
20	*s*-BuLi	*t*-BuOMe	2.0 equiv of *s*-BuLi/**16**	18	−41[h]
21	*s*-BuLi	Et_2O	**17**	89	−30[h]

[a] Unless otherwise specified *s*-BuLi is mixed with 1.3 equiv of **14** and lithiation is carried out at −78 °C for 4 h. [b] The error for the enantiomeric excess (ee) is judged to be ±5%. [c] The TMSCl was added to the reaction mixture before the addition of *s*-BuLi. [d] Numerous products were observed, and (*S*)-**7** was indicated to be present by GC but was not isolated. [e] The product was not purified. [f] Error is ±10%. [g] The electrophile is benzophenone, and the product is (*R*)-**8**, which was not further purified. [h] Enriched in (*R*)-**7**.

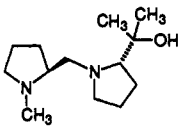
fact that high enantioselectivity is observed even when the sparteine is mixed with the substrate prior to addition of the *s*-BuLi establishes that the critical diastereomeric species for the enantioselective step is formed rapidly.

A reduced enantioenrichment when the number of equivalents of sparteine is less than 1 is shown in entries 14–16 of Table 2. Both the yield and enantiomeric excess of (*S*)-**7** increase as the number of equivalents of sparteine increases, up to 1 equiv. Entries 17–18 apply to the formation of (*R*)-**8** and show the enantioenrichment does not appear to increase with more equivalents of *s*-BuLi/(−)-sparteine.

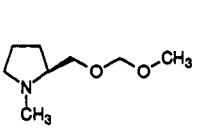
The results of our preliminary search for other chiral ligands which could be effective with *s*-BuLi in inducing enantioselectivity in the lithiation–substitution of **6** are shown for the ligands **15**–**17**



15



16



17

in entries 19–21.[16] The ligand **15** gives enantioenrichments approaching those observed with sparteine **14** but in a substantially reduced yield. Conversion of the primary alcohol of **15** to the tertiary alcohol of **16** provides a ligand which gives lower asymmetric induction with a sense of chirality opposite to that provided by **15**, albeit there is also a difference in solvent. The structurally simpler chiral ligand **17** also gives a low enantioenrichment and one which is opposite to that induced by **14** and **15**. The prospective availability of the enantiomer of **15**, by using the enantioselectivity in the present work, is an especially attractive feature which recommends further development of these and related ligands. The yields in Tables 1 and 2 have not been optimized, and the change in the sense of asymmetric induction between the experiments using **15** and **16** suggests more studies will be needed to develop the best conditions and substrates for this chemistry. Construction of encompassing hypotheses for the detailed pathways of this reaction clearly will require more information.

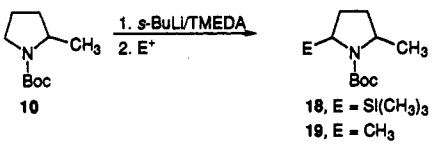
Table 3. Lithiations and Substitutions of (*S*)-2-Methyl-*N*-Boc-pyrrolidine ((*S*)-**10**, 95% ee) with *s*-BuLi/(−)-Sparteine

entry	E	*s*-BuLi /**14** (equiv)	temp (°C)	time (h)	yield[a] (%)	de[b] (%)	ee[c] (%)
1	CH_3	2.0	−78	6	33	80	>99
2	CH_3	4.0	−78	12	75	80	>99
3	CH_3	1.2	−40	5	91	66	
4	TMS	1.2	−78	6	20	80	
5	TMS	1.2	−60	5	67	73	
6	TMS	1.2	−40	5	81	66	

[a] The yields are based on GC except for entries 2 and 3, which are the yields of isolated product. [b] The diastereomeric excesses (de) were determined by GC and CSP GC after flash chromatography. [c] The enantioselectivities (ee) were determined by CSP HPLC analysis of a derivative.

Enantioselective Substitutions of (*S*)-2-Methyl-*N*-Boc-pyrrolidine ((*S*)-10). Enantioselective substitutions of **6** to give enantioenriched 2-substituted-*N*-Boc-pyrrolidine provide the first step in a convenient method for the preparation of highly enantioenriched 2,5-disubstituted pyrrolidines. This class of compounds, as represented by 2,5-dimethylpyrrolidine, has been exceptionally useful as C_2-chiral auxiliaries or ligands.[17] The two-step sequence also provides a nice example of the substantial amplification of enantioenrichment which can be achieved by diastereoselection.[1,18]

The influence of a 2-methyl substituent on the diastereoselectivity of the substitution was initially evaluated by lithiation–substitution of racemic 2-methyl-*N*-Boc-pyrrolidine (**10**) with *s*-BuLi/TMEDA to give the cis and trans isomers of 2-methyl-5-(trimethylsilyl)-*N*-Boc-pyrrolidine (**18**) and 2,5-dimethyl-*N*-



10

18, E = $Si(CH_3)_3$
19, E = CH_3

Boc-pyrrolidine (**19**). Reaction times of 4 h at −78 °C in Et_2O gave **18** in 68% yield and **19** in 50% yield with diastereoselectivities of *ca.* 20% assigned for **19** as favoring the cis isomer.[11] Comparison with the conditions of previous work also suggests that **10** undergoes lithiation more slowly than **6** by somewhat more than the expected statistical factor.[11]

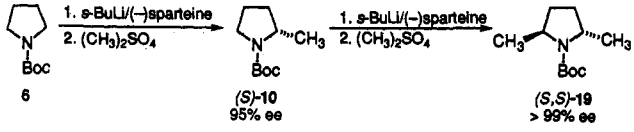
A series of experiments which provides information about the stereoselectivities of the lithiation–substitution with *s*-BuLi/(−)sparteine for (*S*)-**10** is summarized in Table 3. Entries 1 and 2 show that excess *s*-BuLi/**14** and lithiation times of several hours are needed for good yields. The diastereoselectivities of the experiments reported in the table may involve some erosion of configuration of the organolithium intermediate and may not provide accurate indications of the diastereoselectivities of the initial reactions. While further work on this point is needed, entries 3–6 suggest that diastereoselectivity erodes as the temperature increases. The best conditions we have found are shown in entry 2, where a reaction time of 12 h with 4.0 equiv of *s*-BuLi/(−)-sparteine gives a product which can be obtained

(16) The only study of which we are aware which uses a chiral ligand other than **14** to provide significant enantioenrichment in a deprotonation–substitution sequence is the lithiation–benzylation of a cyclohexyl imine which proceeds with 52% ee. Tomioka, K.; Shindo, M.; Koga, K. *Chem. Pharm. Bull.* **1989**, *37*, 1120.

(17) Whitsell, J. *Chem. Rev.* **1989**, *89* 1581.

(18) Schreiber, S. L.; Schreiber, T. S.; Smith D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. Wynberg, H. *Chimia* **1989**, 150. Rautenstrauch, V.; Megard, P.; Bourdin, B.; Furrer, A. *J. Am. Chem. Soc.* **1992**, *114*, 1418 and references cited therein.

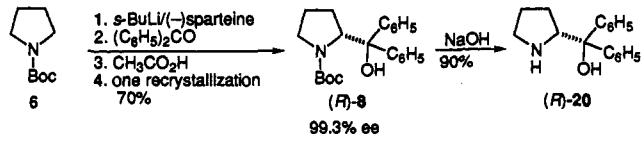
in 9:1 diastereoselectivity after chromatography. The major product (*S,S*)-**19** has an enantioenrichment of >99%. The enantiomeric excess was measured by CSP HPLC of the 3,5-dinitrobenzamide and the assignment of absolute configuration established by comparison with an authentic sample prepared as the Cbz derivative.[12,19] Thus, the first step of the sequence from **6** provides (*S*)-**10** with a 95% enantiomeric excess, while the second step from this material provides (*S,S*)-**19** with an enantiomeric excess of >99%.



The enantioenrichment provided in the sequence is an example of the amplification of enantioselectivity which can be achieved by diastereoselectivity.[18] Our results are consistent with substantial independence of the enantioselectivities in each step of the sequence. Thus the first step provides a 0.975:0.025 ratio of (*S*)-**10** and (*R*)-**10**. Operation of the same enantioselectivity in the second step would be expected to provide (*S,S*)-**10**/(*R,R*)-**10** in a 0.951:0.006 ratio which is >99% enantioenriched. In effect most of the (*R*)-**10** formed in the first step is preferentially removed in the second step by conversion to the (*S,R*)-**19**-diastereoisomer. This amplification makes the general use of this approach for highly enantioselective syntheses of chiral ligands from secondary amines very attractive.

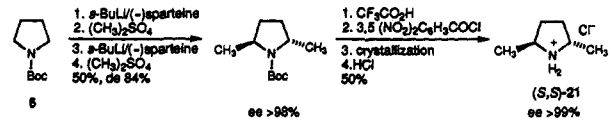
Synthetic Applications. To illustrate the synthetic utility of the methodology, syntheses of (*R*)-α,α-diphenyl-2-pyrrolidinemethanol ((*R*)-**20**), a useful chiral ligand, and of (*S,S*)-2,5-dimethylpyrrolidine ((*S,S*)-**21**), a widely used chiral auxillary, have been carried out.[19,20]

For the preparation of (*R*)-**20**, **6** was converted to the highly enantioenriched benzophenone adduct (*R*)-**8** by procedure B as described in Table 1. The crude solid was recrystallized once to



give (*R*)-**8** in 70% yield with 99.3% ee. Hydrolysis of the Boc group with sodium hydroxide gave (*R*)-**20** in 63% overall yield from **6** on an *ca.* 1-g scale. The overall yield and enantioenrichment of (*R*)-**20** for this synthesis compares favorably with a synthesis of (*S*)-**20** from (*R*)-proline which proceeds in 65% yield with >99% enantiomeric excess.[20] A similar alternative approach with a chiral formamidine auxillary to enantioenriched 2-substituted pyrrolidines uses a 3-pyrroline in a sequence of lithiation, electrophilic substitution, hydrolysis, which also removes the undesired 4-substituted isomer, and reduction of the double bond.[9a]

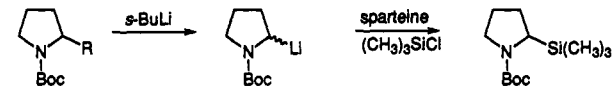
For the synthesis of (*S,S*)-**21**, two sequences of lithiation–methylation were used to convert **6** to (*S,S*)-**19**, which contained 8% (*R,S*)-**19** in 50% overall yield on an *ca.* 1-g scale. The synthesis was completed by removal of the Boc group, addition of the 3,5-dinitrobenzoyl group, and crystallization of the amide to give material with >99% diastereo- and enantioenrichment followed by hydrolysis and formation of the hydrochloride salt (*S,S*)-**21** in an overall yield of 25% from **6**.



These syntheses appear to offer a substantial advantage over previous methodology. Applications of this approach for syntheses of other, especially new, pyrrolidine based chiral ligands and chiral auxiliaries would be direct, efficient, and convenient. We believe that this methodology also should be explored for asymmetric syntheses of related substrates with a variety of chiral external ligands.

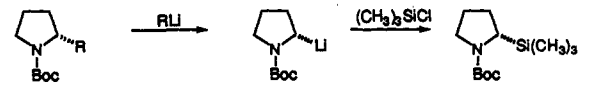
Pathway for the Enantioselective Substitution of 6. There are two limiting mechanisms which could account for these enantioselective substitutions of **6** and of (*S*)-**10**. One possibility is that a *s*-BuLi/(–)-sparteine complex effects asymmetric deprotonations of the *N*-Boc-pyrrolidines to provide highly enantiomerically enriched organolithium intermediates which are configurationally stable and react stereospecifically in electrophilic substitutions. This is the pathway generalized for **1** to **3** via **2** in which the enantiodetermining step is an asymmetric deprotonation. The other limiting possibility is that the deprotonations give racemic 2-lithio-*N*-Boc-pyrrolidines and that (–)-sparteine induces enantioselectivity in the reaction of the organolithium intermediate with the electrophile.[21] In essence the question is whether enantioenrichment is introduced in the first step by asymmetric deprotonation or in the second step by asymmetric substitution.

Two types of experiments have been carried out to differentiate the possibilities. Racemic 2-lithio-*N*-Boc-pyrrolidine (*R,S*)-**22**



was generated both by reaction of **6** with a deficient amount of *s*-BuLi and by tin lithium exchange of racemic **11**. To the racemic **22** at –78 °C was added TMSCl followed by sparteine. The product was found to be essentially racemic with enantiomeric excesses of –10% and 3%, respectively.[22] This failure of sparteine to induce asymmetry in racemic **22** is consistent with entry 9 of Table 2, which shows there is no enantioselectivity for the lithiation–substitution of **6** with *t*-BuLi/(–)-sparteine.

When enantioenriched 2-lithio-Boc-pyrrolidine ((*S*)-**22**), formed by tin lithium exchange from (*S*)-**11**, which had an enantiomeric excess of 96%, with *s*-BuLi, was allowed to react with TMSCl, (*S*)-**7** was formed in 15% yield with 93% enantiomeric excesses.



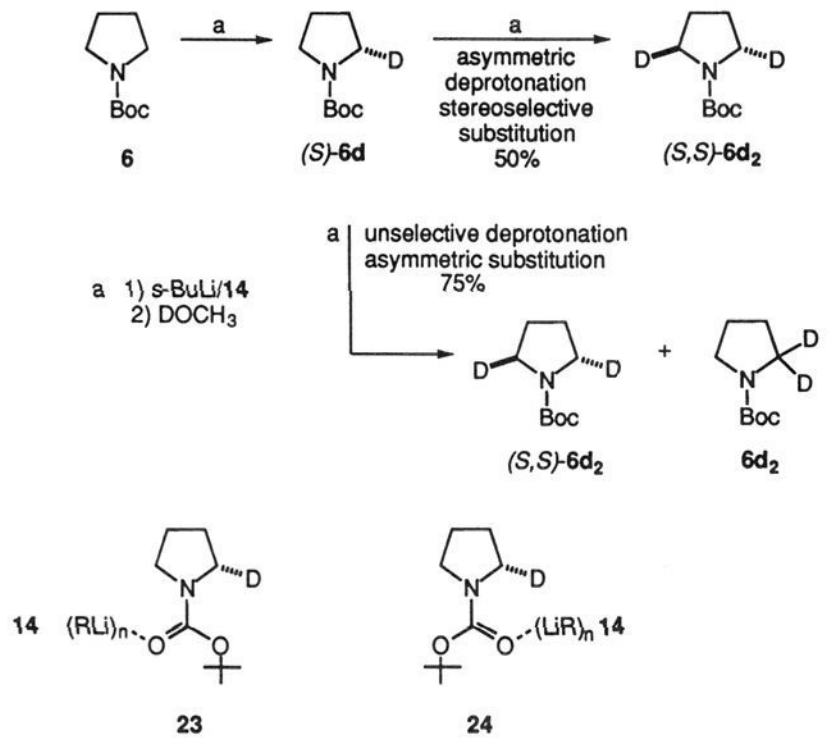
(19) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083. For alternative syntheses, see: Zwaagstra, M. E.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1993**, *10*, 2163. Kim, M. J.; Lee, S. *Syn. Lett.* **1993**, 767 and references cited therein.

(20) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 7925. Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, E. T. T.; Jones, J. J.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751. Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, 1475.

(21) For an example of asymmetric substitution, see: Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516 and references cited therein. These possibilities are not exclusive as both pathways could be operative in a given system. In the case of asymmetric substitution, enantioselectivity could be due to nonequilibrating diastereomeric complexes or to diastereomeric transition states for substitution.

(22) It was shown that the *s*-BuLi has been consumed in the reaction of **6** by establishing that addition of benzaldehyde to a portion of the reaction mixture did not give the addition product of *s*-BuLi to benzaldehyde. The low enantiomeric excess, which is opposite to that observed for the asymmetric deprotonation, observed in this experiment is taken to indicate a low level of asymmetric substitution.[21]

Scheme 1

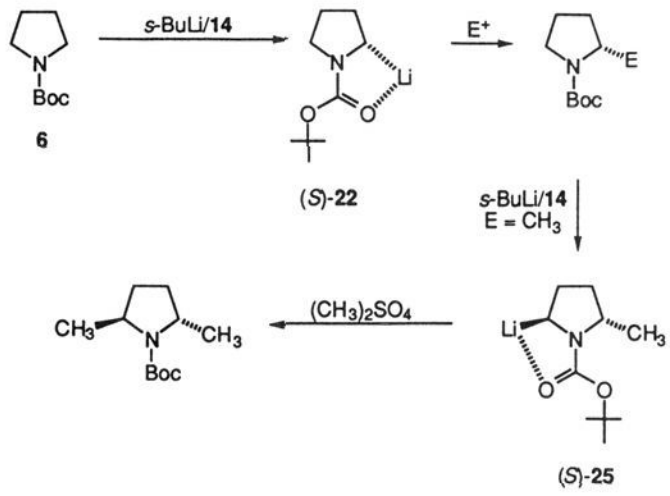


When the reaction of (*S*)-**11** was repeated with *s*-BuLi/TMEDA, the same product was obtained in 36% yield and an enantiomeric excess of 74%. These experiments establish that generation of enantioenriched 2-lithio-*N*-Boc-pyrrolidine does give a species which can maintain its configuration under these reaction conditions.[8,23]

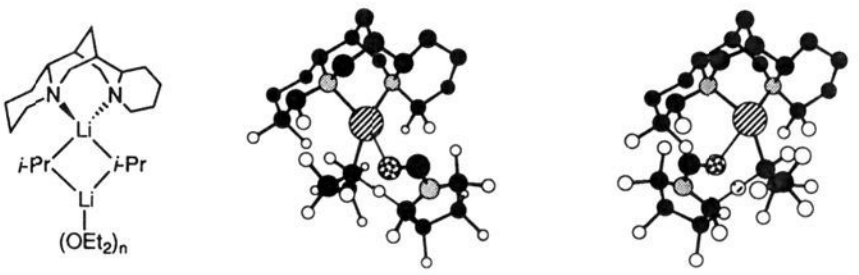
Analysis of the products from a sequence of two steps of lithiation–deuteration also allows distinction between the pathways. Scheme 1 illustrates a reaction which is 100% enantioselective, complete under the reaction conditions, and has a large isotope effect.[24,25] The asymmetric deprotonation pathway from *(S)*-**6**-*d* would give primarily *(S,S)*-**6**-d_2 and 50% deuterium incorporation, assuming there is restricted rotation about the carbon–nitrogen bond at –78 °C over the course of the reaction. On the other hand an unselective deprotonation of *(S,S)*-**6**-*d* followed by asymmetric substitution would give (*S,S*)-**6**-d_2 along with **6**-d_2 in an *ca.* 2:1 ratio with 75% deuteration under the same assumptions. In terms of the possible reaction intermediates, the complexes **23** and **24**, which are presumed to lead to the relevant transition states, would have equal populations and **23** would be expected to undergo deprotonation by either pathway whereas **24** would be deprotonated only if that step were not enantiospecific.

The products shown in the scheme are, as noted, calculated for a hypothetical case. A more complete analysis for the real case requires estimation of the actual composition of the products of the first step in Scheme 1. The initial lithiation–deuteration reaction gives *(S)*-**6**-*d* with an isotope incorporation of 98% d_1. If the pathway of asymmetric deprotonation is assumed to be 97% enantioselective, the average for procedure B in Table 1, a product composition of 95% (*S*)-**6**-*d*, 3% (*R*)-**6**-*d*, and 2% **6** can be assigned. With material of this composition used as the reactant for the second lithiation–deuteration, then the isotopic incorporation can be calculated if the primary isotope effect is large and the secondary isotope effect is negligible.[26] For an asymmetric deprotonation pathway, the predicted isotopic composition for deuteration of **6** is 51% d_2 and 49% d_1. For an unselective deprotonation the expectation for deuteration of **6** is 70% d_2 and 30% d_1. The experimental result is the reaction of *(S)*-**6**-*d* with *s*-BuLi/(–)-sparteine followed by methanol-*d*, which gives **6** which is 53% dideuterated and 47% monodeuterated with an experimental error of ±5%.

On the basis of the above results, the pathway for the highly enantioselective substitutions of the *N*-Boc-pyrrolidines reported in this work is asymmetric deprotonation to give a highly enantiomerically enriched configurationally stable organolithium intermediate which reacts stereoselectively in electrophilic substitution. The intermediates are (*S*)-**22** and (*S*)-**25** with the configurational assignments based on the assumption of retentive electrophilic substitutions.[5,8,11,23,27]



We have reported **26** as the solution structure of the (i-PrLi$_2$)/(–)-sparteine complex which is effective in the asymmetric deprotonation of **6**.[28] However, we have not been able to envision a transition structure for deprotonation of *N*-Boc-pyrrolidine which shows a significant advantage for removal of the *pro-R* hydrogen from **6** with a dimer structure. As a working hypothesis we suggest that the deprotonation proceeds through an i-PrLi/(–)-sparteine/*N*-Boc-pyrrolidine complex which involves a transition structure which can be represented as **27**, in which the *pro*



R hydrogen is being removed. This possibility appears preferable to **28**. Our rationalization of the failure of *tert*-butyllithium to effect asymmetric deprotonation is that replacement of the hydrogen of the isopropyl group of **26** by a methyl group, *i.e.* construction of a transition structure analogous to **26** with *tert*-butyllithium, shows a repulsive interaction with the methylene groups of the (–)-sparteine which prevents the formation of the necessary complex. It is clear that better understanding of the key features of the asymmetric deprotonation is needed for design of better ligands.

Summary

The present work provides methodology for convenient,

(23) Thus (*S*)-**22** appears to have greater configurational stability than related acyclic derivatives studied by Pearson and Chong.[8] For studies of related alkyl systems which show greater configurational stabilities, see: Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515. Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607.

(24) The validity of the assumptions of restricted rotation, the extent of reaction, and the role of complexes in the reactions will be the subject of future work. For a recent general discussion of the later issue in a different case, see: Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628 and references cited therein.

(25) Since the isotopic competition occurs intramolecularly presumably within an initially formed complex, the deprotonation step does not have to be the slow step for the isotope effect to be large. Resek, J. E.; Beak, P. *J. Am. Chem. Soc.*, in press.

(26) The normal isotope effect at –78 °C would be expected to be *ca.* 20. Melander, L.; Saunders, W., Jr. *Reaction Rates of Isotopic Molecules*; Wiley Interscience: New York, 1980. To the extent that the deuterium isotope effect is overestimated the ratio of d_2 to d_1, incorporation would be reduced. For citation of a large isotope effect in a related reaction, see: Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394.

(27) Retentive electrophilic substitutions appear to be the case for alkyl-substituted lithio dipole stabilized carbanions. In cases of analogous allyl or benzyl systems, inversion has been observed.[4]

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

efficient, and highly enantioselective syntheses of 2-substituted and 2,5-disubstituted-*N*-Boc-pyrrolidines from *N*-Boc-pyrrolidine with *s*-BuLi/(−)-sparteine in lithiation–substitution sequences. This approach can provide a wider variety of highly enantioenriched chiral ligands and chiral auxiliaries than is available from the chiral pool. Thus, there is opportunity for rapid testing of hypothesis and better design of chiral ligands as well as for empirical applications to specific enantioselective syntheses. The convenience and efficiency of the chiral ligand methodology appears to offer substantial advantage over chiral auxillary methodology for carbon–carbon bond formation. In the longer term, development of highly enantioselective carbon–carbon bond formations with a variety of organometallics and recoverable external ligands should see more general development and mechanistic analysis.

Experimental Section

General Methods. Materials. All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise indicated. Diethyl ether (Et_2O), *tert*-butyl methyl ether (*t*-BuOMe) and tetrahydrofuran (THF) were distilled from sodium/benzophenone under a nitrogen atmosphere. Hexane used for flash chromatography and MPLC was distilled from molecular sieves. Chloroform ($CHCl_3$), methylene chloride (CH_2Cl_2), (−)sparteine, and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) were distilled from calcium hydride under a nitrogen atmosphere. Dimethyl sulfate (Me_2SO_4) was distilled under vacuum. 3,5-Dinitrobenzoyl chloride was recrystallized from chloroform. Solutions of *s*-BuLi in cyclohexane and *n*-BuLi in hexane obtained from the Lithium Division of FMC Corporation were titrated according to the method of Suffert.[29]

General Reactions Conditions. A −78 °C bath refers to a mixture of dry ice in methanol, 2-propanol, or acetone. All reactions involving air-sensitive reagents were performed under nitrogen or argon using syringe–septum cap techniques. All glassware was oven- or flame-dried prior to use.

Workup and Purification. Brine refers to a saturated solution of sodium chloride. Flash chromatography was performed with Merck 50–200 μm silica gel. Medium pressure liquid chromatography (MPLC) was performed using an ISCO Model 273 fraction collector and an ISCO Model UA-5 absorbance/fluorescence monitor. Chromatographic columns, packed with Merck silica gel (32–63 mesh) and whose length and diameter depended on the amount of material and the difficulty of the separation, were used with mixtures of ethyl acetate and hexane. High-pressure liquid chromatography (HPLC) was performed using a Rainin HPXL pump system coupled to a Rheodyne 7125 syringe loading sample injector and a Knauer UV detector (254 nm). Preparative-scale HPLC was performed on a Dynamax 60-A 8 μm silica column (Rainin Instrument Co., Woburn, MA 01801, 25 cm × 21.4 mm i.d.). Bulb-to-bulb distillations were performed on a Büchi GKR-50 Kugelrohr apparatus. Boiling points refer to air-bath temperatures and are not necessarily an accurate measure of boiling points.

Mass Spectrometric Analysis. Electron impact mass spectra (EI/MS) were performed on Finnigan-MAT CH-5 and 311A spectrometers. Field ionization mass spectra (FI/MS) were performed on a Finnigan-731 spectrometer. Gas chromatography/mass spectrometry (GC/MS) was performed on a Hewlett Packard 5890 gas chromatograph coupled to a Hewlett Packard 5970B electron impact mass detector using a commercially available Ultra-1 capillary column (Hewlett Packard, Palo Alto, CA 94303, 30 m × 0.20 mm i.d., 0.33 μm film). The injector temperature was 250 °C, and the detector temperature was 300 °C. All isotope incorporations were obtained by FI because of the large M − 1 peak obtained by EI/MS and GC/MS.

Enantiomeric Purity Analyses. Enantiomeric purity assays were carried out with both racemic and optically active substrates. Optical rotations were obtained on a JASCO Model DIP-370 digital polarimeter (JASCO Incorporated, Easton, MD 21601) in a cylindrical glass cell (3.5 mm i.d. × 50 mm) with quartz windows. Chiral gas chromatography (GC) was performed on a Hewlett Packard 5790 gas chromatograph coupled to a Hewlett Packard 3390A or 3396A recorder using a commercially available Cyclodex-B column (J & W Scientific, Folsom, CA 95630, 30 m × 0.25 mm i.d., 0.25 μm film). The injector temperature was 230 °C, and the detector temperature was 300 °C. Chiral high-pressure liquid chromatography (HPLC) was performed on a 5-μm Rexchrom reversible, covalent Pirkle column (Regis Chemical Co., Morton Grove, IL 60053-9975, 1-800-8144, 25 cm × 4.6 mm i.d.) with a Hewlett Packard 3396A recorder used for quantitative analysis. The stationary phase was either D-phenylglycine, (*S*)-*N*-naphthylleucine, or (*R,R*)-β-Gem.

Preparation of (−)-Sparteine (14). To sparteine sulfate pentahydrate (50.0 g, 118.3 mmol) (Aldrich Chemical Company) in H_2O (100 mL) was added 40% NaOH (6.0 N, *ca.* 30 mL) dropwise over a period of 10 min until the aqueous solution tested basic by pH paper. The resulting mixture was extracted with ether (3 × 100 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give **14** as a light-yellow viscous oil (27.7 g, 100%). The compound was purified and dried by distillation from calcium hydride (98–102 °C 0.23 mm Hg) to give a colorless viscous oil (22.0 g, 79%).

Asymmetric Deprotonations of Boc-pyrrolidines and Boc-piperidines. Procedure A: Asymmetric Deprotonation of 6.[11] To (−)-sparteine (1.3 equiv) and **6** (1.0 equiv) in Et_2O (0.30 to 0.10 M) at −78 °C was added *s*-BuLi (1.3 equiv). The reaction mixture was stirred for 4–6 h at −78 °C, and then the electrophile (1.5 to 2.0 equiv) was added either directly or after precooling. Direct addition refers to the addition of the pure electrophile to the solution of 2-lithio-*N*-Boc-pyrrolidine, and precooled addition refers to the addition of a solution of the electrophile (0.50 M) which was at −78 °C to a solution of the 2-lithio-Boc-pyrrolidine. The mixture was then allowed to slowly warm to room temperature (3 h). Workup consisted of addition of water (5 mL), extraction of the aqueous layer with Et_2O (2 × 5 mL), extraction of the combined Et_2O extracts with 5% phosphoric acid (H_3PO_4) (5 mL), drying over anhydrous magnesium sulfate ($MgSO_4$), filtration, and concentration *in vacuo*.

Procedure B: Asymmetric Deprotonation of 6. To (−)-sparteine (1.3 equiv) in Et_2O (0.30 to 0.10 M) at −78 °C was added *s*-BuLi (1.3 equiv). The reaction mixture was stirred for 10 min at −78 °C and then was transferred to a solution of **6** (1.0 equiv) in Et_2O (0.30 to 0.10 M) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 4–6 h, and then the electrophile was added either directly or after precooling (*vide supra*). This mixture was then allowed to slowly warm to room temperature (3 h). Workup was as described above.

Preparation of (*S*)-7 Using Procedure A. Lithiation according to Procedure A of **6** (114.3 mg, 0.67 mmol) with direct addition of trimethylsilyl chloride (169 μL, 145.0 mg, 1.33 mmol) and purification by flash chromatography 1/25 (v/v) EtOAc/hexane gave (S)-**7** as a colorless oil (115 mg, 71%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.6–3.4 (bm, 1H, CHN), 3.35–3.10 (bm, 2H, CH_2N), 2.0 (bm, 1H, ring CH_2), 1.8 (bm, 3H, ring CH_2), 1.46 (bs, 9H, $C(CH_3)_3$), 0.05 (bs, 9H, $Si(CH_3)_3$); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 154.8, 154.5, 78.97, 78.14, 47.49, 46.89, 46.87, 46.43, 28.68, 28.40, 27.81, 25.92, 24.75, −2.26; $[\alpha]^{25}_D$ +69.4° (*c* 2.22, $CHCl_3$); GC/MS (EI, 70 eV) *m/z* (relative intensity) 243 (<1, M^+), 186 (35), 172 (61), 142 (89), 114 (16), 75 (23), 73 (100), 70 (52), 57 (65), 55 (15). The spectral data of (*S*)-**7** were identical to the racemic compound reported previously.[11] The enantiomeric purity of (*S*)-**7** was determined to be 94 ± 3% by CSP GC (95 °C isothermal). The *S*-enantiomer (major) had a retention time of 113 min, and the *R*-enantiomer (minor) had a retention time of 116 min.

Preparation of (*S*)-7 Using Procedure B. Lithiation according to procedure B of **6** (180,0 mg, 1.05 mmol) with precooled addition of trimethylsilyl chloride (200 μL, 171.3 mg, 1.58 mmol) and purification by flash chromatography (1/25 (v/v) EtOAc/hexane) gave (*S*)-**7** as a colorless oil (196.0 mg, 76%): $[\alpha]^{25}_D$ +71.8° (*c* 2.62, $CHCl_3$). The other spectral data of (*S*)-**7** were identical to those for the sample prepared by procedure A. The enantiomeric purity of (*S*)-**7** was determined to be 96 ± 3% by CSP GC (95 °C isothermal).

Preparative-Scale Preparation of (*S*)-7. To 1.2 equiv of (−)-sparteine (1.82 g, 1.78 mL, 7.75 mmol) in diethyl ether (15 mL) at −78 °C was added *s*-BuLi (1.18 M, 6.56 mL, 7.75 mmol). The reaction mixture was stirred for 30 min and then was transferred to a precooled solution of **6** (1.11 g, 6.46 mmol) in diethyl ether (10 mL) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 4 h, and 1.5 equiv of TMSCl (1.23 mL, 9.69 mmol) was added directly. The resulting mixture was allowed to slowly warm to room temperature overnight. Workup consisted of addition of H_2O (15 mL), extraction of the aqueous layer with diethyl ether (3 × 25 mL), washing the combined organic layers with 5% phosphoric acid (H_3PO_4) (25 mL), drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. The crude product was obtained as a slightly yellow oil and was purified by flash chromatography (1/20 (v/v) EtOAc/hexane) to give (*S*)-**7** (1.39 g, 87%): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.6–3.4 (bm, 1H, CHN), 3.3–3.1 (bm, 2H, CH_2N), 2.0 (bm, 1H, ring H), 1.8 (bm, 3H, ring H), 1.46 (bs, 9H, $C(CH_3)_3$), 0.05 (bs,

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

9H, $Si(CH_3)_3$). The enantiomeric purity of (*S*)-**7** was determined to be 96 ± 3% by CSP GC (95 °C isothermal). The major *S*-enantiomer had a retention time of 115 min, and the minor *R*-enantiomer had a retention time of 117 min.

Preparation of (*R*)-8 Using Procedure A. Lithiation according to procedure A of **6** (112.1 mg, 0.665 mmol) with addition of precooled benzophenone (167 mg, 0.916 mmol), after purification by flash chromatography (1/20 (v/v) EtOAc/hexane), gave (*R*)-**8** as a white solid (104 mg, 45%): mp 147–149 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.5–7.1 (m, 10H, Ar), 6.7–6.1 (bs, 1H, OH), 4.89 (dd, 1H, *J* = 3.6, 8.6 Hz, CH), 3.34 (m, 1H, NCH_2), 2.87 (bm, 1H, NCH_2), 2.05 (m, 1H, ring CH_2), 1.92 (m, 1H, ring CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.25 (m, 1H, ring CH_2), 0.78 (m, 1H, ring CH_2); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 157.8, 146.4, 143.7, 128.1, 128.0, 128.0, 127.9, 127.8, 127.6, 127.4, 127.3, 127.0, 126.9, 81.60, 80.54, 65.60, 47.75, 29.66, 28.28, 22.82; $[\alpha]^{23}_D$ +177.7° (*c* 2.16, $CHCl_3$); MS (EI, 70 eV) *m/z* (relative intensity) 280 (1), 236 (2), 183 (21), 170 (20), 114 (77), 105 (29), 77 (21), 70 (100), 57 (65). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.67; H, 7.81; N, 3.88. The enantiomeric purity of (*R*)-**8** was determined to be 83% by analytical HPLC of the *(R)*-Mosher amide[13] of *(R)*-**20** (*vide infra*). The optical rotation of *(R)*-**20** from this procedure was compared to the literature: $[\alpha]^{26}_D$ +48.2° (*c* 2.61, MeOH) [lit.[20] $[\alpha]^{21}_D$ +54.3° (*c* 0.261, MeOH)].

Preparation of (*R*)-8 Using Procedure B. Lithiation according to procedure B of **6** (278.7 mg, 1.63 mmol) with addition of precooled benzophenone (445 mg, 2.44 mmol), after purification by flash chromatography (1/10 (v/v) EtOAc/hexane), gave *(R)*-**8** as a white solid (431 mg, 75%): mp 146–148 °C; $[\alpha]^{23}_D$ +132.1° (*c* 1.97, $CHCl_3$). The other spectral data of *(R)*-**8** were identical to those of the sample from procedure A. The enantiomeric purity of *(R)*-**8** was determined to be 90% by analytical HPLC of the *(R)*-Mosher amide[13] of *(R)*-**20** (*vide infra*).

Preparation of (*R*)-9 Using Procedure A. Lithiation according to procedure A of **6** (237.3 mg, 1.38 mmol) with direct addition of carbon dioxide gas (bubbled through the reaction mixture for 30 min) and workup consisting of addition of water (5 mL), acidification of the aqueous to pH 2–3 (Congo paper) with 20% HCl (5 mL), extraction of the aqueous layer with Et_2O (3 × 5 mL), extraction of the combined Et_2O extracts with 5% NaOH (2 × 5 mL), acidification of the aqueous layer with 20% HCl (5 mL), extraction of the aqueous layer with Et_2O (2 × 5 mL), drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo* gave, after purification by flash chromatography with from 1/10 (v/v) EtOAc/hexane to 1/10 (v/v) MeOH/EtOAc, *(R)*-**9** as a white solid (163 mg, 55%): mp 130–132 °C; $[\alpha]^{25}_D$ +66.5° (*c* 7.29, $CHCl_3$). The melting point range, the optical rotation, and the other spectral data compare favorably to those for a sample of *(S)*-**9** synthesized from *(S)*-proline. The enantiomeric purity of *(R)*-**9** was determined to be 88% by CSP HPLC of the 3,5-dimethylanilide of *(R)*-**9**.

Enantiomeric Purity Assay of (*R*)-9. Conversion to the 3,5-dimethylanilide was carried out according to the procedure of Pirkle.[12] A typical procedure for the assay is described below. To **9** (27.2 mg, 0.126 mmol) in CH_2Cl_2 (5 mL) was added dicyclohexylcarbodiimide (26.1 mg, 0.126 mmol) and 3,5-dimethylaniline (17.3 μL, 16.8 mg, 0.139 mmol). The reaction mixture was stirred at room temperature for 12 h and then concentrated *in vacuo*. The resulting mixture was then dissolved in 1/1 (v/v) EtOAc/hexane and passed through a short plug of silica to give a mixture of the desired anilide and 3,5-dimethylaniline as a light-yellow oil. Purification by flash chromatography (1/20 (v/v) EtOAc/hexane) gave the desired anilide as a colorless oil (27.4 mg, 68%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.35 (bs, 0.8H, ArNH), 8.13 (bd, 0.2H, ArNH), 7.15 (m, 2H, Ar), 6.71 (bm, 1H, Ar), 4.46 (bm, 0.8H, CHN), 4.20 (bm, 0.2H, CHN), 3.30–3.75 (bm, 2H, CH_2N), 2.27 (s, 6H, $ArCH_3$), 2.20–1.60 (bm, 4H, ring CH_2), 1.49 (bs, 7.2H, $C(CH_3)_3$), 1.44 (bs, 1.8H, $C(CH_3)_3$); GC/MS (EI, 70 eV) *m/z* (relative intensity) 318 (30, M^+), 245 (6), 207 (5), 170 (22), 121 (18), 115 (10), 114 (94), 77 (7), 70 (100), 57 (44). The ^{1}H-NMR showed evidence for a 80/20 mixture of rotational isomers at room temperature.

The enantiomeric excess of the 3,5-dimethylanilide was determined by CSP HPLC (1/20 (v/v) 2-propanol/hexane) according to the procedure of Pirkle.[12] The chromatographic column used was a Pirkle/Regis, 250 mm × 4.6 mm i.d., column with a stationary phase of *(S)*-*N*-(3,5-dintrobenzoyl)leucine, a flow rate of 2 mL/min, and a detection wavelength of 254 nm. The *R*-enantiomer (major) had a retention time of 8.3 min, and the *S*-enantiomer (minor) had a retention time of 17.5 min.

Preparation of (*S*)-10 Using Procedure A. Lithiation according to procedure A of **6** (240 mg, 1.40 mmol) with direct addition of methyl iodide (113 μL, 259 mg, 1.82 mmol) and purification by flash chromatography (1/20 (v/v) EtOAc/hexane) gave *(S)*-**10** as a colorless oil (90 mg, 35%): $[\alpha]^{23}_D$ +18.8° (*c* 0.40, $CHCl_3$). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.34; H, 10.22; N, 7.31. Although a satisfactory analysis for carbon was not obtained, the other spectral data of *(S)*-**10** were identical to those of the sample prepared from procedure B. The enantiomeric purity of *(S)*-**10** was determined to be 79% by GC analysis of the (*R*)-Mosher amide.[13]

Preparation of (*S*)-10 Using Procedure B. Lithiation according to procedure B of **6** (1.12 g, 6.51 mmol) with direct addition of dimethyl sulfate (0.924 mL, 1.23 g, 9.77 mmol) and purification by flash chromatography (1/25 (v/v) EtOAc/hexane) gave (*S*)-**10** as a colorless oil (0.920 g, 76%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.85 (b, 1H, CHN), 3.35 (b, 2H, CH_2N), 2.05–1.65 (m, 4H, ring CH_2), 1.46 (bs, 9H, $C(CH_3)_3$), 1.16 (b, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 154.4, 78.6, 52.6, 46.0, 32.8, 28.4, 23.2, 20.4; $[\alpha]^{23}_D$ +31.2° (*c* 2.76, $CHCl_3$); GC/MS (EI, 70 eV) *m/z* (relative intensity) 185 (5, M^+), 170 (4), 130 (16), 128 (11), 114 (53), 112 (23), 70 (76), 69 (17), 57 (100), 56 (17). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.82; H, 10.37; N, 7.64. The enantiomeric purity of *(S)*-**10** was determined to be 95% by GC analysis of the (*R*)-Mosher amide.[13]

Gram-Scale Preparation of (*S*)-10. To 1.2 equiv of (–)-sparteine (3.47 g, 3.40 mL, 14.8 mmol) in diethyl ether (20 mL) at –78 °C was added *s*-BuLi (1.08 M, 13.7 mL, 14.8 mmol). The reaction mixture was stirred for 30 min and then was transferred to a precooled solution of **6** (2.12 g, 12.4 mmol) in diethyl ether (15 mL) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 4 h, and then the electrophile (1.5 equiv of Me_2SO_4 (1.76 mL, 18.6 mmol)) was added directly. The resulting mixture was allowed to slowly warm to room temperature overnight. Workup consisted of addition of H_2O (25 mL), extraction of the aqueous layer with diethyl ether (3 × 30 mL), washing the combined organic layers with 5% phosphoric acid (H_3PO_4) (40 mL), drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. The crude product was obtained as a slightly yellow oil, which was purified by flash chromatography (1/25 (v/v) EtOAc/hexane) to give (*S*)-**10** (2.02 g, 88%): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.85 (b, 1H, CHN), 3.30 (m, 2H, CH_2N), 2.05 ~ 1.70 (m, 4H, ring H), 1.41 (s, 9H, $C(CH_3)_3$), 1.10 (d, 3H, CH_3). The enantiomeric purity of *(S)*-**10** was determined to be 94% by GC analysis of the Mosher amide of *(S)*-**10** (150 °C isothermal) and 95% by CSP HPLC analysis of the 3,5-dinitrobenzoyl derivative on a Pirkle column packed with (*S*)-*N*-naphthylleucine.

Preparation of (*S*)-11 Using Procedure A. Lithiation according to procedure A of **6** (196 mg, 1.73 mmol) with direct addition of tri-*n*-butyltin chloride (610 μL, 732 mg, 2.25 mmol) and purification by flash chromatography with 1/200 (v/v) EtOAc/hexane gave *(S)*-**11** as a colorless oil (557 mg, 70%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.72 (m, 0.3H, CHN), 3.42–3.27 (m, 1.7H, CHN and CH_2N), 3.18 (m, 1H, CH_2N), 2.26–2.04 (m, 1H, ring CH_2), 2.0–1.7 (m, 3H, ring CH_2), 1.55–1.40 (m, 6H, CH_2), 1.48 (s, 2.7H, $C(CH_3)_3$), 1.44 (s, 6.3H, $C(CH_3)_3$), 1.30 (m, 6H, CH_2), 0.87 (m, 15H, CH_2 and CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 153.1 (major rotational isomer), 152.9 (minor rotational isomer), 78.28 (minor), 77.34 (major), 46.30 (minor), 45.61 (major), 45.32 (major), 45.04 (minor), 29.38 (major), 28.38 (minor), 28.26 (major), 28.18 (minor), 28.13 (minor), 27.74 (minor), 27.61 (major), 27.04 (minor); $[\alpha]^{23}_D$ +132.2° (*c* 2.92, $CHCl_3$); MS (EI, 70 eV) *m/z* (relative intensity) 348 (3), 235 (10), 177 (2), 130 (26), 112 (34), 86 (29), 84 (6), 69 (11), 57 (100), 56 (12). Anal. Calcd for $C_{21}H_{43}NO_2Sn$: C, 54.80; H, 9.42; N, 3.04; Sn, 25.79. Found: C, 54.87; H, 9.39; N, 2.98; Sn, 25.89. The ^{1}H-NMR and ^{13}C-NMR showed evidence of a 70/30 mixture of rotational isomers at room temperature. The enantiomeric purity of *(S)*-**11** was determined to be 94% by analytical HPLC analysis of the *(R)*-Mosher amide[13] of Boc-deprotected *(S)*-**11**.

Preparation of (*S*)-11 Using Procedure B. Lithiation according to procedure B of **6** (410 mg, 2.39 mmol) with direct addition of tri-*n*-butyltin chloride (909 μL, 1.09 g, 3.35 mmol) and purification by flash chromatography with 1/200 (v/v) EtOAc/hexane gave *(S)*-**11** as a colorless oil (915 mg, 83%). Anal. Calcd for $C_{21}H_{43}NO_2Sn$: C, 54.80; H, 9.42; N, 3.04; Sn, 25.79. Found: C, 54.88; H, 9.41; N, 3.01; Sn, 25.62. The other spectral data of *(S)*-**11** were identical to those of the sample from procedure A. The enantiomeric purity of *(S)*-**11** was determined to be 96% by analytical HPLC analysis of the *(R)*-Mosher amide[13] of Boc-deprotected *(S)*-**11**.

Preparation of (*R*)-12 Using Procedure A. Lithiation according to procedure A of **6** (325 mg, 1.90 mmol) with precooled addition of DMF (294 μL, 278 mg, 3.80 mmol) was followed by addition of acetic acid

(215 μL, 228 mg, 3.80 mmol), and the reaction mixture was allowed to slowly warm to 0 °C before excess sodium borohydride (1.0 g) was slowly added. Workup consisted of addition of water (5 mL), extraction of the aqueous layer with Et_2O (2 × 5 mL), extraction of the combined Et_2O extracts with 5% phosphoric acid (H_3PO_4) (5 mL), drying over anhydrous magnesium sulfate ($MgSO_4$), filtration, and concentration *in vacuo*. Purification by flash chromatography with 1/5 (v/v) EtOAc/hexane gave *(R)*-**12** as a colorless oil (228 mg, 60%): ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 5.0 (s, 0.7H, OH), 4.2 (s, 0.3H, OH), 4.0–3.8 (bm, 1H, NCH), 3.7–3.5 (m, 2H, CH_2O), 3.45–3.25 (m, 2H, NCH_2), 2.05–1.6 (m, 4H, ring CH_2), 1.46 (s, 9H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 156.8 (major rotational isomer), 154 (minor rotational isomer), 79.94 (major), 79.67 (minor), 67.04 (major), 64.17 (minor), 59.87 (major), 58.62 (minor), 47.33 (major), 46.63 (minor), 28.93 (minor), 28.40 (major), 28.27 (major), 27.84 (minor), 23.83 (major), 22.99 (minor); $[\alpha]^{29}_D$ +27.91° (*c* 3.14, $CHCl_3$); MS (EI, 70 eV) *m/z* (relative intensity) 201 (2, M^+), 170 (30), 128 (20), 114 (84), 100 (3), 84 (5), 70 (100), 57 (91), 56 (17), 55 (11). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.72; H, 9.56; N, 6.90. The ^{1}H-NMR and ^{13}C-NMR showed evidence of an *ca.* 70/30 mixture of rotational isomers at room temperature. The enantiomeric purity of *(R)*-**12** was determined to be 59% by comparison of the optical rotation to that of a sample of *(S)*-**12** synthesized from *(S)*-proline *(vide infra)*.

Preparation of (*R*)-13 Using Procedure A. Lithiation according to procedure A of **6** (237 mg, 1.38 mmol) with addition of precooled acetone (132 μL, 104 mg, 1.80 mmol) followed by addition of acetic acid (110 μL, 116 mg, 1.93 mmol) gave, after purification by flash chromatography with 1/5 (v/v) EtOAc/hexane, *(R)*-**13** as a white solid (20 mg, 12%): mp 74–75 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.99 (bs, 1H, OH), 3.87 (t, 1H, *J* = 7.3 Hz, NCH), 3.67 (b, 1H, NCH_2), 3.18 (m, 1H, NCH_2), 2.07 (m, 1H, ring CH_2), 1.85 (m, 1H, ring CH_2), 1.75–1.60 (m, 2H, ring CH_2), 1.48 (s, 9H, $C(CH_3)_3$), 1.17 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 157.7, 80.38, 73.56, 67.27, 48.23, 29.07, 28.32, 27.66, 24.17, 23.09; MS (EI, 70 eV) *m/z* (relative intensity) 171 (7), 156 (11), 115 (28), 114 (100), 70 (95), 69 (9), 59 (29), 57 (57), 56 (7). Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.85; H, 10.09; N, 5.98. The enantiomeric purity of *(R)*-**13** was determined to be 91% by CSP GC (130 °C isothermal). The *R*-enantiomer (major) had a retention time of 61 min, and the *S*-enantiomer (minor) had a retention time of 63 min.

Preparation of (*S*)-6-*d* Using Procedure B. Lithiation according to procedure B of **6** (820 mg, 4.79 mmol) with direct addition of deuterated methanol (389 μL, 317 mg, 9.58 mmol), after concentration *in vacuo*, gave *(S)*-**6**-*d* as a colorless oil (820 mg, 100%). The spectral data for *(S)*-**6**-*d* were identical to those of the sample prepared previously. Analysis by FI/MS showed an isotope incorporation of 98% d_1.

Preparation of Racemic 13. Lithiation according to the above procedure of **6** (227 mg, 1.33 mmol) with inverse addition of acetone (126 μL, 100 mg, 1.72 mmol) followed by addition of acetic acid (106 μL, 111 mg, 1.86 mmol) gave, after purification by flash chromatography with 1/5 (v/v) EtOAc/hexane, **13** as a white solid (64 mg, 20%): mp 74–75 °C. The spectral data for **13** were the same as those reported above for *(R)*-**13**.

Preparation of (*R*)-7 for the Experiments in Table 2. To (–)-sparteine (1.3 equiv) in the appropriate solvent (0.10 M) at –78 °C was added RLi (1.3 equiv). The reaction mixture was stirred for 15 min at –78 °C and then was transferred to a solution of **6** (1.0 equiv) in the same solvent (0.25 M) at –78 °C. The resulting reaction mixture was stirred under the conditions described in Table 2, and then trimethylsilyl chloride (1.5 equiv) was added. This mixture was then allowed to slowly warm to room temperature (*ca.* 3 h). Workup consisted of addition of water (10 mL), extraction of the aqueous layer with Et_2O (2 × 10 mL), extraction of the combined Et_2O extracts with 5% H_3PO_4 (5 mL), drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. Purification by flash chromatography (4% EtOAc/hexane) gave *(R)*-**7** as a colorless oil. The enantiomeric purity of this sample was determined by CSP GC (95 °C isothermal).

Preparation of (*S,S*)-19 from (*S*)-10. To 2.0 equiv of (–)-sparteine (506 mg, 496 mL, 2.16 mmol) in diethyl ether (5 mL) at –78 °C was added *s*-BuLi (1.08 M, 2.00 mL, 2.16 mmol). The reaction mixture was stirred for 30 min and then transferred to a precooled solution of *(S)*-**10** (200 mg, 1.08 mmol) in diethyl ether (5 mL) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 6 h and 2.5 equiv of Me_2SO_4 (255 mL, 2.700 mmol) was added directly. The resulting mixture was allowed to slowly warm to room temperature overnight. Workup consisted of addition of H_2O (5 mL), extraction of the aqueous layer with diethyl ether (3 × 10 mL), washing the combined organic layers with 5% phosphoric acid (H_3PO_4) (15 mL), drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. The crude product was obtained as a slightly yellow oil, which was purified by flash chromatography (1/20 (v/v) EtOAc/hexane). The isomer *(S,S)*-**19** (75 mg, 33%) was obtained as a colorless oil: cis/trans = 1:19, de 90%. The enantiomeric purity of *(S,S)*-**19** was determined to be 99% by CSP HPLC analysis of the 3,5-dinitrobenzoyl derivative on a Pirkle column packed with *(S)*-*N*-naphthylleucine.[13]

A yield of 75% was achieved by increasing the amount of *s*-BuLi/(–)-sparteine complex to 4 equiv and the metallation time to 12 h.

Preparation of (*R*)-20 from 6. To (–)-sparteine (910 mg, 892 μL, 3.88 mmol) in Et_2O (25 mL) at –78 °C was added *s*-BuLi (3.88 mL, 1.0 M, 3.88 mmol). The reaction mixture was stirred for 15 min at –78 °C and then transferred to a solution of **6** (554 mg, 3.24 mmol) in Et_2O (15 mL) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 4 h, and then benzophenone (825 mg, 4.53 mmol) in Et_2O (15 mL), precooled to –78 °C for 15 min, was added. This mixture was stirred at –78 °C for 1 h, and then AcOH (370 μL, 389 mg, 6.47 mmol) was added. The resulting mixture was then allowed to slowly warm to room temperature (3 h). Workup consisted of addition of water (30 mL), extraction of the aqueous layer with Et_2O (2 × 30 mL), extraction of the combined Et_2O extracts with 5% H_3PO_4 (25 mL), drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. Recrystallization from 1/20 (v/v) EtOAc/hexane gave *(R)*-**8** as a white solid (796 mg, 70%): mp 151–152 °C; $[\alpha]^{24}_D$ +145.0° (*c* 3.60, $CHCl_3$). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.80; H, 7.69; N, 3.99. The other spectral data of *(R)*-**8** were identical to those reported (*vide supra*). The enantiomeric purity was determined to be 99.3% by analytical HPLC of the *(R)*-Mosher amide.[13]

To *(R)*-**8** (54.0 mg, 0.153 mmol) in EtOH (5 mL) was added NaOH (13 mg, 0.31 mmol). The reaction mixture was refluxed (79 °C) for 4 h and then cooled to room temperature. Workup consisted of concentration *in vacuo*, dilution with water (5 mL), extraction of the aqueous layer with Et_2O (3 × 3 mL), drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. Purification by flash chromatography (94% CH_2Cl_2, 5% MeOH, 1% 2-propylamine) gave *(R)*-**20** as a white oily solid (34.8 mg, 90%): mp 75–77 °C (lit.[20] mp 79–79.5 °C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.57 (m, 2H, Ar), 7.50 (m, 2H, Ar), 7.38–7.22 (m, 4H, Ar), 7.127 (m, 2H, Ar), 4.26 (t, 1H, *J* = 7.5 Hz, CH), 3.02 (m, 1H, CH_2N), 2.94 (m, 1H, CH_2N), 1.95–1.50 (bm, 6H, NH, OH and ring CH_2); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 148.1, 145.3, 128.2, 127.9, 126.4, 126.3, 125.8, 125.5, 78.32, 64.43, 46.72, 26.24, 25.45.

Preparation of (*S,S*)-21 from 6. To a solution of sparteine (2.94 g, 12.6 mmol) and *sec*-butyllithium (10 mL, 1.26 M, 12.6 mmol) in ether (30 mL) at –78 °C was added **6** (1.71 g, 10 mmol) in ether (20 mL, precooled to –78 °C for 10–15 min). The resulting mixture was stirred at –78 °C for 5 h, and then dimethyl sulfate (1.58 g, 12 mmol) was slowly added. This mixture was then allowed to warm to room temperature. The ether (50 mL) and water (50 mL) were added, and the two layers were separated, the organic layer was extracted by ether (2 × 30 mL), and the combined ethereal layers were washed with aqueous H_3PO_4 (5%, 2 × 20 mL) and then water (2 × 30 mL) and dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was further purified by chromatography (EtOAc/hexane, 1/9) to give *(S)*-**10** as a colorless oil (1.42 g, 76%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.85 (m, 1H), 3.35 (m, 2H), 2.02–1.53 (m, 4H), 1.46 (s, 9H), 1.14 (d, 3H, *J* = 6.06 Hz).

The enantiomeric purity of *(S)*-**10** was determined to be 95.3% by CSP HPLC of the 3,5-dinitrobenzoyl amide derivative of (*S*)-2-methylpyrrolidine on the (*S*)-*N*-naphthylleucine column.

To a solution of (–)-sparteine (3.24 g, 13.8 mmol) and *sec*-butyllithium (11 mL, 1.26 M, 13.8 mmol) in ether (25 mL) at –70 °C was added *(S)*-**10** (1.29 g, 6.9 mmol) in ether (10 mL, precooled to –70 °C for 10–15 min). The resulting mixture was stirred at –70 °C for 12 h, and then dimethyl sulfate (1.10 g, 8.3 mmol) was slowly added. This mixture was then allowed to warm to room temperature. The ether (20 mL) and water (20 mL) were added, and the two layers were separated, the aqueous layer was extracted by ether (3 × 20 mL), and the combined ethereal layers were washed with aqueous H_3PO_4 (5%, 2 × 20 mL) and then water (2 × 30 mL) and dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was further purified by chromatography (EtOAc/hexane, 1/10) to give *(S,S)*-**19** as a colorless oil (1.02 g, 72%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.97 (t, 1H, *J* = 6.40 Hz), 3.86 (t, 1H, *J* = 6.33 Hz), 2.10 (m, 2H), 1.51 (m, 2H), 1.46 (s, 9H), 1.15 (m, 6H).

The ratio of *(S,R)*-**19** was determined to be 7.5:92.5 by GC (80 °C

isothermal), and the enantiomeric purity of *(S,S)*-**19** was determined to be >98% by CSP HPLC of the 3,5-dinitrobenzoyl amide derivative.

To *(S,S)*-**19** (1.02 g, 5 mmol) in CH_2Cl_2 (50 mL) at room temperature was added trifluoroacetic acid (7.5 mL). The reaction mixture was stirred for 4 h at room temperature and then concentrated *in vacuo*. The residue was diluted with 10% NaOH (50 mL) and extracted with ether (3 × 30 mL). The combined ethereal layers were washed with water (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield *(S,S)*-2,5-dimethylpyrrolidine as a light-yellow oil (0.43 g, 86%).

To 3,5-dinitrobenzoyl chloride (1.47 g, 6.4 mmol) in THF (40 mL) was added triethylamine (0.9 mL, 6.4 mmol) and then the mixture of *(S,R)*- and *(S,S)*-2,5-dimethylpyrrolidine (0.43 g, 4.3 mmol) in THF (3 mL). The reaction mixture was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was diluted with 10% NaOH (43 mL) and extracted with ether (3 × 30 mL). The combined ethereal layers were washed with 10% HCl (20 mL) and water (2 × 20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to 10 mL *in vacuo*. The white solid of *(S,S)*-2,5-dimethyl-*N*-(3,5-dinitrobenzoyl)pyrrolidine (0.64 g) was obtained by filtration (100% de, 100% ee). The filtrate was left at 0 °C for 4 h and then was filtered again to give another 0.24 g of product (98% de, 100% ee), for a total of 0.88 g (69%) of *(S,S)*-2,5-dimethyl-*N*-(3,5-dinitrobenzoyl)pyrrolidine: mp 159–160 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.09 (t, 1H, J = 1.84 Hz), 8.66 (d, 2H, J = 1.99 Hz), 4.50 (m, 1H), 4.11 (m, 1H), 2.32–2.41 (m, 1H), 2.16–2.36 (m, 1H), 1.65–1.68 (m, 2H), 1.34 (d, 3H, J = 6.39 Hz), 0.85 (d, 3H, J = 6.43 Hz).

The enantiomeric excess of *(S,S)*-2,5-dimethyl-*N*-(3,5-dinitrobenzoyl)-pyrrolidine was determined by CSP HPLC (2.5% v/v 2-propanol/hexane). The chromatographic column used was a Pirkle/Regis, 250 nm × 4.6 mm i.d., column with a stationary phase of (*S*)-*N*-naphthlleucine, a flow rate of 1.25 mL/min, and a detection wavelength of 254 nm. The ratio of diastereomers and the enantiomeric purity were determined to be >99% by CSP HPLC.

The *(S,S)*-2,5-dimethyl-*N*-(3,5-dinitrobenzoyl)pyrrolidine (0.293 g, 1 mmol) was dissolved in EtOH (saturated by HCCl, 10 mL), the solution was refluxed for 30 min, and then concentrated HCl (5 mL) was added and the resulting mixture was refluxed for 72 h. The solution was evaporated to dryness *in vacuo*, the residue was dried by azotropic distillation of toluene, ether (anhydrous, 20 mL) was added, and the precipitate was formed. The precipitate was filtered and washed with ether (4 mL), giving (*S*,*S*)-**21** as a white solid: 97 mg (72%); mp 195–198 °C (lit.[19] mp 197–200 °C); ^{1}H-NMR (CD_3OD, 300 MHz) δ 1.38 (d, 6H, J = 6.62 Hz), 1.65 (m, 2H), 2.24 (m, 2H), 3.75 (m, 2H); ^{13}C-NMR (CD_3OD, 300 MHz) δ 16.68, 31.77, 55.12.

General Procedure for the Lithium–Tin Exchange between *n*-BuLi and 11. To **11** (1.0 equiv) and the diamine (1.2 equiv) in Et_2O (0.10 M) at −78 °C was added *n*-BuLi (1.2 equiv). The reaction mixture was stirred for 2 h at −78 °C, and then trimethylsilyl chloride (1.5 equiv) was added and the reaction mixture was allowed to warm to room temperature. Workup consisted of dilution with water (5 mL), extraction of the aqueous layer with Et_2O (2 × 5 mL), extraction with 5% H_3PO_4 (1 × 5 mL), drying over anhydrous $MgSO_4$, filtration, and concentration *in vacuo*. Purification by flash chromatography gave **7** as a colorless oil. Analysis by GC established the purity as >95%, and CSP GC was used to determine the enantiomeric excess.

Lithium–Tin Exchange in the Presence of Sparteine. Lithiation of racemic **11** (88.3 mg, 0.192 mmol) according to the procedure above (4-h lithiation) in the presence of sparteine (58.4 mg, 0.249 mmol) followed by purification by flash chromatography (3% EtOAc/hexane) gave **7** as a colorless oil (16 mg, 35%). CSP GC analysis showed a 0% enantiomeric excess.

Lithium–Tin Exchange with No Diamine. Lithiation of *(S)*-**11** (96% ee, 80.3 mg, 0.174 mmol) according to the procedure above with no diamine present, after purification by flash chromatography (3% EtOAc/hexane), gave *(S)*-**7** as a colorless oil (6 mg, 15%). CSP GC analysis showed a 93% enantiomeric excess.

Lithium–Tin Exchange in the Presence of TMEDA. Lithiation of *(S)*-**11** (96% ee, 95.9 mg, 0.208 mmol) according to the procedure above in the presence of TMEDA (41 μL, 31.5 mg, 0.271 mmol), after purification by flash chromatography (3% EtOAc/hexane), gave *(S)*-**7** as a colorless oil (18 mg, 36%). CSP GC analysis showed a 74% enantiomeric excess.

Procedure for the Lithiation of 6 with No Diamine Present. To **6** (200 mg, 1.17 mmol) in Et_2O (6 mL) at −78 °C was added *s*-BuLi (1.17 mL, 1.30 M, 1.52 mmol). The reaction mixture was stirred for at least 12 h at −78 °C, and then trimethylsilyl chloride (296 μL, 254 mg, 2.34 mmol) was added. The reaction mixture was allowed to warm to room temperature and was then worked up as described in procedure A. Purification by flash chromatography (4% EtOAc/hexane) gave **7** as a colorless oil (135 mg, 48%).

Preparation of (*S,S*)-6-d_2. Lithiation according to procedure B of *(S)*-2-deuterio-*N*-(*tert*-butoxycarbonyl)pyrrolidine (*(S)*-**6**-*d*) (98% d_1, 710 mg, 4.12 mmol) with direct addition of deuterated methanol (251 μL, 204 mg, 6.18 mmol), after concentration *in vacuo*, gave *(S,S)*-**6**-d_2 as a colorless oil (664 mg, 93%). The spectral data of *(S,S)*-**6**-d_2 were similar to those of the sample prepared previously. Analysis by FI/MS showed an isotope incorporation of 53% d_2 and 47% d_1.

Acknowledgment. We are grateful to the National Institutes of Health, the National Science Foundation, G. D. Searle, Inc., and the Beckman Institute of the University of Illinois for support of this work. We appreciate illuminating discussions with Professor Eric Jacobsen and Dr. James P. Snyder and a gift of *s*-BuLi from Dr. Terry Rathmann.

Supplementary Material Available: The preparations of **6**, racemic products (*R*)-**13**-d_6, **16**, and (*S,S*)-**19**, diastereomeric and enantiomeric analyses, and experiments for Tables 1 and 3 (17 pages). This material is contained in many 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.