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Asymmetric Deprotonation by BuLi/(−)-Sparteine: Convenient and Highly Enantioselective Syntheses of (*S*)-2-Aryl-Boc-Pyrrolidines

Shengde Wu, Steven Lee, and Peter Beak*

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

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Abstract: Highly enantioselective syntheses of (*S*)-2-aryl-Boc-pyrrolidines (Boc = *tert*-butoxycarbonyl) can be achieved by treatment of the corresponding (arylmethyl)(3-chloropropyl)-Boc-amines with *s*-BuLi/(−)-sparteine. The reactions are solvent dependent with the phenyl, *p*-chlorophenyl, *p*-fluorophenyl, *p*-methylphenyl, *m*-methoxyphenyl, 1-naphthyl, and 2-naphthyl derivatives **1**−**7** providing **11**−**17** in yields of 46−75% with enantiomeric excesses of 84−96% in toluene. The 2-thienyl and 3-furyl analogs **8** and **9** afford the (*S*)-2-heteroaryl-Boc-pyrrolidines **18** and **19** in 51 and 21% yields with 93−96% enantiomeric excesses. The *p*-methoxyphenyl derivative **10** gives **20** as a racemic product in 42% yield under the same conditions. Reactions of *n*-BuLi/(−)-sparteine with **1** and **8** give results comparable to those with *s*-BuLi/(−)-sparteine. Illustrative syntheses of (*S*)-2-phenyl-(*S*)-5-methyl-Boc-pyrrolidine (**22**) and 1,2-(bis-(*S*)-2-phenylpyrrolindyl)ethane (**23**) are reported. The mechanism of the reaction is shown to be an asymmetric deprotonation of **1** to give an enantioenriched organolithium intermediate (*S*)-**24** which undergoes cyclization faster than racemization.

Recent studies have established that reactions of organolithium species complexed to enantioenriched ligands can afford highly enantioenriched products.[1] We have shown that asymmetric deprotonation of Boc-pyrrolidine (Boc = *tert*-butoxycarbonyl) by *s*-BuLi/(−)-sparteine provides (*R*)-2-lithio-Boc-pyrrolidine which subsequently can be reacted with many electrophiles to give 2-substituted Boc-pyrrolidines with high enantiomeric excesses.[2] However, the lack of a general method for enantioselective electrophilic arylation of alkylorganolithium reagents limits this approach for the preparation of enantioenriched 2-aryl-Boc-pyrrolidines.[3,4,5] We now report lithiation−cyclizations which afford (*S*)-2-aryl-Boc-pyrrolidines with high enantiomeric excesses.

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1996.

(1) For recent summaries see: Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1459. Aggarawal, J. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 175. For recent reports and leading references see: (a) Carstens, A; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097. (b) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc*. **1994**, *116*, 9755.

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

(3) Dieter has recently reported arylations of 2-lithio-Boc-pyrrolidines by a copper-catalyzed palladium coupling reaction with aryl iodides: Dieter, R. K.; Li S. *Tetrahedron Lett.* **1995**, *36*, 3613. An earlier report from Dieter's laboratories showed that the enantiointegrity of the 2-lithio-Boc-pyrrolidine was lost on conversion to the copper derivative and addition to α,β unsaturated ketones. Dieter, R. K.; Alexander, C. W., *Syn. lett.* **1993**, 407.

(4) Chiral 2-substituted pyrrolidines, which occur widely as natural products and are useful as chiral auxiliaries, chiral bases, and chiral ligands, are worthy synthetic targets. For summaries and reviews see: Hart, D. J. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1988; Vol. 6, Chapter 3. Hiemstra, H; Speckamp, W. N. *The Alkaloids*; Brossi A., Ed.; Academic Press: New York, **1988**. Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. Tomioka, K. *Synthesis*, **1990**, 541.

(5) For our report of the corresponding racemic reaction see: Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276. For formation of pyrrolidines by cyclization through addition of an α-lithioamine to a double bond see: Coldham, I.; Hufton, R. *Tetrahedron Lett.* **1995**, *36*, 2157.

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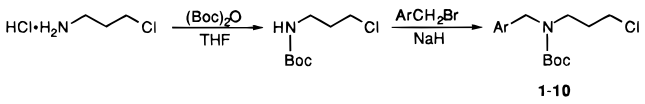
Chiral auxiliary-mediated approaches to enantioenriched 2-arylpyrrolidines have been reported. Burgess and Meyers have used (*R*)-phenylglycinol for highly enantioselective syntheses of 2-phenyl- and 2-alkylpyrrolidines.[6] The same auxiliary was used by Higashiyama and co-workers to prepare enantioenriched 2-aryl and 2,5-diarylpyrrolidines.[7] Savoia and co-workers have used (*S*)-valine as the chiral auxiliary for the synthesis of enantioenriched 2-phenylpyrrolidine.[8]

Catalytic methods have been developed for syntheses of enantioenriched 2-arylpyrrolines and -pyrrolidines. Ozawa and Hayashi have reported palladium acetate 2(*R*)-BINAP asymmetric arylations of carbonates of 2-pyrrolidines give 5-aryl-2-pyrrolidines in good enantiomeric excess along with 5-aryl-3-pyrrolines with poor enantioenrichments.[9] An especially efficient approach to enantioenriched 2-substituted pyrrolidines has been reported by Willoughby and Buchwald who used an enantioselective chiral titanocene-based catalyst to reduce 2-aryl- and 2-alkyl-1-pyrrolidines to 2-aryl- and 2-alkylpyrrolidines with very high enantioselectivities.[10]

We can report convenient highly enantioselective syntheses of (*S*)-2-aryl-Boc-pyrrolidines by lithiation of (arylmethyl)(3-chlorophenyl)-Boc-amines with BuLi/(−)-sparteine. Mechanistic analysis shows that enantioselectivity is introduced by asymmetric deprotonation at the benzylic position by the organolithium/chiral ligand complex.

Results and Discussion

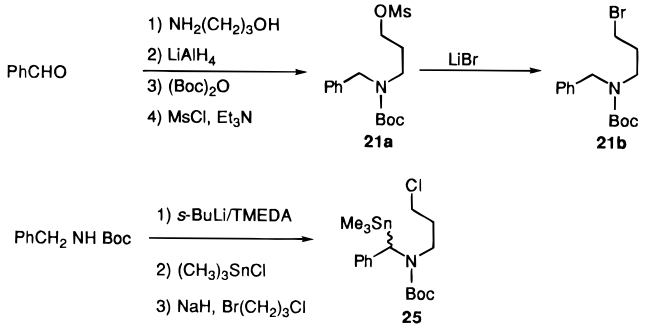
Synthesis of Reactants. Treatment of 3-chloropropylamine hydrochloride with di-*tert*-butyl dicarbonate in THF provided (3-chloropropyl)-Boc-amine, which on reaction with NaH and the appropriate arylmethyl bromide afforded the products **1**−**10** in 42−63% yields.[11] Benzyl [3-(mesyloxy)propyl]-Boc-amine



1-10

1 Ar=Ph (53%); **2** Ar=*p*-Cl-Ph (52%); **3** Ar=*p*-F-Ph (56%); **4** Ar=*p*-Me-Ph (54%); **5** Ar=*m*-MeO-Ph (55%); **6** Ar=1-Naphthyl (51%); **7** Ar=2-Naphthyl (63%); **8** Ar=3-Thienyl (42%); **9** Ar=3-Furyl (45%); **10** Ar=*p*-MeO-Ph (50%)

(**21a**) was prepared by reaction of 3-amino-1-propanol with benzaldehyde, followed by reduction with $LiAlH_4$, reaction with di-*tert*-butyl carbonate, and treatment with mesyl chloride. Reaction of **21a** with LiBr gave benzyl(3-bromopropyl)-Boc-amine (**21b**). The trimethylstannyl derivative **25** was synthesized in low yield from benzyl-Boc-amine by dilithiation, reaction with trimethyltin chloride, and alkylation with 1-bromo-3-chloropropane. The preparation of **1**-d_1 followed the route used for **21a** with lithium aluminum deuteride used in the reduction step to incorporate the deuterium. The mesylate **21a**-d_1 was converted to the labeled chloride **1**-d_1 by treatment with lithium chloride.



Enantioselective Lithiation−Cyclizations of 1−9. Treatment of **1** with 1.5−2.0 equiv of *s*-BuLi/(−)-sparteine at −78 °C in different solvents gives (*S*)-**11** in the yields and enantioselectivities summarized in Table 1. The absolute configuration was assigned to (*S*)-**11** by removal of the Boc group and comparison of the optical rotation to authentic (*S*)-2-phenylpyrrolidine.[6] The enantiomeric excess was determined by derivitization of the pyrrolidine with 3,5-dinitrobenzyl chloride and HPLC comparison of the racemic and enantioenriched 3,5-dinitrobenzamides on the Pirkle chiral stationary phase (*S*)-N_1N-naphthylleucine column.[12]

The data in Table 1 show the enantioselectivities for the lithiation−cyclization of **1** to (*S*)-**11** to be solvent dependent. An essentially racemic product is obtained in THF. Reactions in diethyl ether (Et_2O), *tert*-butyl methyl ether (*t*-BuOMe), or Et_2O:pentane provide (*S*)-**11** in moderate enantiomeric excess while in pentane the enantiomeric excess is 80%.[13] Toluene affords a 72% yield and 96% enantioselectivity. A reaction of **1** in toluene on a 1 g scale with one recrystallization gave (*S*)-**11** from **1** in 58% overall yield with >98% ee. Although the trend of enantioselectivity in Table 1 is generally consistent with an expected increase in influence of the chiral ligand for an organolithium species as the solvent becomes less effective in binding, the improvement in enantioselectivity in toluene relative to pentane does not fit that trend, although solubility may be an important factor.

Analogous lithiation−cyclization reactions were carried out for the (arylmethyl)(3-chloropropyl)-Boc-amines **1**−**10.** Treatment of each substrate with 1.5−2.0 equiv of BuLi/(−)-sparteine at −78 °C in toluene for 6−8 h gives the (*S*)-2-arylpyrrolidines **11**−**20** with high enantioselectivity as shown in Table 2. The *S* configuration is assigned by analogy to the formation of (*S*)-**11** and by consistency with elution order in the determinations

(6) (a) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656. (b) The original source for the determination of the absolute configuration of 2-phenylpyrrolidine was by correlation with the absolute configuration of 2-phenylglutaric acid. Morlacchi, F.; Losacco, V.; Tortorella, V. *Gazz. Chim. Ital.* **1975**, *105*, 349.

(7) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083.

(8) Manescalchi, F.; Nardi, A. R.; Savoia, D. *Tetrahedron Lett.* **1994**, *35*, 2775.

(9) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, *428*, 267.

(10) Willoughby, C. A.; Buchwald, S. L. *J. Org. Chem.* **1994**, *116*, 11703.

(11) The yields were not optimized, and trace amounts of elimination products were observed. The alternative approach with 1-bromo-3-chloropropane and Boc-phenylmethylamine under the same alkylation conditions gave less than 20%of **1** with the elimination product, *N*-Boc-*N*-allyl-*N*-benzylamine, as the major product.

(12) Pirkle, W. H.; McCune, J. E. *J. Chromatogr.* **1989**, *479*, 471, 271.

(13) A limitation of pentane is that **2**−**7** have lower solubilities at lower temperatures. In toluene, these compounds are soluble at −78 °C.

(14) The racemic pyrrolidine of **12** has been reported. (a) Maryanoff, B. E.; Vaught, J. L.; Shank, R. P.; McComsey, D. F.; Costanzo, M. J.; Nortey, S. O. *J. Med. Chem.* **1990**, *33*, 2793. (b) Elslager, E. F.; Johnson, J. L.; Werbel, L. M. *J. Med. Chem.* **1981**, *24*, 140. (c) Elslager, E. F.; Clarke, J.; Werbel, L. M.; Worth, D. F.; Davoll, J. *J. Med. Chem.* **1972**, *15*, 827.

(15) The racemic pyrrolidine of **13** has been reported. (a) Viswanathan, N.; Sidhaye, A. R. *Tetrahedron Lett.* **1979**, *52*, 5025. (b) Seeman, J. I.; Secor, H. V.; Forrest, G. *J. Labelled Compd. Radiopharm.* **1979**, *16*, 387.

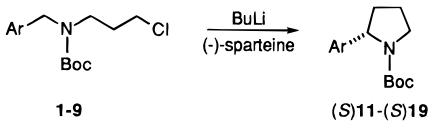
(16) The racemic pyrrolidine of **14** has been reported. (a) See ref. 15a. (b) Severin, T.; Poehlmann, H. *Chem. Ber.* **1977**, *110*, 491.

(17) The racemic pyrrolidine of **15** has been reported. (a) Ferrand, G.; Barbanton, J.; Depin, J.; Chavernac, G. CA Patent 1327364, 1995; *Chem. Abstr.* **1995**, *122*, 31318. (b) Wettlaufer, D. G.; Nemoto, P. A. US Patent 5338739, 1994; *Chem. Abstr.* **1994**, *121*, 280538. (c) Ferrand, G.; Barbanton, J.; Depin, J.; Chavernac, G. EP Patent 360685, 1990; *Chem. Abstr.* **1990**, *113*, 115096.

(18) The racemic pyrrolidines of **16** and **17** have been reported. Grande, M. T.; Sollhuber, M. M. *Chem. Scr.* **1988**, *28*, 411.

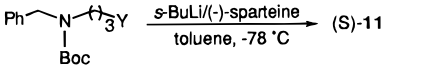
(19) (a) The enantioenriched pyrrolidine of **20** has been reported in ref. 7. The racemic pyrrolidine of **20** has been reported: (b) Wettlaufer, D. G.; Nemoto, P. A. US Patent 5338739, 1994; *Chem. Abstr.* **1994**, *121*, 280538. (c) Viswanathan, N.; Sidhaye, A. R. *Tetrahedron Lett.* **1979**, *52*, 5025.

of enantiomeric excess by chromatography on the (*S*)-N_1N-naphthylleucine column.[12] Since *n*-BuLi is a more available reagent, reaction of **1** with *n*-BuLi/(−)-sparteine was carried out and found to afford (*S*)-**11** in 55% yield with 93% ee in toluene. Reaction with *t*-BuLi/(−)-sparteine affords almost racemic **11** in 14% yield, although the same base/ligand combination in ether provides (*S*)-**11** in 63% yield with 33% ee. The *p*-substituted phenyl derivatives **2**−**5** give the expected pyrrolidines (*S*)-**12**, (*S*)-**13**, (*S*)-**14**, and (*S*)-**15** in useful yields with enantiomeric excess of 84%, 87%, 84%, and 96%, respectively. The (1-naphthylmethyl)-Boc-amine and 2-naphthylmethyl-Boc amine derivatives **6** and **7** give moderate yields of (*S*)-**16** and (*S*)-**17** with enantiomeric excess of 93% and 90% ee with *s*-BuLi/(−)-sparteine. Enantiomeric excesses of 93% and 96% are also observed for (*S*)-**18** and (*S*)-**19** from the heteroaromatic Boc-amine derivatives **8** and **9** but the yields are lower. With **8**, *n*-BuLi/(−)-sparteine is also effective.



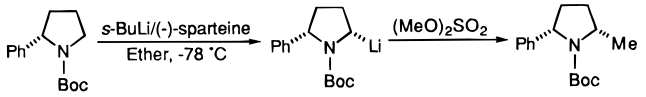
1-9 (*S*)**11**-(*S*)**19**

However, the reaction of (*p*-methoxybenzyl)(3-chloropropyl)-Boc-amine (**10**) with *s*-BuLi/(−)-sparteine gives **20** as a racemic product in modest yield. This lack of enantioselectivity is not attributable to the presence of a methoxy group as a competing site of complexation as shown by the fact that **5** undergoes cyclization−lithiation under the same conditions to provide (*S*)-**15** with a high enantiomeric excess.[20] A brief investigation of the effect of the leaving group on the reaction was carried out with the mesylate **21a** and the bromide **21b**. From the mesylate, (*S*)-**11** was obtained in very low yield but with high ee, while the bromide gave (*S*)-**11** in lower yield and enantioselectivity than from **1**.



21a, Y=OMs from **21a**, 4% yield, 94% ee
21b, Y=Br from **21b**, 44% yield, 78% ee

A combination of this lithiation−cyclization with our earlier enantioselective substitutions of Boc pyrrolidine is illustrated by the synthesis of (*S*)-5-phenyl-(*S*)-2-methyl-Boc-pyrrolidine [(*S*,*S*)-**22**]. Lithiation of (*S*)-**11** with *s*-BuLi/(−)-sparteine gives (*S*)-5-phenyl-(*R*)-2-lithio-Boc-pyrrolidine, which reacts with dimethyl sulfate to provide (*S*,*S*)-**22** in 45% yield with a diastereomeric ratio of 93:7 in favor of the *syn* diastereomer.[21]



(*S*)-**11** (*S*,*S*)-**22** (45%)
syn:*anti* = 93:7

The conversion of (*S*)-**11** to the C_2-symmetric chiral pyrrolidine-based diamine (*S*,*S*)-**23** has been carried out. Cleavage of the Boc group of (*S*)-**11** and reaction with oxalyl chloride

Table 1. Enantioselective Conversion of **1** to (*S*)-**11** with *s*-BuLi/(−)-Sparteine in Different Solvents at −78 °C

solvent	yield (%)	ee[a] (%)
THF	58	3
t-BuOMe	64	58
Et_2O	59	64
Et_2O:pentane (1:1)	40	70
pentane	54	80
toluene	72	96

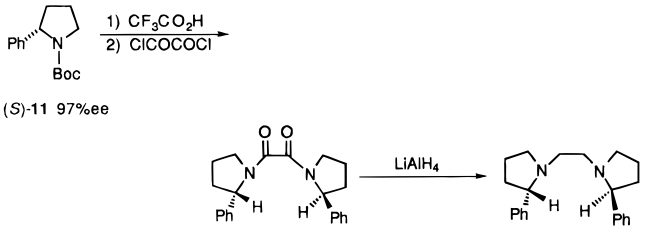
[a] The error is estimated as ±5%.

Table 2. Enantioselective Lithiation−Cyclizations of **1**−**9** with BuLi/(−)-Sparteine To Provide (*S*)-**11**−**19** in Toluene at −78 °C

reactant	Ar	product	base	yield (%)	ee[a] (%)
1	Ph−	(*S*)-**11**	*s*-BuLi	72	96
1	Ph−	(*S*)-**11**	*n*-BuLi	55	93
1	Ph−	(*S*)-**11**	*t*-BuLi[b]	14	-8[c]
2	*p*-ClPh−	(*S*)-**12**[d]	*s*-BuLi	62	84
3	*p*-FPh−	(*S*)-**13**[e]	*s*-BuLi	69	87
4	*p*-MePh−	(*S*)-**14**[f]	*s*-BuLi	75	84
5	*m*-MeOPh−	(*S*)-**15**[g]	*s*-BuLi	46	96
6	1-naphthyl	(*S*)-**16**[h]	*s*-BuLi	68	93
7	2-naphthyl	(*S*)-**17**[h]	*s*-BuLi	70	90
8	3-thienyl	(*S*)-**18**	*n*-BuLi	52	93
8	3-thienyl	(*S*)-**18**	*s*-BuLi	51	93
9	3-furyl	(*S*)-**19**	*s*-BuLi	21	96
10	*p*-MeOPh−	**20**[i]	*s*-BuLi	42	3

[a] The error is ±5%. [b] In ether (*S*)-**11** is obtained in 63% yield with 33% ee. [c] The major enantiomer is (*R*)-**11**. [d] See ref 14. [e] See ref 15. [f] See ref 16. [g] See ref 17. [h] See ref 18. [i] See ref 19.

followed by reduction with lithium aluminum hydride provides the chiral diamine (*S*,*S*)-**23** in 49% overall yield.



(*S*)-**11** 97%ee (*S*,*S*)-**23** (49%)

Pathway of the Lithiation−Cyclization of 1 to (*S*)-11. The enantioselective formation of (*S*)-**11** from **1** could involve either asymmetric deprotonation or asymmetric substitution. Under the first possibility, enantioselective deprotonation of **1** with a BuLi/(−)-sparteine complex would provide (*S*)-**24**, an enantioenriched organolithium intermediate which would cyclize to (*S*)-**11** faster than it racemizes.[22,23] Under the pathway of asymmetric substitution, deprotonation of **1** would provide racemic **24** either directly or by subsequent rapid racemization, and this intermediate would cyclize enantioselectively to (*S*)-**11** under the influence of (−)-sparteine. Precedents for both pathways have been reported for analogous systems.[2,24,25]

The alternative mechanisms can be distinguished by experiments with **1**-d_1.[23−25] If the asymmetric induction occurs through asymmetric deprotonation with cyclization faster than

(20) The source of the low enantiomeric excess with **10** has not been determined. Equilibration by a ring-opening ring sequence promoted by the *p*-methoxy group is possible. It is also noted that a *p*-methoxy group has been reported to have a deleterious effect on a lateral lithiation. Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Nephe, D. B.; Souchet, M. *Synthesis* **1991**, 871

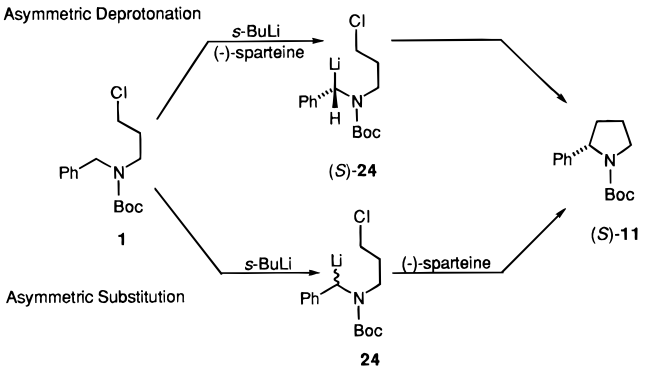
(21) The *R* configuration of the organolithium intermediate is assigned by analogy to our previous work.[2]

(22) The assumption is that the cyclization of (*S*)-**24** would proceed with retention of configuration at the benzylic position.[17] This is not necessarily the case, and the intermediency of (*R*)-**24** which reacts with inversion is also possible.[1]

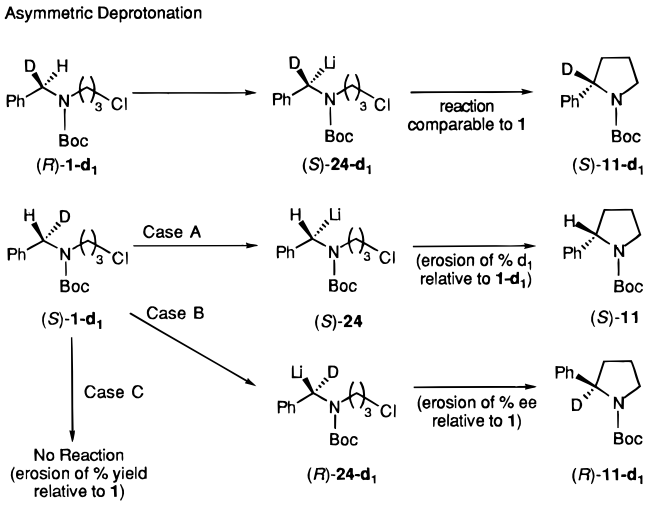
(23) Schlosser and Limat have found that deprotonation of benzylmethyl-Boc-amine with *s*-BuLi/(−)-sparteine is highly asymmetric but that racemization is rapid and that the configuration of the subsequent asymmetric substitution is highly solvent dependent. Schlosser, M. Private communication, June 1994. Contribution by M. Schlosser and D. Limat at the Chiral-2 Workshop in Gwatt, March 1995, Symposium Brochure, p A-4.

(24) Hoppe, D.; Paetau, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394.

(25) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516.



racemization of the enantioenriched intermediate, significant differences should be observed between the reaction of **1** and of racemic **1**-d_1. The possibilities are outlined for the racemic mixture of (*R*)-**1**-d_1 and (*S*)-**1**-d_1. The *R* enantiomer of **1**-d_1 would be expected to undergo deprotonation fully analogous to **1** and lead to (*S*)-**24**-d_1 and (*S*)-**11**-d_1. However, the reaction of (*S*)-**1**-d_1, which has the deuterium in the preferred position for enantioselective removal, could follow three possible courses: the enantiomer (*S*)-**1**-d_1 could undergo removal of the deuterium at a slower rate than reaction of **1**, undergo removal of the hydrogen, or be unreactive.[26] If the deuterium is removed to give (*S*)-**24** (Case A), the deuterium content of (*S*)-**11**-d_1 would be less than that of the reactant **1**-d_1, but the enantiomeric excess of (*S*)-**11**-d_1 would be comparable to that of (*S*)-**11** from **1**. In this case, the facial selectivity in the deprotonation would override the kinetic isotope effect. If the hydrogen is removed from (*S*)-**1**-d_1 to give (*R*)-**24**-d_1 (Case B), the product would be (*R*)-**11**-d_1 and the enantiomeric excess of **11**-d_1 would be eroded relative to the reaction of **1**. In this case, the kinetic isotope effect would override the enantioselectivity. If neither the deuterium nor the hydrogen is removed from (*S*)-**1**-d_1 (Case C), then the product would be (*S*)-**11**-d_1 with a deuterium content comparable to that of **1**-d_1 and an enantiomeric excess comparable to that from **1**, but a reduced yield relative to that of (*S*)-**11** from **1**. In this case, recovered **1**-d_1 would be enriched in (*S*)-**1**-d_1.



If the asymmetric induction occurs only through asymmetric substitution, the enantiodetermining steps occur after the lithiation. In this case there is no chiral preference in the deprotonation and **24**-d_1 should be selectively formed due to the large deuterium isotope effect at −78 °C.[5,24,26] The subsequent cyclization would proceed under the influence of (−)-sparteine,

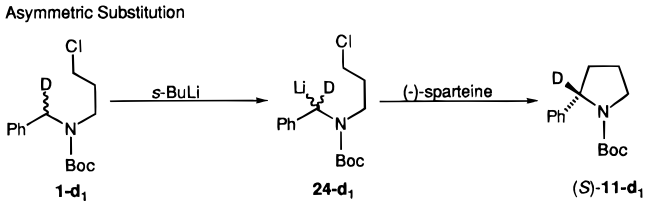
(26) Kaiser, B.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 323.

Table 3. Reactions of **1** and **1**-d_1 with *s*-BuLi/(−)-Sparteine To Provide (*S*)-**11** and (*S*)-**11**-d_1 in Diethyl Ether

reactant	reaction conditions	yield (%)	ee (%)	d_1[a] (%)
1	6 h	53	65[b]	
1-d_1 (96% d_1)	6 h	43	30[b]	88
1, 1-d_1 (50% d_1)	6 h	45	46	46
1-d_1 (96% d_1)	0.5 equiv of *s*-BuLi, 0.55 equiv of (−)-sparteine, 3.75 h	18[c]	44	91
1	0.5 equiv of *s*-BuLi, 0.55 equiv of (−)-sparteine, 3.75 h	26[c]	60	

[a] The deuterium incorporation was determined by FIMS. The error is ±5%. [b] The enantioenrichment was shown not to be dependent on the reaction time. [c] The yield is relative to *s*-BuLi.

(*S*)-**11**-d_1 would be formed with a deuterium content comparable to that of **1**-d_1, and (*S*)-**11**-d_1 would have an enantiomeric excess comparable to that of (*S*)-**11** from **1**. If the pathway involves initial asymmetric deprotonation, rapid racemization, and subsequent asymmetric substitution and if a high isotope effect is operative, the results of Case C above would be expected.[23,24]



The lithiation−cyclizations for **1** and **1**-d_1 were carried out in diethyl ether, which gives a lower enantioselectivity than toluene and has the advantage of a more easily measured response in enantioselectivities to any changes in reaction energetics. The results of the comparison are summarized in Table 3.

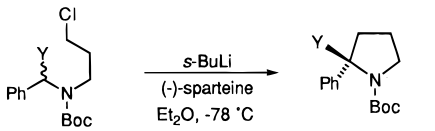
Comparisons of the enantioenrichments and deuterium contents in (*S*)-**11** and (*S*)-**11**-d_1 from the reactions of **1** and **1**-d_1, respectively, are shown in the first two entries. The deuterium content of (*S*)-**11**-d_1 is close to that of **1**-d_1. However, the yield of (*S*)-**11**-d_1 is reduced relative to (*S*)-**11**. Moreover, the 82:17 ratio of 65% ee for (*S*)-**11** from **1** becomes a 65:35 ratio of 30% ee for (*S*)-**11**-d_1 from **1**-d_1. This difference in enantioenrichment and yield is consistent with a combination of Cases B and C and indicates that the pathway of the formation of (*S*)-**11** from **1** by *s*-BuLi/(−)-sparteine is predominately asymmetric deprotonation.[27] Apparently (*R*)-**1**-d_1 behaves as does **1** with *s*-BuLi /(−)-sparteine while (*S*)-**1**-d_1 loses its hydrogen, albeit more slowly than does **1**.

The competitive reaction of a mixture of **1** and **1**-d_1 shows, as expected, an enantioenrichment between the two extremes. The reaction of **1**-d_1 with a deficient amount of *s*-BuLi /(−)-sparteine also provides an enantioenrichment between the two extremes, also as expected. With the deficiency of base, more of (*R*)-**1**-d_1 should react than (*S*)-**1**-d_1. The reaction with **1** in the last entry is a comparison control experiment.

Another test for the possibility of asymmetric substitution has been carried out by the transmetalation of the racemic tin precursor **25** in the presence of (−)-sparteine to generate a racemic **24**. If the asymmetric induction can proceed through enantioselective substitution, racemic **24** should complex with (−)-sparteine and (*S*)-**11** should be formed with 65% enantiomeric excess. The transmetallation of **25** and cyclization in the presence of (−)-sparteine provided nearly racemic **11** in 44%

(27) Similar results were observed in toluene and in pentane.

yield. Thus, the possibility of reaction mainly by asymmetric substitution is unlikely.[28]



1 Y=H (*S*)-**11** Y=H
1-d$_1$ Y=D (*S*)-**11-d$_1$** Y=D
25 Y=Me$_3$Sn **11** Y=H

In summary, the present results provide convenient methodology for syntheses of (*S*)-2-aryl-Boc-pyrrolidines in high enantiomeric excesses.[29] The mechanism of the enantioselective induction is enantioselective deprotonation by a BuLi/(−)-sparteine complex to yield an enantioenriched lithiated species which undergoes cyclization more rapidly than racemization. The methodology of the present work should also be applicable to enantioselective syntheses and mechanistic analysis of a number of related systems.

Experimental Section

General. Compounds which were not submitted for or did not pass elemental analysis were judged to be of >95% purity based on ^{1}H-NMR, ^{13}C-NMR, MS, and GLC analyses unless stated otherwise. The NMR spectra of such compounds are provided. *sec*-Butyllithium (*s*-BuLi) as a solution in cyclohexane, *n*-butyllithium (*n*-BuLi) as a solution in hexanes, and *tert*-butyllithium (*t*-BuLi) as a solution in pentane were obtained from Lithium Corp. and were titrated by using *N*-pivaloyl-*o*-toluidine as the indicator.[30] All reactions involving air-sensitive reagents were performed under nitrogen or argon using syringe−septum cap techniques.

Boc-3-chloropropylamine. To a solution of di-*tert*-butyldicarbonate (10.4 g, 50.0 mmol) and triethylamine (6.30 g, 60 mmol) in THF (100 mL) was added 3-chloropropylamine hydrochloride (6.96 g, 54.0 mmol) at 0 °C. The resulting mixture was stirred for 20 min, warmed to ambient temperature, and then stirred for 18 h. The mixture was diluted with 50 mL of 10% sodium bicarbonate solution and extracted with ether (2 × 40 mL). The extracts were washed with brine, dried ($MgSO_4$), concentrated, and Kugelrohr distilled to give *N*-Boc-3-chloropropylamine as a clear oil (8.25 g, 85%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 1.91 (m, 2H), 3.25 (m, 2H), 3.59 (t, 2H, J = 6.33 Hz), 4.70 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.2, 32.4, 37.7, 42.2, 79.0, 155.9. Anal. Calcd for $C_8H_{16}NO_2Cl$: C, 49.61; H, 8.33; N, 7.23; O, 16.52; Cl, 18.31. Found: C, 49.82; H, 8.22; N, 7.27; Cl, 18.26.

General Procedure for the Preparation of Boc-(arylmethyl)(3-chloropropyl)amines 1−10. Sodium hydride (400 mg, 60% dispersion in mineral oil) was washed with three portions of hexane. Then THF (15 mL) and *N*-(*tert*-butoxycarbonyl)-3-chloropropylamine (1.03 g, 5 mmol) in THF (5 mL) and the arylmethyl bromide (7.5 mmol) were added and heated to reflux for 4 h. Water (10 mL) was added, and the solution was extracted by ether (3 × 20 mL). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by chromatography to give **1**−**10** in 42−63% yields.

Boc-(*S*)-2-phenylpyrrolidine [(*S*)-11]. A solution of **1** (283 mg, 1 mmol) in toluene was transferred to the reaction mixture of (−)-sparteine (364 mg, 1.5 mmol) and *s*-BuLi (1.3 mL, 1.2 M in cyclohexane) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 5 h. Then water (5 mL) and ether (10 mL) were added to quench the reaction. The aqueous layer was extracted with ether (3 × 5 mL) and the combined ether extracts were washed with 5% phosphoric acid (10 mL) and water (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was further purified by chromatography (EtOAc/hexane, 1/9) to give *(S)*-**11** as a colorless oil which solidified at 0 °C (178 mg, 72%): R_f = 0.39 (9:1 hexane/ethyl acetate); mp 58−60 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.16, 1.43 (s, s, 9H), 1.83−1.91 (m, 3H), 2.28 (m, 1H), 3.59 (m, 2H), 4.74, 4.90 (m, m, 1H), 7.14−7.31 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (23.2, 23.3), (28.2, 28.4), (36.0, 36.0), 47.1, 61.3, 79.1, 125.4, 126. 5, 128.1, 154.5. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.87, H, 8.50, N, 5.66. Found: C, 72.89, H, 8.57, N, 5.66. The enantiomeric excess of (*S*)-**11** could be measured directly by chiral stationary phase HPLC on the Whelk-0 column (2.5% iPrOH/hexane; flow rate 1.00 mL/min; R_f of minor peak: 11.1 min, R_f of major peak: 26.0 min). However, the peak from the minor enantiomer was interfered with by trace amounts of unknown highly UV absorptive materials.

Enantiomeric Analysis of (*S*)-11. To a solution of (*S*)-**11** (74 mg, 0.26 mmol) in methylene chloride (2 mL) at ambient temperature was added excess trifluoroacetic acid (15%, 30 mL). The reaction mixture was stirred for 3 h at ambient temperature. The solution was concentrated *in vacuo*, diluted with 10% NaOH (3 mL), and extracted with ether. the combined extracts were washed with water, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give (*S*)-2-phenylpyrrolidine as a light yellow oil (37.4 mg, 86%); $[\alpha]_D$ = −18.6°, c = 0.88 lit.[6a] $[\alpha]_D$ = −22.4°); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.67−2.20 (m, 4H), 2.54 (s, 1H), 2.99 (m, 1H), 3.18 (m, 1H), 4.15, (t, 1H, J = 7.71 Hz), 7.23−7.38 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.5, 34.3, 46.9, 47.1, 62.2, 79.2, 125.5, 126.5, 128.2, 154.6.

To a mixture of (*S*)-2-phenylpyrrolidine in THF (2 mL) and 3,5-dinitrobenzoyl chloride (47 mg, 0.2 mmol) in THF (2 mL) was added triethylamine (30 mL). The resulting mixture was stirred for 2 h at ambient temperature. The solution was concentrated *in vacuo*, diluted with 10% NaOH, and extracted with ether. The combined ethereal extracts were washed with 10% HCl and water, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the 2-phenyl-*N*-(3,5-dinitrobenzoyl)-pyrrolidine as a light yellow solid (83.7 mg, 90%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.97−2.14 (m, 3H), 2.35−2.47 (m, 1H), 3.97 (m, 2H), 4.74, 5.35 (m, m, 1H, ratio: 2:1), 6.93 (m, 1H), 7.19−7.38 (m, 4H), 8.26 (s, 1H), 8.70−9.20 (s,s,s, 2H).

The enantiomeric purity of (*S*)-2-phenyl-*N*-Boc-pyrrolidine was determined to be 96% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative on the (*S*)-N_1N-naphthylleucine column using racemic material as a standard (R_f of minor peak: 41.7 min, R_f of major peak: 46.7 min).[12]

Boc-(*S*)-2-(*p*-chlorophenyl)pyrrolidine (12).[14] Enantioselective cyclization of **2** was carried out using the standard procedure above to give **12** (175 mg, 62%): mp 55−57 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.19, 1.43 (s, s, 9H), 1.85 (m, 3H), 2.29 (m, 1H), 3.57 (m, 2H), 4.72, 4.90 (s,s 2H), 7.07−7.26 (d, d, 4H, J = 8.18 Hz, J = 8.45 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (23.1, 23.4), (28.2, 28.4), 34.8, 36.0), (47.1, 47.3), (60.0, 60.7), 79.4, 126.9, (128.2, 128. 5), (132.1, 132.1), 143.7, 154.4. Anal. Calcd for $C_{15}H_{20}ClNO_2$: C, 64.05; H, 7.11; N, 4.98. Found: C, 64.06; H, 7.18; N, 4.93.

The enantiomeric purity of **12** was determined to be 84% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-(*p*-chlorophenyl)pyrrolidine on the (*S*)-N_1N-naphthylleucine column (R_f of minor peak: 39.6 min, R_f of major peak: 47.5 min).

Boc-(*S*)-2-(*p*-fluorophenyl)pyrrolidine (13).[15] Enantioselective cyclization of **3** was carried out using the standard procedure above to give **13** (182 mg, 69%): mp 69−71 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.18, 1.43 (s, s, 9H), 1.85 (m, 3H), 2.29 (m, 1H), 3.60 (m, 2H), 4.72, 4.90 (s, s 2H), 7.03−7.26 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (23.2, 23.2), (28.2, 28.3), (35.0, 36.1), (47.1, 47.1), (59.9, 60.7), 79.3, (114.7, 114.8), (126.9, 127.0), 140.0,154.5, 159.9, 163.2. Anal. Calcd for $C_{15}H_{21}FNO_2$: C, 67.92; H, 7.54; N, 5.28. Found: C, 67.91; H, 7.54; N, 5.22.

The enantiomeric excess of (*S*)-**13** could be measured directly by chiral stationary phase HPLC on the Whelk-0 column (R_f of minor peak: 10.2 min, R_f of major peak: 24.6 min). The enantiomeric purity of **13** was determined to be 87% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-(*p*-fluorophenyl)pyrrolidine

(28) The possibility that the tin lithium exchange and the deprotonation do not produce the same organolithium intermediate with respect to complexation with (−)-sparteine on the time scale of the experiment is more difficult to rule out, however.

(29) The cyclization to form six-membered rings was attempted, but we were unable to obtain high ee's and good yields.

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

on the (*S*)-N_1N-naphthylleucine column (R_f of minor peak: 40.6 min, R_f of major peak: 47.3 min).

Boc-(*S*)-2-(*p*-tolyl)pyrrolidine (14).[16] Enantioselective cyclization of **4** was carried out using the standard procedure described above to give **14** (165 mg, 65%): mp 65−66 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.19, 1.45 (s,s, 9H), 1.79 (m, 3H), 2.29 (m, 1H), 2.31 (s, 3H), 3.60 (m, 2H), 4.73, 4.74 (s,s, 2H), 7.07−7.26 (d,d, 4H).^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.0, (23.1, 23.1), (28.2, 28.5), (35.0, 36.0), (47.0, 47.2), (60.0, 61.1), 79.1, (125.3, 125.4), (128.7, 129.0), 135.9, (142.0, 142.1), 154.6. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81; N, 5.36. Found: C, 73.63; H, 8.89; N, 5.34.

The enantiomeric purity of **14** was determined to be 86% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-(*p*-methylphenyl)pyrrolidine on the (*S*)-N_1N-naphthylleucine column (R_f of minor peak: 36.1 min, R_f of major peak: 41.3 min).

Boc-(*S*)-2-(*m*-methoxyphenyl)pyrrolidine (15).[17] Enantioselective cyclization of **5** was carried out using the standard procedure above to give **15** (128 mg, 46%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.20, 1.41 (bs, bs, 9H), 1.84 (m, 3H), 2.27 (m, 1H), 3.59 (m, 2H), 3.77 (s, 3H), 4.80 (m, 1H); 6.70−6.75 (m, 3H), 7.16−7.22 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.3, 28.3, 35.9, 47.1, 55.2, 61.2, 79.2, 111.2, 111.7, 117.9, 129.2, 154.6, 159.6.

The enantiomeric purity of **15** was determined to be 96% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-(*m*-methoxyphenyl)pyrrolidine on the (*S*)-N_1N-naphthylleucine column (R_f of minor peak: 37.0 min, R_f of major peak: 41.5 min).

Boc-(*S*)-2-(1-naphthyl)pyrrolidine (16).[18] Enantioselective cyclization of **6** was carried out using the standard procedure above to give **16** (204 mg, 68%): mp 101−103 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.10, 1.49 (s,s, 9H), 1.91 (m, 3H), 2.44 (m, 1H), 3.50−3.78 (m, 2H), 5.59, 5.79 (d, d 2H, J = 6.55 Hz), 7.20−8.02 (m, 7H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (23.0, 23.5), (28.1, 28.5), (33.3, 34.4), (46.9, 47.3), (58.0, 58.2), (79.2, 79.4), (121.4, 121.4), (123.0, 123.3), (125.3, 125.8), (127.1, 127.3), (128.8, 128.8), (128.8, 130.3), (133.8, 139.9), (154.0, 154.6). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.76; H, 7.74; N, 4.71. Found: C, 76.69; H, 7.76; N, 4.74.

The enantiomeric purity of **16** was determined to be 93% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-(1-naphthyl)pyrrolidine on the (*S*)-N_1N-naphthylleucine column (R_f of minor peak: 33.1 min, R_f of major peak: 36.8 min).

Boc-(*S*)-2-(2-naphthyl)pyrrolidine (17).[18] Enantioselective cyclization of **7** was carried out using the standard procedure above to give **17** (205 mg, 70%): mp 95−96 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.14, 1.47 (s, s, 9H), 1.90 (m, 3H), 2.36 (m, 1H), 3.68 (m, 2H), 4.94, 5.15 (s, s 2H), 7.25−7.80 (m, 7H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.19, (28.16, 28.36), (35.81, 35.85), (47.16, 47.19), (61.36, 61.38), 79.26, (123.79, 124.14), (125.34, 125.91), (126.00, 127.59), (127.65, 127.73), (127.97, 128.01), (132.45, 133.27), (154.65, 154.68). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.76; H, 7.74; N, 4.71. Found: C, 76.74; H, 7.72; N, 4.71.

The enantiomeric purity of **17** was determined to be 90% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-(2-naphthyl)pyrrolidine on the (*S*)-N_1N-naphthylleucine column (R_f of minor peak: 42.7 min, R_f of major peak: 52.0 min).

Boc-(*S*)-2-(3-thienyl)pyrrolidine (18). Enantioselective cyclization of **8** was carried out using the standard procedure above to give **18** (127 mg, 51%): mp 42−44 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.28 (bs, 9H), 1.89 (m, 3H), 2.19 (m, 1H), 3.53 (m, 2H), 4.89 (m, 2H), 6.91 (m, 2H), 7.25 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.3, 28.3, 34.7, 46.5, 57.1, 79.2, 119.6, 125.5, 125.9, 145.6, 154.6. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.66; H, 7.50; N, 5.53. Found: C, 61.60; H, 7.47; N, 5.58.

The enantiomeric purity of **18** was determined to be 93% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-(3-thienyl)pyrrolidine on the (*S*)-N_1N-naphthylleucine column (R_f of minor peak: 49.6 min, R_f of major peak: 54.6 min).

Boc-(*S*)-2-(3-furyl)pyrrolidine (19). Enantioselective cyclization of **9** was carried out using the standard procedure above to give **19** (50 mg, 21%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 9H), 1.88 (m, 3H), 2.15 (m, 1H), 3.45 (m, 2H), 4.81 (m, 1H), 6.27 (s, 1H), 7.24 (s, 1H), 7.32 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.4, 28.4, 33.5, 46.2, 52.9, 79.3, 109.0, 128.2, 138.8, 142.9, 154.5.

The enantiomeric purity of **19** was determined to be 96% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-(3-furyl)pyrrolidine on the (*S*)-N_1N-naphthylleucine column (R_f of minor peak: 49.6 min, R_f of major peak: 53.7 min).[31]

Boc-2-(*p*-methoxyphenyl)pyrrolidine (20).[19] Cyclization of **10** was carried out using the standard procedure above (116 mg, 42%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.19 and 1.43 (s, s, 9H), 1.76−1.90 (m, 3H), 2.19−2.38 (m, 1H), 3.59 (brs, 2H), 3.78 (s, 3H), 4.76, 4.90 (s,s 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 4H).[32]

The enantiomeric purity of **20** was measured as 3% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-(*p*-methoxyphenyl)pyrrolidine on the (*S*)-N_1N-naphthylleucine column (R_f of minor peak: (R_f of minor peak: 38.5 min, R_f of major peak: 44.9 min).

One Gram Scale Preparation of Boc-(*S*)-2-phenylpyrrolidine [(*S*)-11]. A solution of **1** (1.13g, 4 mmol) in toluene (40 mL) was transferred to the reaction mixture of (−)-sparteine (1.52 g, 6.26 mmol) and *s*-BuLi (4.8 mL, 1.26 M in cyclohexane) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 8 h, and then water and ether were added to quench the reaction. The aqueous layer was extracted with ether. The combined ether extracts were washed with 5% phosphoric acid and water, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was further purified by chromatography (EtOAc/hexane, 1/9) to give (*S*)-**11** as a colorless oil which solidified at 0 °C (0.65 g, 66%).

The enantiomeric purity of *(S)*-**11** was determined to be 92% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-phenyl-*N*-(*tert*-butoxycarbonyl)pyrrolidine on the (*S*)-N_1N-naphthylleucine column.

The product (0.6 g, 92% ee) was dissolved in hexane (3 mL) and allowed to stand at 0 °C overnight. Needle-like crystals were obtained by filtration (0.53 g, 88%). The enantiomeric purity of (*S*)-**11** was determined to be >98% by chiral stationary phase HPLC of the 3,5-dinitrobenzamide derivative of 2-phenyl-*N*-(*tert*-butoxycarbonyl)-pyrrolidine on the (*S*)-N_1N-naphthylleucine column.

Boc-(*S*)-2-phenyl-(*R*)-5-methylpyrrolidine [(*S,S*)-22]. To a solution of (*S*)-**11** (>98% ee) (130 mg, 0.53 mmol) in ether (2.5 mL) at −78 °C were added (−)-sparteine (291 mg, 1.20 mmol) and *sec*-butyllithium (1 mL, 1.20 M, 1.20 mmol) in ether (2.5 mL, precooled to −78 °C for 15 min). The resulting mixture was stirred at −78 °C for 8 h, and then dimethyl sulfate (253 mL, 216 mg, 2 mmol) was slowly added. This mixture was stirred continuously for another 1 h. Then water was added at −78 °C. The two layers were separated, and the aqueous layer was extracted with ethyl ether. The combined extracts were washed with aqueous H_3PO_4 and water, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was further purified by chromatography (EtOAc/hexane 1/9) to give (*S,S*)-**22** as a colorless oil (60 mg, 45%): ^{1}H-NMR (diastereomerically enriched compound) ($CDCl_3$, 300 MHz) δ 1.07−120 (bs, 9H), 1.38 (d, J = 6.30 Hz, 3H), 1.58 (m, 1H), 1.88 (m, 1H), 2.00 (m, 1H), 2.23 (m, 1H), 4.15 (m, 1H), 4.75 (m, 1H), 7.17−7.32 (m, 5H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 21.0, 28.1, 31.7, 34.7, 54.5, 63.0, 79.0, 125.5, 126.3, 128.1, 144.9, 154.7; HRMS calcd for $C_{16}H_{23}NO_2$ (M+) 261.1729, found 261.1724 (0.5 mDa).

The ratio of diastereomers was measured by GC isothermal conditions at 150 °C (86% de).

1,2-Bis((*S*)-2-phenylpyrrolidinyl)ethane (23). A solution of (*S*)-**11** (97% ee) (0.605g, 2.45 mmol) in methylene chloride (25 mL) at ambient temperature was treated with excess trifluroacetic acid (15%, 3.75 mL) and stirred for 3 h at ambient temperature. The solution was concentrated *in vacuo*, diluted with 10% NaOH (20 mL), and extracted with ether (3 × 20 mL), and the combined extracts were washed with water (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the (*S*)-2-phenylpyrrolidine as a light yellow oil (0.3 g, 83%): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.67−2.20 (m, 4H), 2.54 (s, 1H), 2.99 (m, 1H), 3.18 (m, 1H), 4.15 (t, 1H, J = 7.71 Hz), 7.23−7.38 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.5, 34.3, 47.0, 47.1, 62.2, 79.1, 125.5, 126.5, 128.2, 154.6.

(31) Compound **19** was not characterized in detail due to the impractical yield.

(32) Compound **20** was not characterized in detail due to the low ee.

To a solution of (*S*)-2-phenylpyrrolidine (0.30 g, 2.04 mmol) in methylene chloride (15 mL) were added triethylamine (0.2 mL) and oxalyl chloride (0.132 g, 1.02 mmol) at −78 °C, and the resulting mixture was stirred for 3 h at ambient temperature. The solvent was evaporated *in vacuo*, and the residue was taken up with ether (30 mL), then washed successively with water (10 mL), 5% HCl (10 mL), and water (2 × 20 mL), and dried ($MgSO_4$). The crude product was further purified by chromatography (EtOAc/hexane, 2/3) to give the diamide as a colorless oil which was solidified at 0 °C (0.21 g, 50%); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.61 (m, 3H), 1.91 (m, 2H), 2.10 (m, 1H), 2.47 (m, 1H), 2.87 (m, 1H), 3.63−3.90 (m, 4H), 4.52 (t, 1H), 5.23 (t, 1H), 7.07−7.37 (m, 10H).

A THF (10 mL) solution of the diamide (0.21 g) was added to a stirred suspension of $LiAlH_4$ (0.1 g) in THF (10 mL) at 0 °C, and then the reaction mixture was heated to reflux for 3 h. After the solution was cooled to ambient temperature, aqueous sodium sulfate was added dropwise to the reaction mixture. The resulting precipitate was removed by filtration. The filtrate was dried ($MgSO_4$) and concentrated. The product (*S*,*S*)-**23** was obtained as a white solid (0.16 g, 83%): mp 82−83 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.64−1.89 (m, 6H), 2.10 (m, 5H), 2.65 (m, 2H), 3.21 (m, 4H), 7.20−7.28 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 22.5, 34.9, 53.2, 53.8, 70.5, 126.8, 127.5, 128.2, 143.4. Anal. Calcd for $C_{22}H_{28}N_2$: C, 82.50; H, 8.75; N, 8.75. Found: C, 82.39; H, 8.78; N, 8.73.

General Procedure for the Cyclization of 1 and 1-d_1 To Provide (*S*)-11 and (*S*)-11-d_1. To a solution of (−)-sparteine (0.375 mL, 1.63 mmol) in 5.1 mL of Et_2O at −78 °C was added *sec*-butyllithium (1.28 mL, 1.2 M, 1.53 mmol). After 5 min, a solution of **1** (289 mg, 1.02 mmol) in 5.1 mL of Et_2O at −78 °C was added. After being stirred for 6 h, the reaction mixture was quenched at −78 °C with 10 mL of 0.5 M H_3PO_4 (aq) and allowed to warm to ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography (9:1 hexane/ethyl acetate) yielded a white solid (135 mg, 53%). The enantiomeric excess was determined to be 65% in favor of the *S* enantiomer by chiral stationary phase HPLC (Whelk-0 column; 2.5% *2*-propanol in hexane; 1.0 mL/min). The deuterium enrichment of (*S*)-**11**-d_1 was determined by FIMS: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.31−7.15 (m, 5H), 3.62 (brs, 2H), 2.30 (brs, 1H), 1.84 (m, 3H) 1.44 and 1.18 (brs, 9H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 154.6, 145.0, 128.0, 126.4, 125.4, 79.1, 60.9 (t, J = 21.8 Hz); 47.0, 35.8, 28.1, 23.1.

Boc-*N*-(3-chloropropyl) α-(trimethylstannyl)benzylamine (25). A solution of benzylamine (3.00 g, 28.0 mmol) in CH_2Cl_2 (33 mL) was cooled to 0 °C, and a CH_2Cl_2 solution (17 mL) of di-*tert*-butyl dicarbonate (6.05 g, 27.7 mmol) was added dropwise over 5 min. The resulting solution was stirred for 30 min at 0 °C and for 1 h at ambient temperature and then concentrated *in vacuo*. Recrystallization from hexane gave Boc-benzylamine as white crystals (3.7 g, 64%): mp 52−53 °C; R_f = 0.38 (20:1 hexane/ethyl acetate); ^{1}H-NMR ($CDCl_3$, 300 Mhz) δ 7.26−6.94 (m, 5H), 3.68 (s, 1H), 3.63 and 3.17 (m, 2H), 3.48 (t, J = 6.3 Hz, 2H), 1.95 (qt, J = 6.6 Hz, 2H) 1.51 (s, 9H), −0.03 (s, 9H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 157.4, 143.8, 128.3, 124.5, 124.4, 80.0, 54.9, 46.7, 42.3, 31.5, 28.4, −6.7.

To a solution of Boc-*N*-benzylamine (603 mg, 2.91 mmol) and TMEDA (0.966 mL, 6.40 mmol) in 5.8 mL of THF at −78 °C was added *s*-BuLi (5.33 mL, 6.40 mmol, 1.2 M). After 30 min, trimethyltin chloride (3.2 mL, 3.2 mmol, 1.0 M soln in hexane), was added. The reaction solution was stirred for another 10 min, and then quenched at −78 °C with 30 mL of 0.5 M H_3PO_4 (aq). This was allowed to warm to ambient temperature, the layers were separated, and the aqueous layer was extracted with diethyl ether. The organic extracts were washed with $NaHCO_3$ (aq) and NaCl (aq), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography (silica; 20:1 hexane/ethyl acetate) yielded Boc α-trimethylstannylbenzylamine as a clear, yellow oil (0.82 g, 76%): R_f = 0.38 (20:1 hexane/ethyl acetate). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.28−7.01 (m, 5H), 5.19 (brs, 1H), 4.01 (d, J = 4.0 Hz, 1H), 1.47 (s, 9H), 0.01 (s, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 157.3, 145.0, 128.3, 124.6, 124.2, 79.3, 46.8, 28.3, −7.7.

To a solution of Boc-α-(trimethylstannyl)benzylamine (808 mg, 2.18 mmol) in 4.5 mL of THF at 0 °C was added sodium hydride (131 mg, 60% dispersion in mineral oil, 3.27 mmol). After the mixture was stirred for 15 min, 1-bromo-3-chloropropane (0.323 mL, 3.27 mmol) was added, and this allowed to warm to ambient temperature. After 7 h, the reaction mixture was quenched with NH_4Cl (aq). The aqueous layer was extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (silica; 30:1 hexane/ethyl acetate) yielded **25** as a clear and colorless oil (114 mg, 12%): R_f = 0.37 (30:1 hexane/ethyl acetate); ^{1}H-NMR ($CDCl_3$, 300 Mhz) δ 7.26−6.94 (m, 5H), 3.68 (s, 1H), 3.63 and 3.17 (m, 2H), 3.48 (t, J = 6.3 Hz, 2H), 1.95 (qt, J = 6.6 Hz, 2H) 1.51 (s, 9H), −0.03 (s, 9H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 157.4, 143.8, 128.3, 124.5, 124.4, 80.0, 54.9, 46.7, 42.3, 31.5, 28.4, −6.7.

Transmetalation of 25 to 11. To a solution of **25** (110 mg, 0.246 mmol) and of (−)-sparteine (91 μL, 0.34 mmol) in 2.5 mL of diethyl ether at −78 °C was added *s*-BuLi (0.308 mL, 1.2 M, 0.369 mmol). After 5 h, the reaction mixture was quenched at −78 °C with 5 mL of 0.5 M H_3PO_4 (aq) and allowed to warm to ambient temperature. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification on a preparatory TLC plate (silica; 9:1 hexane/ethyl acetate) yielded a white solid (27 mg, 44%). The enantiomeric excess was measured as 5% in favor of the *S* enantiomer by chiral stationary phase HPLC (Whelk-0 column; 2.5% *2*-propanol in hexane; 1.0 mL/min).

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Supporting Information Available: The specific preparations of **1**−**10**, solvent and organolithium reagent effects on the enantioselective cyclizations of **1**, organolithium reagent effect on the enantioselective cyclization of **8**, the preparations and cyclizations of **21a** and **21b**, the preparation of **1**-d_1, and NMR spectra as criterion of purity of **2**−**5**, **15**, **19**, **20**, and **25** are provided (30 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.

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