Asymmetric Deprotonations: Lithiation of *N*-(*tert*-Butoxycarbonyl)indoline with *sec*-Butyllithium/(−)-Sparteine

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The asymmetric lithiation of *N*-Boc indoline (**1**) with *s*-BuLi/(−)-sparteine and subsequent substitution provides the 2-substituted *N*-Boc indolines **3** and **5**−**11** with excellent enantiomeric ratios and in variable yields. The asymmetric lithiation−substitution sequence with *N*-Boc-7-chloroindoline (**12**) provides products **13**−**19** with good enantiomeric ratios. Mechanistic investigation establishes that the enantioselectivities arise from an initial asymmetric deprotonation to provide the enantioenriched and configurationally stable organolithium intermediates (*S*)-**28** and (*S*)-**29**, which react stereoselectively with electrophiles.

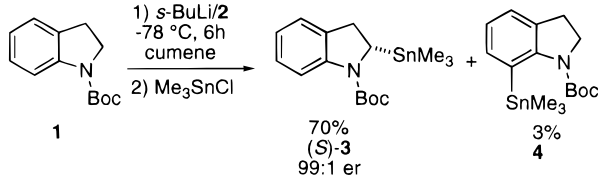
Introduction

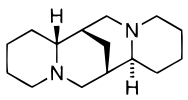
Chiral indoline structures are important in chiral auxiliaries and chiral catalysts as well as in a number of biologically active compounds.[1−4] Syntheses of enantioenriched 2-substituted indolines have included elaborations of the commerically available (*S*)-indoline-2-carboxylic acid[2−4] and chiral auxiliary-mediated cyclizations[5] or reductions.[6] We wish to report asymmetric syntheses of 2-substituted indolines by asymmetric replacement of a prochiral hydrogen in a chiral ligand-mediated asymmetric lithiation−substitution sequence.[7−9]

Lithiation−substitution reactions of *N*-substituted indolines have been reported previously. The *tert*-butyl formamidine functionality has been used as a directing group for the lithiation−substitution of indolines to provide 2-substituted indolines.[10] In contrast, the lithiation of *N*-Boc indoline in the presence of TMEDA occurs regioselectively at the 7-position.[10b,11] However, Meyers and Milot have reported that *N*-Boc-7-deuteroindoline is lithiated to a limited extent at the 2-position.[10b] Indoline lithiocarbamates and dithiolithiocarbamates have recently been reported to undergo lithiation at the 3-position.[12] We now report that *N*-Boc indoline (**1**) and *N*-Boc-7-chloroindoline (**12**) can be metalated selectively in the 2-position with *sec*-butyllithium(*s*-BuLi)/(−)-sparteine (**2**), and the resulting enantioenriched and configurationally stable organolithium intermediates (*S*)-**28** and (*S*)-**29** react readily with electrophiles to provide 2-substituted *N*-Boc indolines with high enantiomeric ratios (er's).

Results and Discussion

Enantioselective Syntheses with (−)-Sparteine. The reaction of **1** with *s*-BuLi/(−)-sparteine (**2**) followed by trimethyltin chloride (Me_3SnCl)[13] provides predominantly the enantioenriched 2-substituted indoline (*S*)-**3** in addition to a small amount of *N*-Boc-7-(trimethylstannyl)indoline (**4**). The lithiation reaction was carried out under the conditions summarized in Table 1. The enantioselectivity of the lithiation−substitution was very high; (*S*)-**3** was formed with a 99:1 er in each reaction carried out at −78 °C.





(-)-sparteine
2

The data in Table 1 show that the regioselectivity of the asymmetric lithiation−substitution and the extent of reaction are dependent on the solvent. When *tert*-butyl

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(1) Bird, C. W.; Cheeseman, G. W. H. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 4, p 89−153.

(2) (a) Kim, Y. H.; Kim, S. H.; Park, D. H. *Tetrahedron Lett.* **1993**, *34*, 6063−6066. Byun, I. S.; Kim, Y. H. (b) Kim, Y. H.; Kim, S. H. *Tetrahedron Lett.* **1995**, *36*, 6895−6898. (c) Choi, J. Y.; Kim, Y. H. *Tetrahedron Lett.* **1996**, *37*, 7795−7796. (d) Corey, E. J.; Harbans, S. S.; Gougoutas, J. Z.; Saenger, W. *J. Am. Chem. Soc.* **1970**, *92*, 2488−2500. (e) Corey, E. J.; McCaully, R. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 2476−2587.

(3) Martens, J.; Dauelsberg, Ch.; Behnen, W.; Wallbaum, S. *Tetrahedron: Asymmetry* **1992**, *3*, 347−350.

(4) (a) Somei, M.; Kawasaki, T. *Chem. Pharm. Bull.* **1989**, *37*, 3426−3428. (b) De Lombaert, S.; Blanchard, L.; Stamford, L. B.; Sperbeck, D. M.; Grim, M. D.; Jenson, T. M.; Rodriguez, H. R. *Tetrahedron Lett.* **1994**, *35*, 7513−7516.

(5) (a) Scholl, v B.; Hansen, H-J. *Helv. Chim. Acta* **1980**, *63*, 1823−1832. (b) Meyers, A. I.; Sielecki, T. M. *J. Org. Chem.* **1992**, *57*, 3673−3676. (c) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566−5572.

(6) Karchava, A. V.; Yurovskaya, M. A.; Wagner, T. R.; Zybailov, L.; Bundel, Y. G. *Tetrahedron: Asymmetry* **1995**, *6*, 2895−2898.

(7) Nozaki, H.; Arantani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905−913.

(8) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfield, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479−1486.

(9) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231−3239.

(10) (a) Meyers, A. I.; Hellring, S. *Tetrahedron Lett.* **1981**, *22*, 5119−5122. (b) Meyers, A. I.; Milot, G. *J. Org. Chem.* **1993**, *58*, 6538−6540.

(11) (a) Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031−1038. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109−1117.

(12) Ahlbrecht, H.; Kornetzky, D.; Purder, T.; Katritzky, A. R.; Ghiviriga, I.; Levell, J. *Synthesis* **1997**, 172−173.

(13) Me_3SnCl is a highly toxic compound and should be handled with appropriate caution. Sax, N. I.; Lewis, R. J. *Dangerous Properties of Industrial Materials*, 7th ed.; Van Nostrand Reinhold: New York, 1988; p 899.

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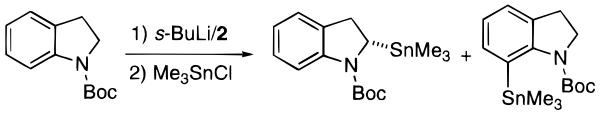
Table 1. Survey of Conditions for the Lithiation−Substitution of 1 To Provide (*S*)-3 and 4[a]



1 (*S*)-3 4

T (°C)	time (h)	solvent	yield (*S*)-**3** (%)	er (*S*)-**3**[b]	yield **4** (%)	**1** (%)
−78	5.5	cumene	70	99:1	3	15
−78	3	cumene	61	99:1	3	25
−78	3	MTBE	58	99:1	17	9
−78	3	toluene	42	99:1	3	48
−40	1	cumene	29	97:3	2	36
−40	0.75	MTBE	23	97:3	20	16

[a] Isolated yields of pure materials are reported. [b] The enantiomeric ratios were determined by chiral stationary phase (CSP) HPLC.

methyl ether (MTBE) was used, the products (*S*)-**3** and **4** were formed in a 3:1 ratio. A 20:1 ratio of (*S*)-**3** to **4** was obtained when cumene was used as the solvent. The reaction was nearly complete after 3 h in MTBE, and only 9% of the starting material was recovered. When the reaction was carried out in cumene for the same amount of time, 25% of the starting material was recovered. A 5.5-h lithiation in cumene followed by electrophilic substitution provided a 70% yield of (*S*)-**3** as well as 15% of the starting material. Although a highly regioselective lithiation−substitution took place in toluene, 48% of the starting material was recovered after a 3-h lithiation.

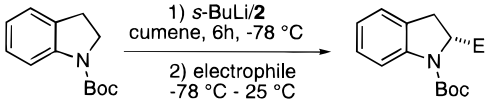
As indicated in Table 1, the reaction could also be carried out at −40 °C to provide (*S*)-**3** with a 97:3 er. At this temperature the regioselectivity of the reaction was also much higher in cumene than in MTBE. Nearly a 1:1 ratio of regioisomers was obtained in MTBE, but the reaction in cumene provided (*S*)-**3** and **4** in a 15:1 ratio. The yields for the reactions carried out at −40 °C were unoptimized, but the high enantioselectivity and regioselectivity of the reaction in cumene demonstrate its utility.

The conditions that were selected for the investigation of the scope of the lithiation−substitution were lithiation for 6 h in cumene at −78 °C followed by the addition of the electrophile. Carbonyl compounds, silyl and stannyl chlorides, and dimethyl sulfate (Me_2SO_4) were used as electrophiles to provide products **5**−**9** with excellent er's and useful yields as summarized in Table 2. In these reactions up to 25% of the starting material was recovered, and the 7-substituted Boc indoline was obtained in <5% yield. A diastereoselectivity of 5:1 was obtained when benzaldehyde was used as the electrophile. The major diastereomer was formed with an er of 98:2, and the minor diastereomer had an er of 91:9.

Low yields of 2-substituted products **10** and **11** were obtained when benzophenone, allyl bromide, and allyl chloride were used as electrophiles. *N*-Boc indole was isolated in 52% yield as the major product from the reaction with benzophenone, and (*R*)-**10** was formed in 11% yield with a 92.5:7.5 er. *N*-Boc indole was also obtained in 23% yield from the reaction with allyl bromide.[14] Indoline (*S*)-**11** was obtained in low yield with an approximate er of 65:35 when allyl chloride and allyl bromide were used as electrophiles. The low enantioselectivity may be explained by low stereoselectivity in the substitution step (*vide infra*). When *N*,*N*′-dimethylpropyleneurea (DMPU) was added to the reaction mixture immediately before the addition of allyl chloride, (*S*)-**11** was obtained in 15% yield with an er of 99:1. Enolizable ketones were unsuccessful as electrophiles in this sequence; the use of cyclohexanone as an electrophile resulted in the recovery of starting material.

When the 7-position of Boc indoline is blocked by a chloro substituent, a lithiation−substitution can be carried out at the 2-position to provide 2-substituted *N*-Boc-7-chloroindolines with good enantioselectivities and in good yields. *N*-Boc-7-chloroindoline (**12**) was prepared by lithiation of *N*-Boc indoline followed by reaction with hexachloroethane as described by Iwao.[11a] The treatment of indoline **12** with a premixed solution of *s*-BuLi/(−)-sparteine in MTBE and subsequent addition of carbonyl electrophiles or trialkyltin chlorides provided products **13**−**17** in good yields with er's of approximately 87:13 as shown in Table 3. Careful recrystallization of enriched indoline (*R*)-**14** enhanced its enantioenrichment to 96:4 er. Although the enantioselectivity for the asymmetric lithiation−substitution of **12** is lower than that of **1**, the deprotonation is actually more facile. A competition

Table 2. Asymmetric Lithiation−Substitution of 1 To Provide 3, 5−11

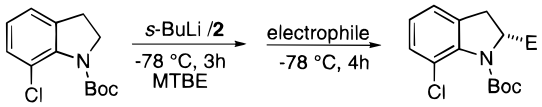


1 3, 5-11

product	electrophile	E	yield (%)[a]	er[b]
(*S*)-**3**	Me_3SnCl	$SnMe_3$	70	99:1
(*R*)-**5**	CO_2	CO_2Me[c]	65	>99:1
(*R*)-**6**, (*R*)-**7**[d]	PhCHO	CH(OH)Ph	61, 13	98:2, 91:9
(*S*)-**8**[e]	Me_2SO_4	Me	52	98.5:1.5
(*S*)-**9**	TMSCl	$SiMe_3$	57	97.5:2.5
(*R*)-**10**	Ph_2CO	$C(OH)Ph_2$	11	92.5:7.5
(*S*)-**11**	C_3H_5Br	$CH_2CH{=}CH_2$	28	68:32
(*S*)-**11**	C_3H_5Cl	$CH_2CH{=}CH_2$	18	65:35
(*S*)-**11**	C_3H_5Cl/DMPU	$CH_2CH{=}CH_2$	15	99:1

[a] Isolated yields of pure materials are reported. [b] The er's were determined by CSP HPLC. [c] The crude product mixture was treated with diazomethane to afford the ester, and the yield of the ester is reported. [d] Two diastereomers of the 2-substituted indoline were obtained. [e] A 3-h lithiation time was used.

Table 3. Asymmetric Lithiation and Substitution of Indoline 12 To Give Enantioenriched 13−17



12 13-17

product	electrophile	E	yield (%)[a]	er[b]
(*R*)-**13**	CO_2	COOH	90	89:11[c]
(*R*)-**14**	Ph_2CO	$C(OH)Ph_2$	77	86:14[d]
(*S*)-**15**	Me_3SnCl	$SnMe_3$	75	87:13
(*S*)-**16**	Bu_3SnCl	$SnBu_3$	69	86.5:13.5
rac-**17**	C_3H_5Br	$CH_2{=}CHCH_2$	32[e]	55:45

[a] Isolated yields of pure materials are reported. [b] The er's were determined by CSP HPLC. [c] The er was determined by conversion of the carboxylic acid to 2-carbethoxy-7-chloroindoline and analysis by CSP HPLC.[16] [d] After recrystallization, the product was obtained with a 96:4 er. [e] Boc-7-chloroindole was isolated in 20% yield.

(14) The indole may arise from oxidation of the 2-lithioindoline with benzophenone or allyl bromide.

experiment between **1** and **12** with *s*-BuLi/(−)-sparteine in cumene established that **12** was lithiated eight times faster than **1**. The presence of the 7-chloro substituent may change the orientation of the Boc group with respect to the α-protons during the lithiation−substitution sequence and thereby alter the rate and enantioselectivity of the reaction.[15]

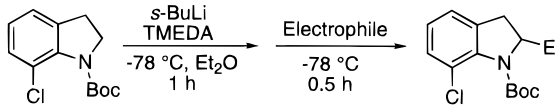
Under optimal conditions the metalation of **12** was carried out in MTBE for 3−4 h at −78 °C, and after the addition of the electrophile, the solution was stirred at −78 °C for an additional 4 h before the addition of aqueous NH_4Cl. The enantioselectivity of the asymmetric lithiation−substitution of **12** was generally not affected by the reaction time or the choice of solvent except for the case of THF. The use of toluene, pentane, or diethyl ether as solvents with Bu_3SnCl as the electrophile provided (*S*)-**16** with an 85:15 er, but racemic **16** was obtained from the reaction carried out in THF.[17] Lower yields were obtained with shorter reaction times and when pentane or toluene was used as a solvent.

The yields of products **13**−**16** from the lithiation−substitution were satisfactory for carbonyl and alkyltin chloride electrophiles as shown in Table 3, and products arising from lithium−chlorine exchange were produced in less than 3% yield when *s*-BuLi and (−)-sparteine were premixed before metalation.[18] When *s*-BuLi was added to a solution of **12** and (−)-sparteine, significantly more lithium−chlorine exchange took place, and the 2- and 7-substituted products were formed in approximately a 3:1 ratio. Lithium−chlorine exchange was the major reaction pathway when **12** was treated with *s*-BuLi in the absence of diamine; therefore, the premixing of *s*-BuLi and (−)-sparteine to complex the free *s*-BuLi is required for high chemoselectivity in the asymmetric lithiation−substitution. In contrast, premixing *s*-BuLi and (−)-sparteine did not have a significant effect on the regiochemical outcome of the lithiation of **1** in MTBE.

The scope of the asymmetric lithiation−substitution of indoline **12** is not as general as for **1**. Methyl iodide (MeI), Me_2SO_4, TMSCl, and allyl chloride were unsuccessful electrophiles. Lithiated **12** appears to be less easily oxidized than **1** since no indole product was isolated during the preparation of (*R*)-**14**. However, a significant amount of *N*-Boc-7-chloroindole[14] was isolated from the reaction mixture when allyl bromide was used as the electrophile, along with a 32% yield of nearly racemic indoline **17**.

Syntheses of Racemic Products with Achiral Diamines. Syntheses of racemic indolines **3**, **5**−**11**, and **13**−**17** were necessary for the verification of the enantiomeric ratios of the enantioenriched products by chiral stationary phase (CSP) HPLC. When 7-chloroindoline **12** was treated with *s*-BuLi/TMEDA at −78 °C for 1−3 h followed by the addition of electrophiles, the 2-substituted *N*-Boc-7-chloroindolines **13**−**17** were obtained as shown in Table 4. As in the asymmetric sequence, the reaction with carbonyl electrophiles or trialkyltin chlorides provides products **13**−**16** in useful yields, and a low yield of **17** was obtained when allyl bromide was the electrophile. TMSCl and MeI were also used successfully as electrophiles in this sequence to provide indolines **18** and **19**, respectively.

Table 4. Lithiations and Substitutions of 12 To Give Racemic 13−19



12 13-19

product	electrophile	E	yield (%)[a]
13	CO_2[b]	COOH	85
14	Ph_2CO	$C(OH)Ph_2$	79
15	Me_3SnCl[c]	$SnMe_3$	83
16	Bu_3SnCl	$SnBu_3$	89
17	C_3H_5Br[d]	$CH_2CH{=}CH_2$	25[e]
18	TMSCl	TMS	88
19	MeI	Me	55

[a] Isolated yields of pure material are reported. The remainder of the mass balance is starting material. [b] The metalation time was 3.5 h, and the reaction was carried out in MTBE. The reaction was quenched at room temperature. [c] The metalation conditions were 2 h in MTBE followed by a room temperature quench. [d] The metalation was for 3 h followed by room temperature quench. [e] *N*-Boc-7-chloroindole was isolated in 19% yield.

Racemic indolines **3**, **5**−**11** cannot be prepared by a lithiation and substitution of indoline **1** in the presence of TMEDA because 7-lithiation is dominant under those conditions.[10b,11] Similarly, the treatment of indoline **1** with *s*-BuLi in the absence of diamine and subsequent reaction with Me_3SnCl afforded only *N*-Boc-7-(trimethylstannyl)indoline in low yield. Racemic indolines **5** and **10** were synthesized from commercially available racemic indoline-2-carboxlic acid in the same way that (*S*)-**5** and (*S*)-**10** were obtained from (*S*)-indoline-2-carboxylic acid (*vide infra*). The achiral ligand **20**, which is structurally similar to (−)-sparteine, was used in the lithiation reaction to provide racemic **3**, **6**−**9**, and **11** along with 7-substituted products **4** and **21**−**24**. As the data in Table 5 indicate, the regioselectivities observed for the lithiations in the presence of bispidine **20** are similar to those observed in the presence of (−)-sparteine in MTBE; therefore, **20** is a better (−)-sparteine mimic than TMEDA.

Determination of Absolute Configuration. The absolute configurations of the lithiation−substitution products were determined by CSP HPLC and optical rotation data comparisons to compounds of known configuration. Ester (*R*)-**5** was prepared by lithiation of **1** and substitution with CO_2 followed by treatment of the crude product mixture with diazomethane (CH_2N_2). The CSP HPLC profile and the optical rotation for (*R*)-**5** were compared to (*S*)-**5**, which was synthesized from (*S*)-indoline-2-carboxylic acid (**25**). Reaction of (*S*)-**25** with thionyl chloride and methanol followed by Et_3N and Boc-O-Boc provided (*S*)-**5** in 76% overall yield. Treatment of (*S*)-**5** with PhMgBr afforded (*S*)-**10**, whose CSP HPLC profile and optical rotation were compared to (*R*)-**10** prepared by asymmetric lithiation−substitution. In

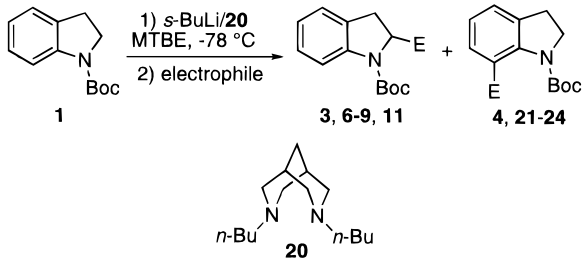
(15) Gross, K. M. B.; Beak, P. Unpublished work. The effect of directing group orientation on benzamide and benzylic alkoxide directed *ortho* lithiation reactions has been reported. Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628−10636.

(16) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. S.; Field, R. E. *J. Chromatog.* **1985**, *348*, 89−96.

(17) Lowered enantioselectivities in the presence of THF have been reported for other (−)-sparteine-mediated reactions of organolithium reagents. (a) Hoppe, I.; Marsch, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2158−2160. (b) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715−721. (c) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757−3758.

(18) These minor products can be removed readily from the enantiomerically enriched products by chromatographic purification. Lithium−halogen exchange of aryl chlorides is not a common reaction and may be facilitated in this case by complexation of the lithiating reagent with the Boc group.[28a] When *tert*-butyllithium/(−)-sparteine was used as a chiral base for the lithiation−substitution of **12**, only the product from lithium−chlorine exchange was isolated.

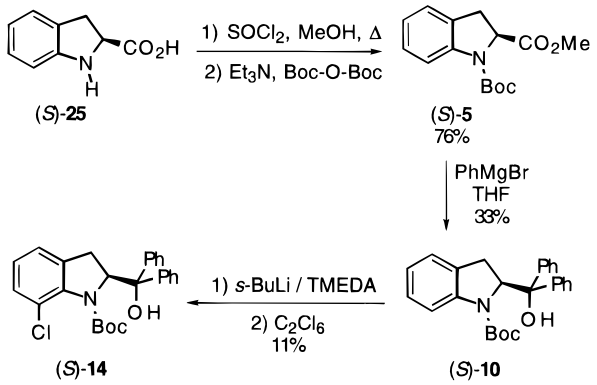
Table 5. Reaction of 1 with *s*-BuLi/20 To Provide Regioisomeric Products[a]



electrophile	E	2-product	yield (%)	7-product	yield (%)
Me_3SnCl[b]	$SnMe_3$	**3**	46	**4**	21
PhCHO[b]	CH(OH)Ph	**6**, **7**	28, 5	**21**	38
MeI[c]	Me	**8**	43	**22**	19
TMSCl[c]	$SiMe_3$	**9**	11	**23**	19
C_3H_5Br[d]	$CH_2CH{=}CH_2$	**11**	26	**24**	8

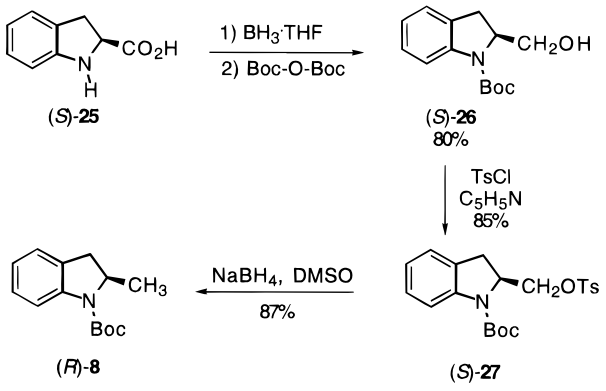
[a] Isolated yields of pure materials are reported. [b] 18-h lithiation. [c] 3-h lithiation. [d] 7-h lithation.

order to determine whether the presence of the chloro substituent changes the sense of enantioselectivity for the asymmetric lithiation−substitution, (*S*)-**10** was allowed to react with *s*-BuLi/TMEDA followed by hexachloroethane to provide (*S*)-**14** in 11% yield along with 70% of the starting material. Each of the products (*S*)-**5**, (*S*)-**10**, and (*S*)-**14** prepared from (*S*)-**25** were found to have a configuration at C-2 that is opposite to the configuration of the products obtained from asymmetric lithiation−substitution.[19]



The absolute configuration of (*S*)-**8** was determined in order to establish the facial selectivity of the reaction of alkylating agents with lithiated **1**. Indoline (*S*)-**25** was reduced to the alcohol with BH_3·THF, and the amine was treated with Boc-O-Boc to provide (*S*)-**26** in 80% yield over two steps. The alcohol was converted to the tosylate (*S*)-**27** in 85% yield, and the tosylate was reduced to (*R*)-**8** with $NaBH_4$ in 87% yield. Indoline (*R*)-**8** was found to have the opposite CSP HPLC profile and optical rotation to (*S*)-**8** formed from the asymmetric lithiation−substitution sequence. Therefore, both carbonyl and alkylating electrophiles were found to give products arising from the same facial selectivity.

(19) We found that (*R*)-**14** is the more retained enantiomer on the (*S*,*S*)-Whelk-O 1 column while (*S*)-**5** is more retained than (*R*)-**5** on the same column. The presence of the 7-chloro may change the conformation of the Boc group, thereby changing the interaction of the substrate with the chiral stationary phase. In contrast, the 7-chloro substituent does not affect the elution order of the 2-carbethoxyindolines.[16]



The absolute configuration of 2-trialkyltin indolines was assigned as *S* since the treatment of optically enriched indoline (*S*)-**3** with *n*-butyllithium (*n*-BuLi) followed by CO_2 or Me_2SO_4 afforded predominantly (*R*)-**5** or (*S*)-**8**, respectively (*vide infra*). Similarly, treatment of 7-chloroindoline (*S*)-**15** with *n*-BuLi followed by benzophenone provided (*R*)-**14**. These assignments involve the assumption that the tin−lithium exchange and reaction with electrophiles proceed with retention of configuration.[20,21] The absolute configurations of (*R*)-**6**, (*R*)-**7**, (*S*)-**9**, and (*S*)-**11** were assigned by analogy to products of known configuration.

Reaction Pathway. Two limiting pathways are available for the enantioselective lithiation−substitution of prochiral substrates with a chiral base: asymmetric deprotonation and asymmetric substitution.[22] In an asymmetric deprotonation a *s*-BuLi and (−)-sparteine complex selectively removes a prochiral proton to give a configurationally stable organolithium intermediate,[9,21] which reacts with electrophiles stereoselectively to give enantioenriched products. In an asymmetric substitution the enantioselectivity is determined during a post-deprotonation step.[23] The series of tin−lithium exchange experiments shown in Table 6 have been carried out with **3** and **15** to distinguish between these alternative pathways.

A tin−lithium exchange experiment with enriched indoline (*S*)-**3** (99:1 er) and *n*-BuLi in cumene followed by addition of CO_2 and subsequent treatment with CH_2N_2 gave the ester (*R*)-**5** in 25% isolated yield with a 99:1 er as shown in Table 6. Similarly, when an enriched sample of (*S*)-**3** of 99:1 er was treated with *n*-BuLi in MTBE in the presence of bispidine **20** followed by the addition of Me_2SO_4 or CO_2/CH_2N_2, (*S*)-**8** and (*R*)-**5** were obtained in 55% and 59% isolated yields, respectively, with er's of 98:2. These experiments established the configurational stability of organolithium intermediate (*S*)-**28** under the reaction conditions both in the absence and in the presence of **20**. The transmetalation in MTBE of en-

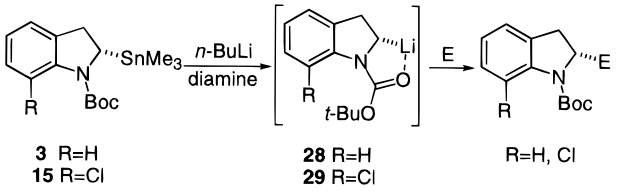
(20) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. Recently a nonstereospecific tin−lithium exchange was reported: Clayden, J.; Pink, J. H. *Tetrahedron Lett.* **1997**, *38*, 2565−2568.

(21) For studies on configurational stability of dipole-stabilized carbanions, see (a) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546−8548. (b) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220−2222. (c) Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *50*, 6077−6088. (d) Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089−6096. (e) Aggarwal, V. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 175.

(22) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560.

(23) (a) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516. (b) Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. (c) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575−1576.

Table 6. Tin−Lithium Exchange Experiments with 3 and 15 To Afford 5, 8, 11, and 14



substrate(er)	diamine	*T*, °C	electrophile	product (er)[a]	yield (%)
(*S*)-**3** (99:1)[b]	none	−78	CO_2	(*R*)-**5** (99:1)	25
(*S*)-**3** (98.5:1.5)[c]	**20**	−78	CO_2	(*R*)-**5** (98.5:1.5)	59
(*S*)-**3** (99:1)[c]	**20**	−78	Me_2SO_4	(*S*)-**8** (98:2)	55[d]
(*S*)-**3** (99:1)[c]	**20**	−40[e]	Me_2SO_4	(*S*)-**8** (97:3)	71[d]
(*S*)-**3** (99:1)[c]	**2**	−78	Me_2SO_4	(*S*)-**8** (95:5)	47[d]
3 (50:50)[c]	**2**	−78	Me_2SO_4	**8** (55:45)	28[d]
(*S*)-**3** (99:1)[c]	**20**	−78	C_3H_5Br	(*S*)-**11** (67:33)	27[d,f]
(*S*)-**15** (88:12)[g]	none	−78	Ph_2CO	(*R*)-**14** (87:13)	38[d]
(*S*)-**15** (87:13)[c]	TMEDA	−78	Ph_2CO	(*R*)-**14** (88:12)	46[d]
15 (50:50)[c]	**2**	−78	Ph_2CO	**14** (50:50)	63[d]

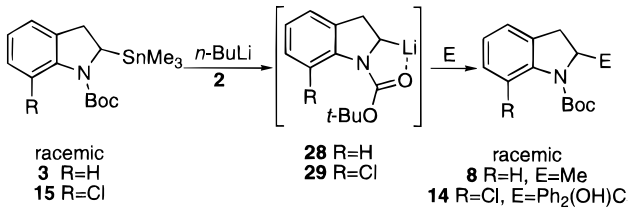
[a] The er's were determined by CSP HPLC. [b] The reaction was carried out in cumene. [c] The reaction was carried out in MTBE. [d] A substantial amount of destannylated material was recovered from the reactions. [e] The transmetalation was carried out at −78 °C, and **28** was allowed to warm to −40 °C over 1 h. The reaction was maintained at −40 °C for 1.25 h and was cooled to −78 °C before reaction with the electrophile. [f] Boc indole was recovered from the reaction. [g] The reaction was carried out in diethyl ether.

riched (*S*)-**3** in the presence of (−)-sparteine followed by substitution with Me_2SO_4 provided enantioenriched (*S*)-**8** with the same absolute configuration obtained for the lithiation−substitution sequence.[24] The organolithium (*S*)-**28** was also determined to be configurationally stable at −40 °C in MTBE in the presence of **20**. The transmetalation of enriched (*S*)-**3** at −78 °C followed by warming to −40 °C for 1.5 h, cooling to −78 °C, and treating with Me_2SO_4 provided (*S*)-**8** in 71% yield and a 97:3 er. The choice of the bispidine ligand **20** was important for these experiments because tin−lithium exchange experiments with (*S*)-**3** in the presence of TMEDA provided very little of the desired substitution product.

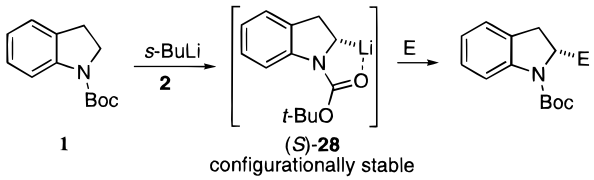
The organolithium (*S*)-**29** was also determined to be configurationally stable by transmetalation experiments. A tin−lithium exchange was carried out with enriched indoline (*S*)-**15** (88:12 er) and *n*-BuLi in diethyl ether, and subsequent reaction with benzophenone provided the alcohol (*R*)-**14** in 38% yield and with an 87:13 er as shown in Table 6. Similarly, when (*S*)-**15** with an 87:13 er was treated with *n*-BuLi in the presence of TMEDA in MTBE, (*R*)-**14** was isolated in 46% yield with an 88:12 er.

A configurationally stable organolithium intermediate is required if an asymmetric deprotonation is the enantiodetermining step for the reaction. The results from the two series of transmetalation experiments indicate that the organolithium intermediates (*S*)-**28** and (*S*)-**29** are configurationally stable under the conditions tested.

In order to test for an asymmetric substitution pathway for the reaction of **1** and **12**, the racemic tin-substituted indolines **3** and **15** were treated with *n*-BuLi in the presence of (−)-sparteine in MTBE to generate racemic **28** and racemic **29**, respectively. The organolithium **28** was allowed to react with Me_2SO_4 in the presence of (−)-sparteine to provide racemic **8** in 28% yield. Racemic **14** was obtained in 63% after racemic **29** was allowed to react with benzophenone in the presence of (−)-sparteine. In these experiments (−)-sparteine did not induce asymmetry in the electrophilic substitution of racemic organolithium intermediates **28** and **29**. Therefore, an asymmetric substitution mechanism can be discounted.



The evidence from the mechanistic studies supports an asymmetric deprotonation pathway for the reaction of **1** and **12** with *s*-BuLi/(−)-sparteine. The generated intermediates (*S*)-**28** and (*S*)-**29** are configurationally stable and react stereoselectively with electrophiles to give enantiomerically enriched products. The facial selectivity of the deprotonation step is lower in the presence of the chloro substituent. The asymmetric deprotonation pathway is also operative in the enantioselective lithiation−substitution of *N*-Boc pyrrolidine, and the sense of enantioselectivity is the same for the two cyclic, five-membered Boc amines.[9] The fact that the carbonyl and alkylating electrophiles give the same sense of chirality in the products is taken to indicate retentive substitutions. The configurational assignments of (*S*)-**28** and (*S*)-**29** are in agreement with the configuration of structurally related (*S*)-*N*-Boc-α-lithiopyrrolidine, which was established previously.[25]



The low enantioselectivity observed for the lithiation of **1** and substitution with allyl bromide or allyl chloride is probably explained by low facial selectivity in the substitution step. The undesired oxidation reaction that occurred in the presence of allyl bromide is not responsible for the erosion of enantioselectivity since this side reaction is minimal in the presence of allyl chloride, and the two electrophiles provide products with the same er. As shown in Table 6, the transmetalation of (*S*)-**3** with a 99:1 er and subsequent reaction with allyl bromide provided indoline (*S*)-**11** with a 67:33 er. It has been demonstrated that the organolithium (*S*)-**28** is configurationally stable under these reaction conditions. It can be concluded that the electrophilic substitution with allyl bromide occurs with 66% retention and 34% inversion of configuration.

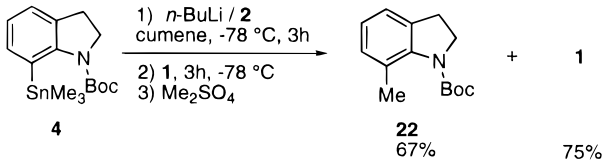
Regioselectivity of the Lithiation. The ligands TMEDA and (−)-sparteine exhibit different regioselectivities in the lithiation of **1**, and differences between

(24) Inversions of configuration have been observed in transmetalation substitutions of enantioenriched tin-substituted amine derivatives in the presence of (−)-sparteine.[17c] (a) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218−12219. (b) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574−1575.

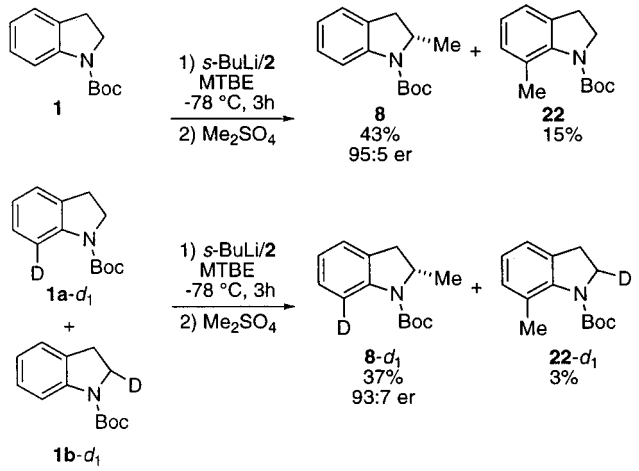
(25) Studies of the deprotonation of (*S*,*S*)-*N*-Boc-dideuteropyrrolidine with *s*-BuLi/(−)-sparteine indicated that the removal of the pro-*S* proton occurs with 94% enantioselectivity. Kerrick, S. T., Ph.D. Thesis, University of Illinois at Urbana−Champaign, 1992.

these two ligands have been observed previously.[26] The present work establishes that dibutyl bispidine **20** is a better analog of (−)-sparteine than is TMEDA.

The regioselectivity of the lithiation of **1** is not determined by a thermodynamic equilibration. The generation of *N*-Boc-7-lithioindoline from **4** in the presence of (−)-sparteine in cumene followed by the addition of **1** resulted in the isolation of only **22** and recovered **1** in 67% and 75% yields, respectively, after preparative HPLC.



We also observed a large kinetic isotope effect for the lithiation of *N*-Boc-7-deuteroindoline in the presence of (−)-sparteine in MTBE. When indoline **1** was treated with *s*-BuLi/(−)-sparteine in MTBE and subsequently allowed to react with Me_2SO_4, (*S*)-**8** and **22** were isolated in 43% yield and 15% yield, respectively. In addition 8% of **1** was recovered. A sample of **1**-d_1 of 99% d_1 was prepared by reaction of **1** with *s*-BuLi/TMEDA followed by MeOD. The product **1**-d_1 was formed as an 81:19 ratio of **1a**-d_1 and **1b**-d_1 as indicated by ^{2}H NMR.[27] When **1**-d_1 was treated with *s*-BuLi/(−)-sparteine in MTBE followed by Me_2SO_4, the products (*S*)-**8**d_1 and **22**-d_1 were isolated in 37% yield and 3% yield, respectively, along with 19% of the starting material. The 86% deuterium incorporation for **22**-d_1 was established by GC/MS and is consistent with the ^{2}H NMR data. From these results, a kinetic isotope effect of approximately 30 can be calculated for the deprotonation of **1a**-d_1. These results show that the regioselectivity in the lithiation of **1** is kinetically determined.



It is reasonable that a prelithiation complex is formed between **1** and *s*-BuLi/(−)-sparteine prior to reaction and that in this complex the Boc carbonyl group should point in the direction of the proton removed in the lithiation of **1**.[28,15] It is possible that the **1**/*s*-BuLi/(−)-sparteine complex that would lead to the transition state for lithiation at C-7 is more sterically conjested than the complex leading to removal of H-2, and consequently a regioselective lithiation at C-2 takes place. Complexes **1**/*s*-BuLi and **1**/*s*-BuLi/TMEDA leading to 7-lithiation may be sterically less encumbered and therefore give rise to a different regiochemical outcome for the reaction.

Summary. The present work demonstrates that *N*-Boc indoline **1** can be deprotonated regioselectively in the 2-position with *s*-BuLi/(−)-sparteine and allowed to react with electrophiles to afford 2-substituted *N*-Boc indolines in variable yields and excellent er's. The regioselectivity of this lithiation−substitution is dependent upon the choice of ligand and solvent, with a 20:1 regioselectivity observed with (−)-sparteine in cumene. In addition, *N*-Boc-7-chloroindoline **12** can be deprotonated in the 2-position with *s*-BuLi/(−)-sparteine and allowed to react with electrophiles to provide 2,7-disubstituted indolines with satisfactory yields and er's. The enantiomerically enriched products obtained from these sequences complement the series of indoline ligands and auxiliaries[2,3] that are available from the commercially available (*S*)-indoline-2-carboxylic acid. The source of enantioselectivity is an asymmetric deprotonation. The organolithium intermediates (*S*)-**28** and (*S*)-**29** formed in these reactions are configurationally stable and react stereoselectively with a variety of electrophiles.

Experimental Section

General. Organolithium reagents were handled under dry nitrogen. All reagents were obtained from commercial sources and were used without further purification unless otherwise noted. (−)-Sparteine was obtained from (−)-sparteine sulfate pentahydrate and distilled under vacuum from calcium hydride as reported previously.[9] TMEDA, toluene, and TMSCl were distilled from calcium hydride under a nitrogen atmosphere. Benzaldehyde, Me_2SO_4, DMPU, and DMSO were distilled from calcium hydride under vacuum. Diethyl ether (Et_2O), MTBE, THF, and pentane were distilled from sodium and benzophenone under nitrogen. Cumene was distilled from sodium metal. Allyl bromide and allyl chloride were passed through a plug of neutral alumina prior to use. Solutions of *s*-BuLi in cyclohexane and *n*-BuLi in hexanes were titrated using the method of Suffert.[29] Either the Regis Rexchrom Pirkle Concept D-phenylglycine column, the (*R*,*R*)-Beta-Gem 1 column or the Regis (*S*,*S*)-Whelk-O 1 column was used for the separation of enantiomers. Retention times (rt) are given in minutes.

General Procedure for the Asymmetric Deprotonation of 1-(*tert*-Butoxycarbonyl)indoline. To a 0.1 M solution of **1** (1 equiv) under a N_2 atmosphere was added (−)-sparteine (**2**) (1.3 equiv), and the solution was cooled to −78 °C. A 1.3 M solution of *s*-BuLi (1.3 equiv) in cyclohexane was added, and the yellow solution was allowed to stir at −78 °C for several hours. An excess of the electrophile (1.5 equiv) was added, and the solution was allowed to come to room temperature slowly and stirred overnight. The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O. The organic extracts were washed with 5% H_3PO_4 solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Crude product mixtures were purified by flash chromatography and preparative HPLC.

Preparation of Enantiomerically Enriched (*S*)-1-(*tert*-Butoxycarbonyl)-2-(trimethylstannyl)indoline (3). To a solution of **1** (91.4 mg, 0.417 mmol) and **2** (125 μL, 0.542 mmol)

(26) Other reports indicate that TMEDA and (−)-sparteine do not effect the same configurational stability in intermediate organolithiums.[23c,24]

(27) This result is dependent upon experimental conditions. When a bottle of *s*-BuLi that was not filtered through Celite was used for the reaction, a 96:4 ratio of 7-substituted to 2-substituted products was obtained as determined by ^{2}H NMR.

(28) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356−363. (b) Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092−7093.

(29) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509−510.

in cumene was added *s*-BuLi (0.42 mL, 1.3 M, 0.54 mmol) at −78 °C. After 5.5 h a solution of Me_3SnCl[13] (0.63 mL, 1.0 M, 0.63 mmol) in hexanes was added, and the solution was allowed to come to room temperature and stirred overnight. Following flash chromatography on basic alumina with 100% hexane and preparative HPLC with 0.5% EtOAc/hexane, 110.8 mg (70%) of **3** was isolated as a colorless oil: $[\alpha]^{25}_D$ +95° (*c* 0.0203, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.9 (br, 0.3H), 7.50 (br, 0.7H), 7.15 (d, J = 7.1 Hz, 2H), 6.94 (t, J = 7.35 Hz, 1H), 4.25 (br, 0.3H), 4.08 (br, 0.7H), 3.46−3.34 (br, 1H), 3.15−3.04 (br, 1H), 1.58 (s, 9H), 0.09 (s, J(Sn−C) = 52 Hz, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.6, 142.2, 133.0, 127.1, 124.7, 122.0, 114.9, 81.1, 49.1, 31.8, 28.5, −9.1 (J(Sn−H) = 335 Hz, 330 Hz). Anal. Calcd for $C_{16}H_{25}NO_2Sn$: C, 50.30; H, 6.59; N, 3.67. Found: C, 50.29; H, 6.66; N, 3.71. The enantiomers of **3** were separated by CSP HPLC using the (*S*,*S*)-Whelk-O 1 column (100% hexane, 0.5 mL/min): rt = 11.7 min (1%), 12.7 min (99%).

In addition 1-(*tert*-butoxycarbonyl)-7-(trimethylstannyl)indoline (**4**) (4.7 mg, 3%) was produced as a white solid, and starting material **1** (13.3 mg, 15%) was recovered from this reaction.

Preparation of Enantiomerically Enriched (*R*)-1-(*tert*-Butoxycarbonyl)-2-carbomethoxyindoline (5). To a solution of **1** (132 mg, 0.601 mmol) and **2** (180 μL, 0.78 mmol) in cumene was added *s*-BuLi (0.60 mL, 1.3 M, 0.78 mmol) at −78 °C. After 6 h CO_2 was bubbled through the flask for 5 h, and the reaction was allowed to come to room temperature slowly and stirred overnight under a positive pressure of CO_2. After the reaction was quenched with water, the layers were separated, and 5% HCl was added to bring the aqueous solution to pH 2. The aqueous layer was extracted with Et_2O (3 × 15 mL), and the combined organic extracts were treated with CH_2N_2[30] in Et_2O at 0 °C until a yellow color persisted. The solution was allowed to stand at room temperature overnight and was concentrated *in vacuo*. The crude material was purified by flash chromatography with 5% EtOAc/hexane, and **5** (108.0 mg, 65%) was obtained as a colorless oil: $[\alpha]^{25}_D$ +63° (*c* 0.0073, $CHCl_3$). The ^{1}H NMR data matched that of (*S*)-**5** (*vide infra*). The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (0.75% IPA/hexane, 1.5 mL/min): rt = 14.6 (0.5%), 15.5 (99.5%).

In addition 21% (27.3 mg) of the starting material was recovered, and a material tentatively identifed as *N*-(*tert*-butoxycarbonyl)-7-carbomethoxyindoline (4.8 mg, 3%) was isolated as an off-white solid.

Preparation of Enantiomerically Enriched (*R*)-1-(*tert*-Butoxycarbonyl)-α-phenyl-2-indoline Methanol (6 and 7). To a solution of **1** (95.4 mg, 0.435 mmol) and **2** (130 μL, 0.566 mmol) in cumene was added *s*-BuLi (0.44 mL, 1.3 M, 0.57 mmol) at −78 °C. After 6 h benzaldehyde (66 μL, 0.66 mmol) was added, and the solution was allowed to come to room temperature and stirred overnight. Following flash chromatography and preparative HPLC with 10% EtOAc/hexane, the major diastereomer, **6** (86.5 mg, 61%), was isolated as a colorless oil: $[\alpha]^{25}_D$ +37° (*c* 0.0127, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (br, 1H), 7.36−7.26 (m, 5H), 7.17 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.95 (t, J = 7.3 Hz, 1H), 4.81 (m, 1H), 4.65 (d, J = 8.8 Hz, 1H), 3.07 (dd, J = 9.8, 16.6 Hz, 1H), 2.63 (d, J = 16.6 Hz, 1H), 1.65 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3, 145.4, 141.2, 130.4, 128.4, 128.0, 127.4, 127.3, 124.7, 123.0, 116.2, 82.6, 77.4, 64.9, 30.8, 28.4. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.93; H, 7.09; N, 4.52. The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (2.5% IPA/hex, 1.25 mL/min): rt = 15.0 (2%), 28.8 (98%). The ^{13}C NMR and elemental analysis data were obtained for the racemic compound.

The minor diastereomer **7** (18.7 mg, 13%) was isolated as a white solid, difficult to purify: mp 109−112 °C; $[\alpha]^{25}_D$ +38° (*c* 0.0090, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.5 (br, 1H), 7.41 (d, J = 7.5, 2H), 7.34 (br, 2H), 7.27 (br, 1H), 7.15−7.08 (m, 2H), 6.92 (t, J = 7.3 Hz, 1H), 5.31 (d, J = 2.2 Hz, 1H), 4.71 (br, 1H), 3.11−2.99 (br m, 2H), 1.60 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.2, 130.9, 128.3, 127.4, 127.1, 125.9, 124.4, 122.7, 115.1, 81.7, 74.4, 65.0, 28.4, 28.0; HRMS calcd for $C_{20}H_{23}NO_3$ (M^+) 325.1677, found 325.1678 (0.0 mDa). The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (2.5% IPA/hex, 1.25 mL/min): rt = 14.6 (9%), 18.7 (91%). The resonances of the carbonyl carbon and one aromatic carbon are quite broad and are not listed in the ^{13}C data.

Preparation of Enantiomerically Enriched (*S*)-1-(*tert*-Butoxycarbonyl)-2-methylindoline (8). To a solution of **1** (131 mg, 0.596) and **2** (180 μL, 0.78) in cumene was added *s*-BuLi (0.60 mL, 1.3M, 0.78 mmol) at −78 °C. After 3 h Me_2SO_4 (85 μL, 0.89 mmol) was added, and the solution was allowed to come to room temperature and stirred overnight. Following purification by preparative HPLC with 1% EtOAc/hexane, **8** (71.7 mg, 52%) was isolated as a colorless oil: $[\alpha]^{25}_D$ +39° (*c* 0.0101, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (br, 1H), 7.15 (m, 2H), 6.93 (td, J = 1.0, 7.4 Hz, 1H), 4.51 (br, 1H), 3.34 (dd, J = 9.8, 15.9 Hz, 1H), 2.61 (d, J = 15.9 Hz, 2H), 1.58 (s, 9H), 1.29 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.2, 141.7, 129.9, 127.2, 124.9, 122.2, 115.2, 80.5, 55.1, 35.6, 28.4, 21.1. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.89; H, 8.43; N, 6.02. The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (0.5% IPA/hexane, 1.25 mL/min): rt = 10.0 (1.5%), 11.3 (98.5%).

In addition, **1** (30.0 mg, 23%) was recovered from the reaction as well as **22** (3.6 mg, 3%). The ^{1}H NMR data of **22** matched the previously reported data.[11a]

Preparation of Enantiomerically Enriched (*S*)-1-(*tert*-Butoxycarbonyl)-2-(trimethylsilyl)indoline (9). To a solution of **1** (173 mg, 0.788 mmol) and **2** (234 μL, 1.02 mmol) in cumene was added *s*-BuLi (0.66 mL, 1.55 M, 1.02 mmol) at −78 °C. After 6 h TMSCl (150 μL, 1.2 mmol) was added, and the solution was allowed to come to room temperature and stirred overnight. Following chromatography on basic alumina with hexane, **9** (130 mg, 57%) was isolated as a colorless oil: $[\alpha]^{25}_D$ +96° (*c* 0.0145, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.4 (br, 1H), 7.15−7.09 (m, 2H), 6.90 (td, J = 0.98, 7.6 Hz, 1H), 4.03 (dd, J = 2.9, 11.7 Hz, 1H), 3.43 (br m, 1H), 2.87 (dd, J = 3.0, 15.7 Hz, 1H), 1.56 (s, 9H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.7, 142.9, 132.4, 127.1, 124.3, 122.3, 115.8, 80.6, 50.2, 30.2, 28.4, −3.1; HRMS calcd for $C_{16}H_{25}NO_2Si$ (M^+) 291.1650, found 291.1655 (0.5 mDa). The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (1% IPA/hex, 1.25 mL/min): rt = 5.4 (2.3%), 6.5 (97.7%).

In addition, **1** (43.8 mg, 25%) was recovered from this reaction as well as **23** (13 mg, 3%). The ^{1}H NMR data of **23** agreed with the previously reported data.[11a]

Chromatography on silica gel causes decomposition of (*S*)-**9**.

Preparation of Enantiomerically Enriched (*R*)-1-(*tert*-Butoxycarbonyl)-2-(diphenylhydroxymethyl)indoline (10). To a solution of **1** (117 mg, 0.534 mmol) and **2** (160 μL, 0.70 mmol) in cumene was added *s*-BuLi (0.53 mL, 1.3 M, 0.70 mmol) at −78 °C. After 7 h a solution of benzophenone (146 mg, 0.801 mmol) in cumene was added, and the solution was allowed to come to room temperature and stirred overnight. Following flash chromatography (5−10% EtOAc/hexane), (*R*)-**10** (22.9 mg, 11%) was isolated as a white solid: mp 88−92 °C. The spectral data for enriched (*R*)-**10** agreed with that reported for (*S*)-**10** (*vide infra*). The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (2.5% IPA/hexane, 1.25 mL/min): rt = 9.5 (92%) and 20.6 (8%).

The major product from this reaction was 1-(*tert*-butoxycarbonyl)indole (60.2 mg, 52%), which was identified by comparison of its ^{1}H NMR data to previously reported data.[31] Starting material (23.7 mg, 20%) was also recovered.

Preparation of Enantiomerically Enriched (*S*)-1-(*tert*-Butoxycarbonyl)-2-allylindoline (11). To a solution of **1** (112 mg, 0.511 mmol) and **2** (150 μL, 0.67 mmol) in cumene was added *s*-BuLi (0.51 mL, 1.3 M, 0.67 mmol) at −78 °C. After 6 h allyl bromide (66 μL, 0.77 mmol) was added, and the solution was allowed to come to room temperature and stirred overnight. Following purification by preparative HPLC with 1% EtOAc/hexane, (*S*)-**11** (37.6 mg, 28%) was isolated as a colorless oil: $[\alpha]^{25}_D$ +29° (*c* 0.0099, $CHCl_3$); ^{1}H NMR ($CDCl_3$,

(30) Black, T. H. *Aldrichim. Acta* **1983**, *16*, 3−10.

400 MHz) δ 7.75 (br, 1H), 7.18−7.12 (m, 2H), 6.93 (td, J = 0.98, 7.6 Hz, 1H), 5.79−5.68 (m, 1H), 5.11−5.05 (m, 2H), 4.46 (br, 1H), 3.24 (dd, J = 9.8, 16.1 Hz, 1H), 2.79 (dd, J = 2.0, 16.1 Hz, 1H), 2.52 (br, 1H) 2.32−2.25 (m, 1H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.2, 140, 133.7, 130, 127.3, 124.8, 122.3, 117.9, 118.1, 82.5, 58.5, 39.0, 32.7, 28.4. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.69; H, 8.08; N, 5.41. The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (0.5% IPA/hexane, 1.00 mL/min): rt = 10.1 (32%), 11.2 (68%).

In addition, 1-(*tert*-butoxycarbonyl)indole[31] (25.2 mg, 23%) and **1** (28.6, 26%) were isolated from this reaction.

Preparation of Enantiomerically Enriched (*S*)-1-(*tert*-Butoxycarbonyl)-2-(trimethylstannyl)indoline (3) at −40 °C. To a solution of **1** (116 mg, 0.527 mmol) and **2** (160 μL, 0.69 mmol) in 5.5 mL of cumene at −40 °C was added *s*-BuLi (0.53 mL, 1.3 M, 0.69 mmol). The solution stirred at −40 °C for 1 h, and a solution of Me_3SnCl[13] (0.79 mL, 1.00 M, 0.79 mmol) in hexanes was added. The solution was maintained at −40 °C for 1 h, and then the reaction was quenched with water. The workup was as described above. Following flash chromatography with 2% EtOAc/hexane and preparative HPLC with 0.5% EtOAc/hexane, (*S*)-**3** (59.3 mg, 29%) was isolated as a colorless oil. The enantiomers were separated by CSP HPLC using the (*R*,*R*)-Beta-Gem column (100% hexane, 0.25 mL/min): rt = 18.4 min (3%), 20.2 min (97%).

In addition **1** (41.9 mg, 36%) was recovered from the reaction as well as **4** (4.4 mg, 2.2%).

General Procedure for the Asymmetric Deprotonation of 1-(*tert*-Butoxycarbonyl)-7-chloroindoline (12). To a solution of (−)-sparteine (**2**) (1.2 equiv) in MTBE was added a solution of *s*-BuLi (1.2 equiv) in cyclohexane at −78 °C. The solution was stirred for 10 min, and a precooled solution of **12** (1 equiv) in MTBE was added to the *s*-BuLi/(−)-sparteine. The solution was stirred for 3.5 h, and then an excess of electrophile (1.5 equiv) was added. After 3 h, the reaction was quenched at −78 °C with 5 mL of 15% NH_4Cl solution. The mixture was allowed to come to room temperature slowly and stirred overnight. The aqueous solution was then extracted with ether (3 × 10 mL). The combined organic layers were washed with 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude products were purified by flash chromatography. The er's were determined by analytical CSP HPLC.

Preparation of Enantiomerically Enriched (*R*)-1-(*tert*-Butoxycarbonyl)-7-chloro-2-(diphenylhydroxymethyl)indoline (14). To a 0.28 M solution of **2** (330 μL, 1.4 mmol) and *s*-BuLi (1.07 mL, 1.35 M, 1.44 mmol) at −78 °C was added a 0.06 M solution of **12** (304 mg, 1.20 mmol). A 0.36 M solution of benzophenone in MTBE was added. Following the workup and chromatographic purification with 5% EtOAc/hexane as the eluent, indoline (*R*)-**14** (403 mg, 77%) was isolated as a white solid: mp 138−141 °C; $[\alpha]^{26}_D$ +78° (*c* 0.0046, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.32 (m, 7H), 7.14−7.11 (m, 3H), 6.97 (t, J = 4.5 Hz, 1H), 6.75 (d, J = 4.9 Hz, 2H), 5.44 (dd, J = 1.1, 9.4 Hz, 1H), 4.46 (br, 1H), 3.64 (dd, J =9.5, 16.6 Hz, 1H), 2.92 (d, J = 16.8 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, 144.5, 141.7, 140.4, 135.5, 128.3, 127.9, 127.6, 127.3, 127.0, 124.9, 123.7, 121.9, 82.7, 80.7, 69.0, 33.4, 27.9. Anal. Calcd for $C_{26}H_{26}NO_3Cl$: C, 71.63; H, 6.01; N, 3.22. Found: C, 71.60; H, 6.02; N, 3.25. The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (5% IPA/hexane, 1.25 mL/min): rt = 6.7 (14%), 7.6 (86%). The elemental analysis data were obtained for racemic material.

Recrystallization of 273 mg of (*R*)-**14** from Et_2O/pentane yielded 177 mg (65%) of crystals: mp 145−147 °C. The er of the product was determined to be 96:4 by HPLC. The crystals of enriched (*R*)-**14** were optically pure but were accompanied by a small amount of racemic powder, which also crystallized from the mother liquor.

Preparation of Enantiomerically Enriched (*S*)-1-(*tert*-Butoxycarbonyl)-7-chloro-2-(trimethylstannyl)indoline (15). To a 0.04 M solution of indoline **12** (102.1 mg, 0.402 mmol) was added a 0.10 M solution of **2** (110 μL, 0.48 mmol) and *s*-BuLi (0.43 mL, 1.1 M, 0.48 mmol). After the addition of Me_3SnCl[13] (1.0 M, 0.60 mL, 0.60 mmol), the solution was stirred at −78 °C for 5 h. Following chromatographic purification (2.5−5% EtOAc/hexane), 15.4 mg of starting material was recovered, and (*S*)-**15** (131.4 mg, 78%) was obtained as a colorless oil: $[\alpha]^{25}_D$ +51° (*c* 0.0094, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 7.1 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 4.22 (dd, J = 7.0, 8.7 Hz, 1H), 3.34 (dd, J = 8.9, 15.5 Hz, 1H), 2.89 (dd, J = 6.8, 15.5 Hz, 1H), 1.52 (s, 9H), 0.07 (s, J(Sn−H) = 53.1 Hz, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.6, 140.9, 138.5, 128.7, 124.9, 123.8, 122.4, 81.2, 53.4 (J(Sn−C) = 388.9 Hz), 34.6, 28.1, −9.4 (J(Sn−C) = 339.5 Hz, 324.3 Hz); HRMS calcd for $C_{16}H_{24}ClNO_2Sn$ (M^+) 413.0513, found 413.0513 (0.0 mDa). The enantiomers were separated on the (*R*,*R*)-Beta-Gem column (100% hexane, 0.5 mL/min): rt = 7.5 (12%), 8.4 (88%).

In addition **4** (2 mg, 1%) was isolated as a white solid.

Preparation of Enantiomerically Enriched (*S*)-1-(*tert*-Butoxycarbonyl)-7-chloro-2-(tributylstannyl)indoline (16). To a 0.07 M solution of **2** (85 μL, 0.37 mmol) and *s*-BuLi (0.29 mL, 1.3 M, 0.37 mmol) was added a 0.03 M solution of **12** (77.9 mg, 0.307 mmol). Bu_3SnCl was added, and following the workup and chromatographic purification (2.5% EtOAc/hexane), indoline (*S*)-**16** (116 mg, 69%) was isolated as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 7.0 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 4.46 (dd, J = 4.1, 9.3 Hz, 1H), 3.51 (dd, J = 9.4, 15.3 Hz, 1H), 2.89 (dd, J = 4.0, 15.4 Hz, 1H), 1.53 (s, 9H), 1.40 (m, 6H), 1.25 (sextet, J = 7.0 Hz, 6H), 0.85 (t, J = 7.1 Hz, 9H), 0.8−0.9 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 140.8, 138.6, 128.7, 125.0, 124.2, 122.5, 81.0, 53.4, 35.0, 29.0, 28.2, 27.4, 13.6, 9.4. Anal. Calcd for $C_{25}H_{42}NO_2ClSn$: C, 55.32; H, 7.80; N, 2.58. Found: C, 55.37; H, 7.88; N, 2.53. The enantiomers were separated on the (*R*,*R*)-Beta-Gem column (100% hexane, 1.0 mL/min): rt = 2.9 (13.5%), 3.2 (86.5%). The elemental analysis data were obtained for the racemic compound.

Preparation of Enantiomerically Enriched (*S*)-2-Allyl-1-(*tert*-butoxycarbonyl)-7-chloroindoline (17). To a 0.03 M solution of indoline **12** (71.0 mg, 0.280 mmol) were added **2** (77 μL, 0.34 mmol, 0.07 M) and *s*-BuLi (0.26 mL, 1.3 M, 0.34 mmol) at −78 °C. Allyl bromide (36 μL, 0.42 mmol) was added, and following chromatographic purification with 2.5−5% EtOAc/hexane and preparative HPLC with 1% EtOAc/hexane, **17** (26 mg, 32%) was isolated as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.95 (t, J = 7.7 Hz, 1H), 5.85−5.64 (m, 1H), 5.07−5.02 (m, 2H), 4.61 (q, J = 7.3 Hz, 1H), 3.35 (dd, J = 8.5, 15.9 Hz, 1H), 2.59 (d, J = 15.9 Hz, 1H), 2.39 (m, 1H), 2.21 (m, 1H), 1.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 139.5, 135.7, 133.9, 128.9, 125.0, 124.2, 123.7, 117.6, 81.4, 62.0, 39.4, 34.2, 28.2. Anal. Calcd for $C_{16}H_{20}NO_2Cl$: C, 65.41; H, 6.86; N, 4.77. Found: C, 65.44; H, 6.76; N, 4.86. The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (2% IPA/hexane, 1.00 mL/min): rt = 6.1 (55%), 6.6 (45%).

Also isolated from this reaction were a colorless oil tentatively identified as *N*-Boc-7-chloroindole (7.7 mg, 11%) and **12** (12.2 mg, 17%).

Preparation of Enantiomerically Enriched (*R*)-1-(*tert*-Butoxycarbonyl)-7-chloroindoline-2-carboxylic Acid (13). To a 0.08 M solution of indoline **12** (95.4 mg, 0.376 mmol) at −78 °C was added a 0.09 M precooled solution of **2** (104 μL, 0.451 mmol) and *s*-BuLi (0.34 mL, 1.3 M, 0.45 mmol). After 3.5 h, a stream of CO_2 was passed through the flask for 0.5 h. The solution was stirred at −78 °C for 3 h under a positive pressure of CO_2. The reaction was quenched with water, and the aqueous solution was acidified to pH 2 with 10% HCl and extracted with Et_2O. Following chromatographic purification with 10−50% MeOH/EtOAc, *N*-Boc-indoline-7-carboxylic acid (3.1 mg, 3%) was obtained as a white solid,[11a] and (*R*)-**13** (100.5 mg, 90%) was obtained as a white solid.

To indoline (*R*)-**13** (76.9 mg, 0.258 mmol) in ethanol (10 mL) was slowly added thionyl chloride (23 μL, 0.31 mmol) at −10 °C. The solution was allowed to stir at room temperature for 45 min and was then heated at 65 °C for 2 h. The thionyl chloride was removed by successive additions of ethanol (3 ×

(31) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157−164.

15 mL) followed by concentration *in vacuo*: The crude oil was chromatographed on silica gel with 5% EtOAc/hexane containing 0.5% Et_3N to give 2-carbethoxy-7-chloroindoline (30.8 mg, 53%) as a colorless oil: $[\alpha]^{23}_D$ +36.5° (*c* 0.0139, methanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.66 (t, J = 7.7 Hz, 1H), 4.55 (br, 1H), 4.42 (dd, J =6.1, 9.7 Hz, 1H), 4.21 (q, J = 7.1 Hz), 3.4 (*AB*-X q's, C+ = 1027.7 Hz, C− = 1020.6 Hz, J(A−B) = 15.9 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2, 147.1, 128.1, 127.3, 122.5, 120.0, 115.2, 61.4, 59.5, 34.2, 14.0. Anal. Calcd for $C_{11}H_{12}NO_2Cl$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.94; H, 5.37; N, 6.39. The enantiomers were separated on the D-phenylglycine column (5% IPA/hexane, 2.00 mL/min): rt = 5.4 (11%), 7.2 (89%).

In addition the indole ethyl ester (9.8 mg, 19%) was obtained as a white solid: mp 105−106 °C (lit.[32] 113.5−114 °C).

General Procedure for the Deprotonation of 1-(*tert*-Butoxycarbonyl)-7-chloroindoline (12) in the Presence of TMEDA. To a 0.03 M solution of **12** in Et_2O or MTBE was added TMEDA (1.2 equiv), and the solution was cooled to −78 °C. A solution of *s*-BuLi in cyclohexane (1.2 equiv) was added, and the solution was allowed to stir for 1−4 h. An excess of the electrophile (1.5 equiv) was added, and the solution was either allowed to stir for 0.5 h at −78 °C or allowed to come to ambient temperature slowly and stirred overnight. A 15% solution of NH_4Cl in water was added to quench the reaction. The aqueous solution was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude materials were purified by flash chromatography.

Preparation of Racemic 1-(*tert*-Butoxycarbonyl)-7-chloro-2-(trimethylsilyl)indoline (18). TMSCl was used as the electrophile to provide after chromatographic purification 170 mg (88%) of indoline **18**, which was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, J = 7.9 Hz, 1H), 7.03 (d, J = 7.3 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 4.14 (dd, J = 1.4, 10.5 Hz, 1H), 3.53 (dd, J = 10.6, 15.5 Hz, 1H), 2.71 (d, J = 15.5 Hz, 1H), 1.52 (s, 9H), −0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.7, 140.9, 137.8, 128.6, 125.1, 124.4, 122.4, 81.0, 54.0, 31.3, 28.2, −3.9. Anal. Calcd for $C_{16}H_{24}NO_2ClSi$: C, 58.97; H, 7.42; N, 4.30. Found: C, 58.99; H, 7.22; N, 4.13.

Preparation of Racemic 1-(*tert*-Butoxycarbonyl)-7-chloro-2-methylindoline (19). MeI was used as the electrophile to provide after chromatographic purification 110 mg (55%) of indoline **19**, which was obtained as an off-white solid: mp 74−76 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 6.95 (t, J = 7.8 Hz, 1H), 4.70 (m, 1H), 3.42 (dd, J =7.9, 15.6 Hz, 1H), 2.45 (d, J = 15.6 Hz, 1H), 1.55 (s, 9H), 1.25 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 139.0, 135.6, 129.0, 124.9, 124.2, 123.2, 81.2, 58.7, 36.8, 28.2, 21.3. Anal. Calcd for $C_{14}H_{18}NO_2Cl$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.71; H, 6.79; N, 5.22.

Preparation of (*S*)-1-(*tert*-Butoxycarbonyl)-2-carbomethoxyindoline (5). To (*S*)-indoline-2-carboxylic acid **25** (259.8 g, 1.59 mmol) in methanol (20 mL) was added thionyl chloride (140 μL, 1.9 mmol) at −10 °C. The solution was allowed to stir at −10 °C for 0.5 h and then was heated at reflux for 3 h. The thionyl chloride was removed by successive additions of methanol (3 × 15 mL) followed by concentration *in vacuo*, and the resulting yellow amine hydrochloride salt was carried on without purification. To the salt was added CH_2Cl_2, and the solution was cooled to 0 °C followed by the addition of Et_3N (550 μL, 4.0 mmol) and di-*tert*-butyldicarbonate (Boc-O-Boc) (462 mg, 2.11 mmol). The solution was stirred at room temperature for 24 h. The reaction was quenched with water (10 mL), and the aqueous solution was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Following chromatographic purification with 5% EtOAC/hexane as the eluent, methyl ester (*S*)-**5** (335.4 mg, 76%) was obtained as a white solid: mp 51−53 °C; $[\alpha]^{22}_D$ −73° (*c* 0.0088, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (br, 0.66 H), 7.43 (br, 0.33H), 7.19 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 7.4 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 4.9 (br, 1H), 3.75 (s, 3H), 3.4 (m, 1H), 3.11 (dd, J = 4.4, 17 Hz, 1H), 1.50 (br s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 151.4, 142.4, 128.7, 127.7, 124.2, 122.4, 114.4, 81.1, 60.2, 52.1, 32.4, 28.0. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.01; H, 7.06; N, 5.12. The enantiomeric purity of the product was verified using the (*S*,*S*)-Whelk-O 1 column (0.75% IPA/hexane, 1.5 mL/min): rt = 14.6 (100%).

Preparation of (*S*)-1-(*tert*-Butoxycarbonyl)-2-(diphenylhydroxymethyl)indoline (10). A solution of (*S*)-**5** (1.17 g, 4.24 mmol) in 25 mL of THF was cooled to 0 °C. A solution of PhMgBr (3.0 M, 2.96 mL, 8.89 mmol) in Et_2O was added to the solution slowly. After stirring for 7 h at 0 °C to room temperature, the solution was quenched with 10% aqueous H_2SO_4 (3 mL). The aqueous solution was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Following flash chromatographic purification with 5−20% EtOAc/hexane, pure indoline (*S*)-**10** (418 mg, 25%) was obtained as a white solid: mp 88−92 °C; $[\alpha]^{26}_D$ −110° (*c* 0.0052, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4−7.26 (m, 8H), 7.11 (d, J = 4.4, 3H), 7.02 (t, J = 7.7, 1H), 6.87−6.78 (m, 2H), 5.46 (dd, J = 2.5, 10.3 Hz, 1H), 4.9 (br, 1H), 3.43 (dd, J = 16.2, 16.8 Hz, 1H), 2.94 (dd, J = 2.0, 16.7 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.8, 145.0, 142.2, 131.0, 127.9, 127.5, 127.4, 127.2, 127.1, 126.9, 126.8, 123.8, 122.7, 115.9, 82.3, 82.1, 66.8, 33.0, 28.1. Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.53; H, 7.21; N, 3.27. The enantiomeric purity was verified using the (*S*,*S*)-Whelk-O 1 column (2.5% IPA/hexane, 1.25 mL/min): rt = 20.5 (100%).

Preparation of (*S*)-1-(*tert*-Butoxycarbonyl)-7-chloro-2-(diphenylhydroxymethyl)indoline (14) from (*S*)-1-(*tert*-Butoxycarbonyl)-2-(diphenylhydroxymethyl)indoline (10). To a solution of (*S*)-**10** (325.9 mg, 0.812 mmol) and TMEDA (0.37 mL, 2.4 mmol) in MTBE (30 mL) at −78 °C was added *s*-BuLi (1.7 mL, 1.4 M, 2.4 mmol). After 7 h at −78 °C, a solution of hexachloroethane (636.6 mg, 2.69 mmol) in MTBE (15 mL) was added to the red anion. The solution was allowed to come to room temperature slowly and stirred overnight. The reaction was quenched with water (5 mL), and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic extracts were washed with 5% H_3PO_4 (5 mL), dried over $MgSO_4$, filtered, and concentrated. Following flash chromatography with 5% EtOAc/hexane and preparative HPLC using 5% EtOAc/hexane, (*S*)-**14** (37.5 mg, 11%) was isolated as an oil: $[\alpha]^{26}_D$ −116° (*c* 0.0203, $CHCl_3$). The enantiomeric purity of the product was verified by analysis on the (*S*,*S*)-Whelk-O 1 column (2.5% IPA/hexane, 1.25 mL/min): rt = 7.3 (100%). The remainder of the material isolated from this reaction was identified as starting material (*S*)-**10** (224 mg, 69%).

Preparation of (*R*)-1-(*tert*-Butoxycarbonyl)-2-methylindoline (8) from (*S*)-2-indolinecarboxylic Acid (25). To a solution of (*S*)-**25** (979 mg, 6.00 mmol) in 12 mL of THF at 0 °C was added BH_3·THF (15.0 mL, 15.0 mmol), and the solution was allowed to come to room temperature and stirred for 24 h. Water was added to quench the reaction, and the aqueous solution was extracted with Et_2O (3 × 20 mL). The organic solution was washed with saturated $NaHCO_3$ (2 × 5 mL) and brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 2-(hydroxymethyl)indoline (752 mg, 84%) as an off-white solid: mp 60−62 °C (lit. 68−69 °C[2e]). To a solution of 2-(hydroxymethyl)indoline in CH_2Cl_2 (5 mL) at 0 °C was added Boc-O-Boc (1.10 g, 5.03 mmol) in CH_2Cl_2 (2 mL), and the solution was allowed to stir for 16 h. Following concentration *in vacuo* and Kugelrohr distillation (125−135 °C @ 0.05 mmHg), (*S*)-**26** (1.17 g, 94%) was obtained as a viscous oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (br, 1H), 7.18−7.11 (m, 2H), 6.96 (td, J = 0.98, 7.6 Hz, 1H), 4.61 (br, 1H), 3.79−3.69 (m, 2H), 3.35 (dd, J = 10.3, 16.4 Hz, 1H), 2.87−2.49 (br, 2H), 1.59 (s, 9H). The material was converted to the tosylate without further purification.

To a solution of (*S*)-**26** (1.17 g, 4.69 mmol) in 11 mL of pyridine and 5 mL of CH_2Cl_2 at 0 °C was added tosyl chloride (1.79 g, 9.38 mmol), and the solution was allowed to stir for 18 h. Water was added, and the mixture was allowed to stir

(32) Ishii, H.; Murakami, Y.; Furuse, T.; Hosoya, K.; Ikeda, N. *Chem. Pharm. Bull.* **1973**, *21*, 1495−1505.

for 1 h before separating the layers. The aqueous layer was extracted with Et_2O (3 × 30 mL). The extracts were washed with 6 M HCl, saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide 1.71 g of a mixture of starting material (0.44 mmol, 9%) and (*S*)-**27** (3.97 mmol, 85%) as an off-white solid: mp 78−81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.14 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 4.60 (br, 1H), 4.20 (dd, J = 3.7, 9.7 Hz, 1H), 3.99 (br, 1H), 3.76−3.71 (m, 0.2 H), 3.28 (dd, J = 10.1, 16.4 Hz, 1H), 2.95 (dd, J = 1.6, 16.7 Hz, 1H), 2.43 (s, 3H), 1.59 (s, 1H), 1.49 (s, 9H). The product mixture was used in the reduction without purification.

To a mixture of (*S*)-**27** (3.80 mmol) and $NaBH_4$ (374 mg, 9.89 mmol) was added freshly distilled DMSO.[33] The reaction was heated to 100 °C and stirred for 12 h. The solution was diluted with water, and the aqueous solution was extracted with Et_2O (3 × 40 mL). The organic layers were washed with water (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Following purification by flash chromatography using 5% EtOAc/hexane, (*R*)-**8** (769 mg, 87%) was isolated as a colorless oil: $[\alpha]^{26}_D$ −41.7° (*c* 0.0247, $CHCl_3$). The product was identified by comparison of its ^{1}H NMR data to (*S*)-**8**. The enantiomeric purity of (*R*)-**8** was established by analysis on the (*S*,*S*)-Whelk-O 1 column (0.5% IPA/hexane, 1.25 mL/min): rt = 9.1 (100%).

Preparation of 3,7-Dibutyl-3,7-diazabicyclo[3.3.1]-nonane (20). To a solution of butylamine (6.00 g, 82.0 mmol), K_2CO_3 (23.0 g, 172 mmol), ethanol (250 mL), and water (125 mL) heated at reflux was added dropwise a solution of 4-methylpiperidone methiodide (29.5 g, 0.115 mol), which was prepared by the published method.[34] The reaction was heated at reflux for 1.5 h and cooled to room temperature, and the ethanol was removed *in vacuo*. The water layer was extracted with Et_2O (3 × 50 mL), and the combined Et_2O layers (red color) were dried over K_2CO_3. Filtration, concentration *in vacuo*, and Kugelrohr distillation (70−85 °C, 0.8 mmHg) provided 4-butyl-1-piperidone as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63 (t, J = 5.8 Hz, 4H), 2.35 (t overlapping with m, 6H), 1.41 (m, 2H), 1.27 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.2, 57.2, 53.1, 41.2, 29.5, 20.6, 14.0. The ^{13}C data are consistent with previously reported data.[35]

The conversion of 4-butyl-1-piperidone to **20** was carried out using a modification of the approach of Smissman and Ruenitz.[36] To a solution of 4-butyl-1-piperidone (7.36 g, 47.5 mmol) in ethanol (100 mL) were added butylamine (3.47 g, 47.5 mmol) and acetic acid (2.70 mL, 47.5 mmol), and the solution was heated at reflux for 7 h. The ethanol was removed *in vacuo* to provide a thick red oil that was treated with 50% KOH (100 mL) and extracted with Et_2O (3 × 100 mL). The combined Et_2O layers were dried over Na_2SO_4, filtered, and concentrated to provide a red oil that was carried on to the next step without purification.

The red oil was rinsed into a steel bomb with butanol (100 mL), and anhydrous hydrazine (5.20 mL, 166 mmol) and potassium *tert*-butoxide (10.7 g, 95.0 mmol) were added. The bomb was sealed and heated at 180 °C for 12 h. The reaction vessel was cooled and the contents poured into a separatory funnel. The bomb was rinsed with Et_2O (200 mL), and the mixture was separated. The organic layer was washed with brine (200 mL), and the brine was extracted with Et_2O (2 × 200 mL). The combined organic layers were dried over K_2CO_3, filtered, and concentrated to provide a brown oil, which was distilled (97−100 °C, 0.4 mmHg) to afford **20** (4.87 g, 43% from 4-butyl-1-piperidone) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.72 (m, 4H), 2.20 (m, 8H), 1.86 (m, 2H), 1.26−1.50 (m, 8H), 0.90 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 59.3, 58.4, 21.1, 30.2, 29.6, 21.2, 14.3. These data are consistent with data previously reported for this compound.[36]

General Procedure for the Deprotonation of *N*-Boc Indoline with *s*-BuLi/20. To a 0.1 M solution **1** in MTBE and **20** (1.3 equiv) at −78 °C under a N_2 atmosphere was added a 1.3 M solution of *s*-BuLi (1.3 equiv) in cyclohexane. The yellow solution was stirred at −78 °C for 18 h, and then an excess of the electrophile (1.5 equiv) was added. The solution was allowed to come to room temperature slowly and stirred overnight. The reaction was quenched with water, and the aqueous solution was extracted with Et_2O. The combined organic layers were washed with 5% H_3PO_4, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product mixtures were purified by flash chromatography or preparative HPLC.

General Procedure for Tin−Lithium Exchange Experiments with (*S*)-1-(*tert*-Butoxycarbonyl)-2-(trimethylstannyl)indoline (3) and (*S*)-1-(*tert*-Butoxycarbonyl)-7-chloro-2-(trimethylstannyl)indoline (15). To a 0.02−0.1 M solution of (*S*)-**3** or (*S*)-**15** and diamine (1.3 equiv) was added a solution of *n*-BuLi (1.3 equiv) in hexanes at −78 °C, and exchange was allowed to take place for several hours. An excess of electrophile (1.5 equiv) was added at −78 °C, and the reaction was allowed to warm to room temperature slowly and stirred overnight before the aqueous quench in the case of (*S*)-**3**. For the reactions with (*S*)-**15**, following the addition of the electrophile the reaction temperature was maintained at −78 °C for 2−3 h before quenching with a 15% NH_4Cl solution (5 mL). The aqueous solution was extracted with Et_2O (3 × 10 mL), and the organic layers were washed with brine (5 mL) or 5% H_3PO_4 (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product mixtures was carried out using flash chromatography.

Tin−Lithium Exchange Experiment with (*S*)-1-(*tert*-Butoxycarbonyl)-2-(trimethylstannyl)indoline (3) at −40 °C. To a solution of (*S*)-**3** (165 mg, 0.432 mmol) and **20** (142 mg, 0.598 mmol) at −78 °C in MTBE was added *n*-BuLi (0.39 mL, 1.5 M, 0.598 mmol). The yellow solution was maintained at −78 °C for 20 min and then allowed to warm to −40 °C over 45 min. The solution was maintained at −40 °C for 1.25 h and recooled to −78 °C over 20 min. Me_2SO_4 (82 μL, 0.86 mmol) was added, and the solution was allowed to come to room temperature slowly and stirred overnight. The reaction was quenched with water, and the aqueous solution was extracted with Et_2O (3 × 20 mL). The organic extracts were washed with 5% H_3PO_4 (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Following purification by preparative HPLC (1% EtOAc/hexane), (*S*)-**8** (78.5 mg, 78%) was isolated as a colorless oil. The enantiomers were separated on the (*S*,*S*)-Whelk-O 1 column (0.5% IPA/hexane, 1.25 mL/min): rt = 10.0 (1.5%), 11.3 (98.5%).

Preparation of (*S*)-1-(*tert*-Butoxycarbonyl)-2-allylindoline (11) via Tin−Lithium Exchange. To a solution of (*S*)-**3** (99:1 er, 118 mg, 0.307 mmol) and **20** (86.5 mg, 0.363 mmol) in 4 mL of MTBE at −78 °C was added *n*-BuLi (0.25 mL, 1.5 M, 0.36 mmol). After 2.5 h at −78 °C, allyl bromide (40 μL, 0.46 mmol) was added, and the solution was allowed to come to room temperature slowly and stirred overnight. Following preparative HPLC with 1% EtOAc/hexane, (*S*)-**11** (21.5 mg, 27%) was isolated as a colorless oil along with **1** (8.7 mg, 13%) and *N*-Boc indole (16.3 mg, 24%). The enantiomers of **11** were separated on the (*S*,*S*)-Whelk-O 1 column (0.5% IPA/hexane, 1.00 mL/min): rt = 9.9 (33%), 11.1 (67%).

General Procedure for Tin−Lithium Exchange Experiments with Racemic 1-(*tert*-Butoxycarbonyl)-2-(trimethylstannyl)indoline (3) and 1-(*tert*-Butoxycarbonyl)-7-chloro-2-(trimethylstannyl)indoline (15) in the Presence of (−)-Sparteine. To a 0.02−0.1 M solution of **3** or **15** and **2** (1.3 equiv) was added a solution of *n*-BuLi (1.3 equiv) in hexanes at −78 °C, and exchange was allowed to take place for several hours. An excess of electrophile (1.5 equiv) was added at −78 °C, and the reaction was allowed to warm to room temperature slowly and stirred overnight before the aqueous quench in the case of **3**. For the reaction with **15**, following the addition of the electrophile the reaction temper-

(33) Hutchins, R. O.; Kandasamy, D.; Dux, F.; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259−2267.

(34) Thompson, M. D.; Holt, E. M.; Berlin, K. D. *J. Org. Chem.* **1985**, *50*, 2580−2581.

(35) von Luppen, J.; Lepoivre, J.; Lemière, G.; Alderweireldt, F. *Heterocycles* **1984**, *22*, 749−761.

(36) Smissman, E. E.; Ruenitz, P. C. *J. Org. Chem.* **1976**, *41*, 1593−1597.

ature was maintained at −78 °C for 2−3 h before quenching with a 15% NH_4Cl solution (5 mL). The aqueous solution was extracted with Et_2O (3 × 10 mL), and the organic layers were washed with brine (5 mL) or 5% H_3PO_4 (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product mixtures was carried out using flash chromatography.

Evaluation of the Kinetic Isotope Effect for the Deprotonation of 1-(*tert*-Butoxycarbonyl)indoline (1). To a solution of **1** (126.7 mg, 0.578 mmol) and **2** (173 μL, 0.751 mmol) in MTBE (6 mL) at −78 °C was added *s*-BuLi (0.58 mL, 1.3 M, 0.75 mmol). The yellow solution was stirred for 3 h, and then Me_2SO_4 (82 μL, 0.87 mmol) was added. The solution was allowed to come to room temperature slowly and stirred overnight, and the standard workup procedure was used (*vide supra*). Following purification by preparative HPLC (1% EtOAc/hexane), (*S*)-**8** (58.1 mg, 43%) was isolated as a colorless oil. The enantiomers of (*S*)-**8** were separated on the (*S,S*)-Whelk-O 1 column (0.5% IPA/hexane, 1.25 mL/min): rt = 10.0 (5%), 11.3 (95%). Indoline **22** (20.2 mg, 15%) was isolated as a colorless oil, and its characterization data matched the previously reported data. In addition, 8% (10.0 mg) of **1** was recovered from the reaction.

To a solution of **1a**-d_1 and **1b**-d_1 (120.5 mg, 0.550 mmol, 81:19 ratio determined by ^2H NMR, 99% d_1) and **2** (164 μL, 0.714 mmol) in MTBE (6 mL) at −78 °C was added *s*-BuLi (0.55 mL, 1.3 M, 0.71 mmol). The yellow solution was stirred for 3 h, and then Me_2SO_4 (78 μL, 0.82 mmol) was added. The solution was allowed to come to room temperature slowly and stirred overnight, and the standard workup procedure was used (*vide supra*). Following purification by preparative HPLC (1% EtOAc/hexane), (*S*)-**8**-d_1 (47.1 mg, 37%) was isolated as a colorless oil. The enantiomers of (*S*)-**8**-d_1 were separated on the (*S,S*)-Whelk-O 1 column (0.5% IPA/hexane, 1.25 mL/min): rt = 10.0 (7%), 11.3 (93%). Indoline **22**-d_1 (4.0 mg, 3%) was isolated as a colorless oil, and its deuterium incorporation was determined to be 86.1% by GC/MS analysis. In addition, 19% (22.6 mg) of **1** was recovered from the reaction.

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Supporting Information Available: The experimental details for the synthesis of racemic products **3**, **5**−**11**, and **13**−**17** are available. The characterization data for 7-substituted products **4**, **21**−**24**, and *N*-Boc-7-carbomethoxyindoline, *N*-Boc indole, *N*-Boc-7-chloroindole, and 2-carbethoxy-7-chloroindole. The experimental details for the formation of (*S*)-**3** and **4** in various solvents are reported as well as the details of the tin−lithium exchange experiments in Table 6. The competition experiment between **1** and **12** and the transmetalation of **4** in the presence of **1** are described. The calculation of the kinetic isotope effect is provided. The ^{13}C and ^1H NMR spectra are provided for those compounds for which no elemental analysis data were reported (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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