Asymmetric Syntheses of N-Boc 2-Substituted Pyrrolidines and Piperidines by Intramolecular Cyclization

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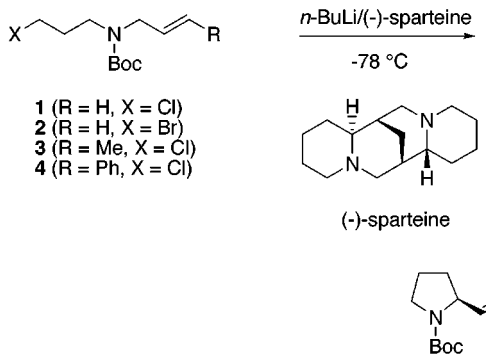
Asymmetric lithiation-substitutions by *n*-BuLi/(−)-sparteine with the *N*-Boc-*N*-(3-halopropyl)-allylamines **1**−**4** provide the *N*-Boc-2-alkenylpyrrolidines (*S*)-**5**, (*S*)-**6**, and (*S*)-**7** in yields of 31−93% with enantiomeric ratios (ers) from 65:35 to 90:10. These reactions are shown to involve an initial asymmetric deprotonation, but the enantiodetermining step is a subsequent asymmetric cyclization under the influence of the chiral ligand. Extension to formation of a piperidine is illustrated by reaction of *N*-Boc-(4-chlorobutyl)cinnamylamine (**9**) to afford (*S*)-*N*-Boc-2-(*trans*-*β*-styryl)piperidine ((*S*)-**10**) in 68% yield with an enantiomeric ratio (er) of 84:16. Analogous reactions with epoxide ring openings of *N*-Boc-*N*-(oxaalkenyl)benzylamines **11** and **12** afford the corresponding *N*-Boc-2-phenyl-3-(hydroxymethyl)pyrrolidine (**13**) in 67% yield with a diastereomeric ratio (dr) of 50:50 and ers of 97:3 and 95:5 and the corresponding *N*-Boc-2-phenyl-3-(hydroxymethyl)piperidine (**14**) in 29% yield with a dr of 86:14 and ers of 81:19 and 86:14.

Recent studies have established that reactions of organolithium species complexed to (−)-sparteine can afford highly enantioenriched products in lithiation−substitution sequences.[2] We have reported an intramolecular version in which (*S*)-*N*-Boc-2-arylpyrrolidines are obtained in >91:9 enantiomeric ratios (ers) by the lithiation−cyclization of the corresponding *N*-Boc-(3-chloropropyl)arylmethylamines with *s*-BuLi/(−)-sparteine.[3] We now report enantioselective syntheses of *N*-Boc-2-alkenylpyrrolidines, a *N*-Boc-2-alkenylpiperidine, a *N*-Boc-2-phenyl-3-(hydroxymethyl)pyrrolidine, and a *N*-Boc-2-phenyl-3-(hydroxymethyl)piperidine by lithiation−cyclizations of the appropriate *N*-Boc-allylmethylamine or *N*-Boc-arylamine derivative with the *n*-BuLi/(−)-sparteine complex.

The lithiation−cyclization of *N*-Boc-*N*-(3-chloropropyl)-allylamine (**1**) with 1.2 equiv of *n*-BuLi/sparteine at −78 °C in ether for 3 h provides (*S*)-**5** in 93% yield with an enantiomeric ratio (er) of 83:17. The cyclization is regiospecific at the α-position of the allyl group; the possible seven-membered ring product from cyclization at the *γ*-position is not observed.[4] With bromine as the leaving group, **2** affords (*S*)-**5** in 31% yield in toluene with an er of 65:35. The absolute configuration of (*S*)-**5** is based on comparison of optical rotation to the *N*-ethoxycarbonyl carbamate of previously assigned enantiomers.[5]

The double bond geometry of the reactant is retained in the product. Treatment of *N*-Boc-*N*-(3-chloropropyl)-cinnamylamine (**4**) with *n*-BuLi/sparteine in Et_2O at −78 °C for 2 h followed by warming to −25 °C for 1 h affords (*S*)-**7** in 85% yield with an er of 90:10.[6] After one recrystallization from hexane, the enantiomeric ratio of **7** is increased to 97:3 with a 70% yield for the recrystallization. The absolute configuration of (*S*)-**7** was determined by oxidative cleavage of the olefin to afford *N*-Boc-proline followed by synthesis of the amide derivative for CSP−HPLC analysis.[7] When the 3:1 mixture of trans and cis **3** was treated with *n*-BuLi/sparteine in ether at −78 °C for 4 h, the products **6** are obtained in a trans:cis ratio of 3:1 in 70% yield with ers of 92:8 and 75:25, respectively.



The mechanism of lithiation−cyclization of **4** to (*S*)-**7** could involve either an asymmetric deprotonation or an asymmetric substitution as the enantiodetermining step.[2] If an asymmetric deprotonation is operative, a *n*-BuLi/

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(6) When **4** was treated with *n*-BuLi/(−)-sparteine at −78 °C for 10 h in ether and quenched with water at −78 °C, **7** was produced in 16% yield with an er of 90:10.

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Table 1. Reactions of 4 and *rac*-4-d_1 in Ether to Provide 7 and 7-d_1

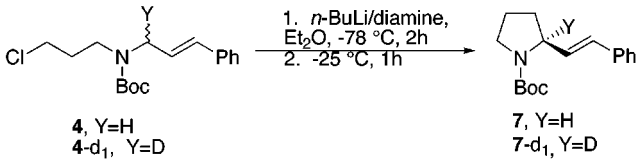
reactant	diamine	yield (%)	product	er	d_1 (%)[a]
4	TMEDA	70	*rac*-**7**		
4	(−)-sparteine	85	(*S*)-**7**	90:10	
rac-**4**-d_1	TMEDA	62	*rac*-**7**-d_1		95
rac-**4**-d_1	(−)-sparteine	45	(*S*)-**7**-d_1	90:10	73

[a] Deuterium incorporation determined by GC/MS.

(−)-sparteine complex would act as a chiral base and provide an enantioenriched lithium intermediate which cyclizes faster than it epimerizes. In the case of asymmetric substitution, deprotonation of **4** with *n*-BuLi/(−)-sparteine would provide a racemic organolithium intermediate either directly or by epimerization, and this intermediate could then undergo diastereoselective cyclization under the influence of the (−)-sparteine to give (*S*)-**7**. These possibilities can be distinguished by experiments with *rac*-**4**-d_1 and *rac*-**8**.

If the stereodetermining step is an asymmetric deprotonation, significant differences in deuterium contents, ers, and yields of the products should be observed between the reaction of **4** and *rac*-**4**-d_1 (97% d_1). If the asymmetric induction occurs only through asymmetric substitution and there is no facial selectivity in deprotonation, (*S*)-**7**-d_1 should be formed selectively with a deuterium content comparable to that of *rac*-**7**-d_1 due to the large deuterium isotope effect at −78 °C.[3,8]

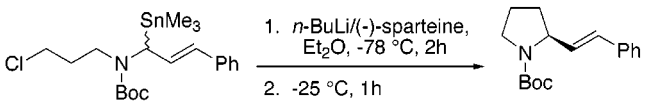
Lithiation−cyclizations of **4** and *rac*-**4**-d_1 were carried out in Et_2O, and comparison of the deuterium content for *rac*-**7**-d_1 and (*S*)-**7**-d_1 and the enantiomeric ratios for (*S*)-**7** and (*S*)-**7**-d_1 are shown in Table 1. The deuterium content (73%) of (*S*)-**7**-d_1 is appreciably different from the deuterium content (95%) of *rac*-**7**-d_1, a result which indicates that an asymmetric deprotonation is operative. The yield is decreased for the lithiation−cyclization of *rac*-**4**-d_1 which shows the asymmetric deprotonation by *n*-BuLi/(−)-sparteine is retarded by the kinetic isotope effect. The lower yield, decreased percent deuterium, and same ers within experimental error (±5%) indicate that both the deuterium kinetic isotope effect and the enantioselectivity are sufficiently high to limit reaction of *rac*-**4**-d_1 and that the facial selectivity in the deprotonation step can override the kinetic isotope effect. The asymmetric deprotonation does not, however, determine the enantiomeric ratio of the product.



4, Y=H
4-d_1, Y=D

7, Y=H
7-d_1, Y=D

The ers of the products from the reaction of **4** and *rac*-**4**-d_1 with *n*-BuLi/(−)-sparteine have the same value as shown in Table 1. This indicates the enantiodetermining step is the asymmetric substitution. Confirmation of the pathway has been carried out by the transmetalation of racemic tin precusor **8** to generate the racemic lithium intermediate in the presence of (−)-sparteine to provide (*S*)-**7** in 41% yield and an er of 89:11. This result confirms that the asymmetric induction occurs via an asymmetric substitution.

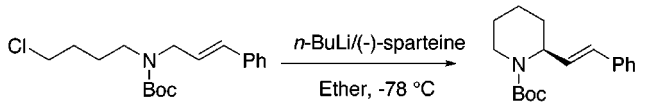


8

89:11 er
41% yield
(*S*)-**7**

The data establish that reaction pathway involves an initial asymmetric deprotonation. On the basis of our recent assignment of absolute configuration of *N*-Boc-*N*-(*p*-methoxyphenyl)-3-phenylallyllithium intermediate,[9] this lithiated species can be assumed to have (*R*) configuration. The lithio intermediate must not maintain its configuration and undergoes epimerization faster than cyclization as the asymmetric induction arises in a subsequent asymmetric substitution.

Extension of this methodology to asymmetric synthesis of a 2-alkenylpiperidine has been demonstrated. The treatment of *N*-Boc-(4-chlorobutyl)cinnamylamine (**9**) with *n*-BuLi/sparteine at −78 °C followed by gradual warming to room temperature affords (*S*)-**10** in 68% yield with an er of 84:16.[10] The absolute configuration of (*S*)-**10** was determined by oxidative cleavage of the olefin to give (*S*)-*N*-Boc-pipecolic acid and conversion of the acid to the amide which was analyzed by CSP−HPLC.[7]



9

(*S*)-**10** 84:16 er
68% yield

The methodology also can be used intramolecularly to open an epoxide ring. This approach has been used to provide the enantioenriched 2-phenyl-3-(hydroxymethyl)-pyrrolidine (**13**) and 2-phenyl-3-(hydroxymethyl)piperidine (**14**) by reactions of the racemic epoxides **11** and **12** with *n*-BuLi/(−)sparteine for 2 h at −78 °C followed by slow warming to room temperature.[8,11] The pyrrolidine **13** is obtained in 67% yield with a dr (diastereomeric ratio) of 50:50 by lithiation−cyclization. The ers of two diastereomers are 97:3 and 95:5. The inseparable two diastereomers of piperidine **14** are obtained in 29% yield with a dr of 86:14. The er of major diastereomer is 81:19, and the er of minor diastereomer is 86:14. The absolute configurations of 2-position are assigned to be (*S*) by analogy to the reaction of related *N*-Boc-benzylamines with *n*-BuLi/(−)-sparteine.[3,8]

(7) The ers and absolute configurations of (*S*)-**7** and (*S*)-**10** were determined by converting the amino acids to dimethylaniline derivatives. Comparison of CSP−HPLC retension times to those of optically pure amides from commercially available (*S*)-amino acids showed the configuration to be (*S*). Pirkle, W. H.; McCune, J. E. *J. Chromatogr.* **1989**, *479*, 471, 271.

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(10) The synthesis of **9** was achieved by use of the Ing−Manske preparation of primary amines. Ing, H. R.; Manske, R. H. F. *J. Chem. Soc.* **1926**, 2348. Refluxing potassium pthalamide and cinnamyl bromide in DMF afforded *N*-cinnamyl pthalamide in 79% yield. The amine is then liberated by refluxing pthalamide in EtOH in the presence of hydrazine and subsequently protected to provide *N*-Boc-cinnamylamine in 82% yield. Alkylation to afford **9** in 60% yield is performed by refluxing the amine with sodium hydride and 1-bromo-4-chloropropylamine in THF.

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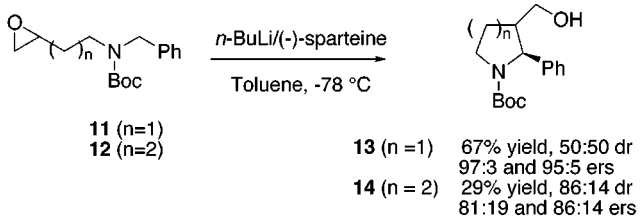

The present work provides methodology for the convenient preparation of moderately enantioenriched 2-alkenyl- or -aryl-substituted pyrrolidines and piperidines by a lithiation−intramolecular cyclization sequence. Application of this methodology and extensions to other systems are under further study.

Experimental Section

Preparation of *N*-(*tert*-Butoxycarbonyl)-*N*-(3-chloropropyl)allylamine (1). Sodium hydride (2.55 g, 60% dispersion in mineral oil) was washed with three portions of hexane to remove the mineral oil. The system was filled with nitrogen followed by THF (15 mL). A solution of *N*-(*tert*-butoxycarbonyl)-allylamine (5 g, 31.85 mmol) in THF (10 mL) and 1-bromo-3-chloropropane (7.5 g, 47.77 mmol) were then added. The resulting mixture was stirred at room temperature overnight. Water (10 mL) was then added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined extracts were purified by chromatography (Hexane/EtOAc, 9/1) to give **1** as a colorless oil (3.7 g, 50%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.79 (s, 9H), 2.0 (br, 2H), 3.2 (m, 2H), 3.5 (m, 2H), 3.7 (br, 2H), 5.0 (m, 2H), 5.8 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.5, 30.6, 41.6, (43.2−43.6), (48.7−49.5), 78.69, (115.2−115.8), 133.19, 154.48; GC/MS (EI, 70 eV) 177 (M^+ − 56), 114 (10), 70 (41), 57 (100). Anal. Calcd for $C_{11}H_{20}NO_2Cl$: C, 56.65; H, 8.58; N, 6.34. Found: C, 56.75; H, 8.87; N, 6.34.

Preparation of *N*-(*tert*-Butoxycarbonyl)-*N*-(3-bromopropyl)allylamine (2). A procedure identical with that described above for preparation of **1** was used to produce **2** (200 mg, 12%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 2.07 (br, 2H), 3.29−3.33 (t, 2H, J = 6.35 Hz), 3.37−3.41 (t, 2H, J = 6.84 Hz), 3.8 (br, 2H), 5.1 (br, 2H), 5.7 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.2, (30.7−30.8), (31.3−31.5), (44.9−45.3), (49.5−50.3), (79.6) (2), (116.4−116.7), 133.8, 155.3; GC/MS (EI, 70 eV) 221 (M^+ − 56, 30), 223 (30), 142 (29), 114 (18), 70 (46), 57 (100). Anal. Calcd for $C_{11}H_{20}NO_2Br$: C, 47.65; H, 7.22; N, 5.05. Found: C, 47.34; H, 7.11; N, 5.38.

Cyclizations To Produce (*S*)-*N*-(*tert*-Butoxycarbonyl)-2-vinylpyrrolidine ((*S*)-5). A mixture of (−)-sparteine (200 mg, 0.86 mmol) and *n*-BuLi (0.41 mL, 1.27 M in cyclohexane) in 2 mL of Et_2O at −78 °C was transferred to a solution of **1** in 1 mL of Et_2O. The resulting reaction mixture was stirred at −78 °C for 2.5 h. Water (5 mL) was added to quench the reaction. The aqueous layer was extracted with ether (3 × 5 mL), and the combined ether extracts were washed with 0.5 M phosphoric acid (10 mL), dried over $MgSO_4$ (anhydrous), filtered, and concentrated in vacuo at room temperature. The crude product was further purified by flash chromatography (hexane/EtOAc, 9/1) to give (*S*)-*N*-(*tert*-butoxycarbonyl)-2-vinylpyrrolidine ((*S*)-**5**) as a colorless and volatile oil (78 mg, 93%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H), 1.50−2.02 (m, 4H), 3.3 (br, 2H), 4.21−4.28 (br, 1H), 5.0 (m, 2H), 5.68−5.75 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (23.8−24.2), 28.4, (32.2−33.5), 47.8, 58.4, 79.4, 116.3, (138.2−139.2), 155.6; GC/MS (EI, 70 eV) 197 (4), 142 (10), 141 (76), 124 (23), 96 (42), 57 (100). The ^{1}H NMR of product was identical to those of the authentic material reported previously.[12a] The enantiomeric purity of (*S*)-**5** was determined to be 83:17 er by gas chromatography using Cyclodex-B chiral column (isothermal at 60 °C, t_R = 266 (minor) and 277 (major)).

Reaction of **2** was carried out using a standard procedure above in the reaction of **1** (27 mg, 31% yield). The enantiomeric purity of (*S*)-**5** was determined to be 65:35 er by gas chromatography using Cyclodex-B chiral column.

Determination of Absolute Configuration of *N*-(*tert*-butoxycarbonyl)-2-vinylpyrrolidine (5). To a solution of (*S*)-*N*-(*tert*-butoxycarbonyl)-2-vinylpyrrolidine (**5**) (100 mg, 0.51 mmol, 67% ee by GC) in CH_2Cl_2 (5 mL) was added an excess of trifluoroacetic acid (0.2 mL, 2.6 mmol). The resulting mixture was stirred at room temperature for 3 h, and then 10% NaOH (2 mL) was added and followed by extraction with CH_2Cl_2 (2 × 5 mL). To this stirred organic solution were added 4 N NaOH (1 mL) and ethyl chloroformate (0.2 mL, 2.1 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was neutralized with 10% HCl and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated. The residue was chromatographed (hexane/EtOAc, 9/1) to give a colorless oil (70 mg, 81%): $[\alpha]^{22}_D$ = −23.3 (c = 1, EtOH), lit.[5] $[\alpha]^{22}_D$ = −22.2 c = 1, EtOH); 83:17 er by GC, using cyclodex-B column, isothermal at 60 °C, t_R = 233 (minor) and 251 (major) min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, J = 7 Hz), 1.6−2.2 (m, 4H), 3.3−3.6 (m, 2H), 3.9−4.5 (m, 1H), 4.1 (q, 2H, J = 7 Hz), 4.9−5.3 (m, 2H), 5.8 (ddd, 1H, J = 17.9, 5.5 Hz); GC/MS (EI, 70 eV) 169 (42), 142 (38), 140 (84), 96 (98), 70 (100), 68 (64).

Preparation of *N*-(*tert*-Butoxycarbonyl)-*N*-(2-butenyl)-3-chloropropylamine (3). Sodium hydride (0.3 g, 60% dispersion in mineral oil) was washed with three portions of hexane to remove the mineral oil, and the system was filled with nitrogen followed by THF (20 mL). *N*-(*tert*-Butoxycarbonyl)-3-chloropropylamine (1 g, 5.18 mmol) in THF (5 mL) and crotyl bromide (1.049 g, 6.21 mmol, as a mixture cis/trans 1/3) were then added under nitrogen. The resulting mixture was stirred at room temperature overnight. Water (10 mL) was then added, and the solution was extracted with ethyl acetate (3 × 20 mL).The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (hexane/EtOAc, 9/1) to give **3** as a colorless oil (1 g, 78%, as a mixture of cis/trans, 1/3): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 1.66 (d, 3H, J = 6.2 Hz), 1.95 (br, 2H), 3.25−3.29 (m, 2H), 3.49−3.54 (m, 2H), 3.69−3.73 (m, 2H), 5.36−5.40 (m, 1H), 5.52−5.57 (m, 1H, J = 15.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) (mixture of cis/trans, 1/3) δ (12.5−17.4), 28.1, (31.1−31.2), (42.2−42.3), (43.0−43.1), (48.5−48.8), (79.2−79.3), (126.5−126.5), (127.8−128.1), (155.2 (2)); GC/MS (EI, 70 eV) 191 (M^+ − 56, 26), 156 (19), 57 (100). Anal. Calcd for $C_{12}H_{22}NO_2Cl$: C, 58.29; H, 8.90; N, 5.66; Cl, 14.17. Found: C, 58.29; H, 9.28; N, 5.60; Cl, 14.03.

Cyclization of 3 To Produce *N*-(*tert*-Butoxycarbonyl)-2-(propen)pyrrolidine ((*S*)-6). A mixture of (−)-sparteine (279 mg, 1.19 mmol) and *n*-BuLi (0.62 mL, 0.60 mmol), 1.3 M in cyclohexane) in 3 mL of the appropriate solvent at −78 °C was transferred to a solution of **3** (0.2 g, 0.81 mmol) in 2 mL of solvent. The resulting reaction mixture was stirred at −78 °C for 4 h. Water (5 mL) was added to quench the reaction. The aqueous layer was extracted with ether (3 × 5 mL), and the combined ether extracts were washed with 0.5 M phosphoric acid (10 mL), dried over $MgSO_4$ anhydrous, filtered, and concentrated in vacuo at room temperature. The crude product was further purified by flash chromatography (hexane/EtOAc, 9/1) to give (*S*)-**6** as a colorless oil (70%; mixture of trans/cis 3/1): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 1.65−1.67 (d, 3H, J = 6.7 Hz), 1.69−2.0 (m, 4H), 3.28−3.36 (br, 2H), 4.1−4.4 (m, 1H), 5.29−5.33 (br, 1H), 5.43−5.49 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4, (22.8 (2)), 28.3, 32.3, (45.9 (2)), (58.6 (2)), 78.8, (124.8−124.9), (131.6 (2)), 155; GC/MS (EI, 70 eV) 211 (1), 155 (47), 140 (77), 96 (28), 57 (100). The ^{1}H NMR of product was identical to those of the authentic material reported previously.[12b] The enantiomeric purity of (*S*)-*N*-(*tert*-butoxycarbonyl)-2-(propen-1-yl)pyrrolidine (**6**) was determined to be 85% for trans isomer and 51% for cis isomer by gas chromatography using Ciclodex-B column (isothermal at 80 °C t_R = 147 (minor) and 154 (major) min for trans and 167

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(minor) and 174 (major) min for cis isomer with 92:8 er for trans and 75:25 er for cis.

Preparation of *N*-(*tert*-Butoxycarbonyl)-*N*-(3-*trans*-phenyl-2-propenyl)-3-chloropropylamine (4). A procedure identical with that described above for preparation of **3** was used to produce *N*-(*tert*-butoxycarbonyl)-*N*-(3-*trans*-phenylpropene-2-yl)-3-chloropropylamine (1 g, 63%, as pure trans isomer): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (s, 9H), 1.91−1.94 (br, 2H), 3.27 (br, 2H), 3.43−3.46 (t, 2H, J = 6.11 Hz), 3.87−3.90 (br, 2H), 6.04−6.06 (br, 1H), 6.35−6.38 (d, 1H, J = 15.4 Hz), 7.12−7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 31.1, 42.1, (43.4−43.5), (49.5 (2)), 79.3, 125.0, 126.0, 127.2, 128.2, (131.3 (2)), 136.2, 155.0; GC/MS (EI, 70 eV) 253 (M^+ − 56, 59), 208 (44), 138 (32), 116 (100), 57 (49). Anal. Calcd for $C_{17}H_{24}NO_2Cl$: C, 66.02; H, 7.76; N, 4.53; Cl, 11.32. Found: C, 65.87; H, 7.85; N, 4.61; Cl, 10.91.

Cyclization of 4. Cyclization of **4** was carried out using a procedure identical with that described above for asymmetric cyclization of **1** except that reaction was stirred for 2 h at −78 °C and for 1 h at −25 °C. The product *N*-(*tert*-butoxycarbonyl)-2-(2-phenyl)ethenylpyrrolidine ((*S*)-**7**) was formed as a white solid (mp 99−101 °C, 140 mg, 85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 1.75−2.06 (m, 4H), 3.41−3.47 (m, 2H), 4.43 (br, 1H), 6.05−6.10 (dd, 1H, J = 16, 6.4 Hz), 6.37−6.42 (d, 1H, J = 16 Hz), 7.21−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0, 28.4, 32.5, 46.1, 58.9, 79.1, 126.1, 127.2, 128.4, 129.3, 130.6, 136.9, 156.4; GC/MS (EI, 70 eV) 217 (M^+ − 56, 47), 200 (14), 172 (70), 130 (100), 57 (48). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.72; H, 8.42; N, 5.12. Found: C, 75.03; H, 8.48; N, 5.16. The enantiomeric purity of *N*-(*tert*-butoxycarbonyl)-2-(2-phenyl)ethenylpyrrolidine ((*S*)-**7**) was determined to be 90:10 er by HPLC using chiral Regis (*R*,*R*)-β-GEM column (1% 2-propanol/hexane, flow rate 1.75 mL/min, t_R = 5.3 min for (*S*) enantiomer (major) and 7.5 min for (*R*) enantiomer (minor)).

Determination of Absolute Configuration of *N*-(*tert*-Butoxycarbonyl)-2-(2-phenyl)ethenylpyrrolidine (7). To 5.8 mL of carbon tetrachloride, 5.8 mL of acetonitrile, and 11.6 mL of water were added 290 mg (1.06 mmol) of (*S*)-**7** and 917 mg (4.1 equiv) of sodium metaperiodate. To this biphasic solution was added 5.8 mg (2.2 mol %) of ruthenium trichloride hydrate, and the entire mixture was stirred for 2 h at room temperature; 10 mL of CH_2Cl_2 was then added, and the phases were separated. The (upper) aqueous phase was extracted 3 times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (EtOAc) to give *N*-(*tert*-butoxycarbonyl)proline as a white solid (23 mg, 10%, mp 130−132 °C [lit.[13] 134−136 °C]): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 6H), 1.51 (s, 3H), 1.87−1.95 (br, 2H), 2.04−2.09 (br, 1H), 2.26−2.29 (br, 1H), 3.34−3.46 (br, 2H), 4.10−4.36 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) mixture of rotamers δ (23.52−24.14), (28.1−28.3), (29.2−30.7), (46.2−46.7), (58.7−58.8), (80.3−80.6), (153.9−155.4), (176.6−178.4); $[\alpha]^{24}_D$ = −52 (c = 1, $CHCl_3$), lit.[13] $[\alpha]^{25}_D$ = −57.2 (c = 2.0, AcOH). To *N*-(*tert*-butoxycarbonyl)proline (23 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) were added dicyclohexylcarbodiimide (22 mg, 0.11 mmol), 3,5-dimethylanilide (0.015 mL, 0.12 mmol), and HOBT (16.4 mg, 0.11 mmol). The reaction mixture was stirred at room temperature for 12 h. The solvent was removed in vacuo, 10 mL of EtOAc was added, and the solids were filtered and the EtOAc solution was concentrated in vacuo and purified by column chromatography (hexane/EtOAc, 20/1) to give an amide (22 mg, 65%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (br, 0.8H), 8.13 (br, 0.2H), 7.13 (m, 2H), 6.71 (br, 1H), 4.46−4.20 (br, 1H), 3.30−3.75 (br, 2H), 2.27 (s, 6H), 1.60−2.20 (m, 2H), 1.44−1.49 (br, 9H). The enantiomeric purity of the 3,5-dimethylanilide derivative was determined to be 99.5% by HPLC on Whelk-O column (5% 2-propanol/hexane, flow rate = 2 mL/min). The (*R*) enantiomer (minor) had a retention time of 13.65 min, and the (*S*) enantiomer (major) had a retention time of 19.17 min. Both pure (*S*)-3,5-dimethylanilide and racemic 3,5-dimethylanilide were independently prepared using the same procedure described above to confirm the stereochemical assignment and the enantiomeric ratio by comparison the elution time of the enantiomers on HPLC.

Synthesis of *rac*-4-d_1. To a suspension of cinnamyl aldehyde (4 g, 30.3 mmol) and $MgSO_4$ (6.7 g, 55.6 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (3.0 mL, 36.2 mmol) and 3-chloropropylamine hydrochloride. The resulting mixture was stirred overnight at room temperature. The solvent was evaporated, and the residue was diluted with water (920 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), the organic phases were dried over $MgSO_4$ and filtered, and the solvent was evaporated to give an imine (2 g, 32%) which was used in the next step. To a solution of the imine (2 g, 9.7 mmol) in MeOH (20 mL) was added $NaBD_4$ (9.45 g, 10.7 mmol) in 3 portions at 0 °C for 1 h; the reaction was then warmed to room temperature and stirred for 2 h. Water (10 mL) was added, and the aqueous layers were extracted with EtOAc (3 × 10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography using EtOAc as the eluent, and the deuterated amine was obtained as a yellow oil (0.78 g, 38%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.22 (m, 5H), 6.53 (d, J = 15.9 Hz, 1H), 6.28 (dd, J = 15.9, 6.3 Hz), 3.64 (t, 2H, J = 6.4 Hz), 3.40 (d, J = 6.2 Hz), 2.81 (t, J = 6.8 Hz, 2H), 1.95 (m, 2H, 1.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.8, 131.0, 128.3, 128.0, 127.1, 126.0, t (50.9, 51.1, 51.3), 45.9, 42.8, 32.6. A procedure identical with that described for the preparation of *N*-(*tert*-butoxycarbonyl)allylamine was used for *rac*-**4**-d_1 (1 g, 87%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.22 (m, 5H), 6.4 (d, J = 15.4 Hz, 1H), 6.1 (br, 1H), 3.9 (br, 1H), 3.5 (br, 2H), 3.3 (br, 2H), 2.0 (br, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.3−131.8, 128.5, 127.6, 126.3, 125.3, 79.8, 49.5 (m), 44.2, 42.3, 31.8, 28.4−27.3. The deuterium content for all products was determined by GC-MS from the M^+ − 56 peak.

Preparation of *rac*-*N*-(*tert*-Butoxycarbonyl)-*N*-(3-*trans*-phenyl-1-(trimethylstannyl)propen-2-yl)-3-chloropropylamine (8). To a solution of **4** in Et_2O (5 mL) was added TMEDA (0.12 mL, 0.78 mmol). The solution was cooled to −78 °C followed by addition of *n*-BuLi (0.5 mL, 1.3 M solution in cyclohexane). The resulting solution was stirred at −78 °C for 30 min, then trimethyltinchloride (0.65 mL, 1 M in cyclohexane) was added, and the mixture was stirred for 2 h at −78 °C. Water (5 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography to give **8** (50 mg): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.16 (m, 5H), 6.29 (dd, J = 15.8, 7.7 Hz, 1H), 6.08 (d, J = 15.8 Hz, 1H), 3.59−3.32 (m, 5H), 2.00 (m, 2H), 1.47 (s, 9H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 137.5, 130.9, 128.1, 126.0, 125.5, 122.8, 79.6, 53.9, 46.3, 42.1, 31.4, 28.0, −7.3. In addition, γ-substituted product (100 mg, 33%) was obtained: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (m, 3H), 7.02 (m, 2H), 5.91 (br, 1H), 5.88 (br, 1H), 3.63−3.39 (br, 5H), 1.98 (br, 2H), 1.48−1.43 (br, 9H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 143.7, 128.8, 125.2, 125.4, 124.1, 122.9, 80.6, 46.6, 42.8, 34.7, 31.5, 28.6, −9.2.

Transmetalation of 8 To Provide (*S*)-7. A mixture of (−)-sparteine (49.6 mg, 0.22 mmol) and *n*-BuLi (0.08 mL, 1.3 M solution in cyclohexane) in 2 mL of Et_2O was transferred to a solution of **8** (50 mg, 0.11 mmol) in 1 mL of Et_2O. The resulting mixture was stirred at −78 °C for 2 h, then warmed to −25 °C, and stirred at this temperature for 1 h. Water (5 mL) was added to quench the reaction, the aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic phases were washed with 0.5 M H_3PO_4, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (hexane/EtOAc, 9/1) to give (*S*)-**7** as a white solid (mp 99−102 °C, 12 mg, 41%). The data of (*S*)-**7** were identical to those of (*S*)-**7** prepared from **4**.

Synthesis of *N*-(*tert*-Butoxycarbonyl)-(4-chlorobutyl)-cinnamylamine (9). To a solution of potassium pthalamide (23.10 g, 124.7 mmol) in DMF (270 mL) was added *trans*-

(13) Azuse, I.; Tamura, N., Kinomura, K.; Okai, H.; Kouge, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3103.

cinnamyl bromide (23.72 g, 116.7 mmol), and the resulting solution was refluxed for 4.5 h. After the reaction was cooled to room temperature, the reaction mixture was poured over water (400 mL) and filtered. The collected solid was then recrystallized from toluene to afford *N*-cinnamyl pthalamide as a white solid (24.20 g, 79%): mp 155−156 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 2H, 7.72 (m, 2H), 7.35 (m, 2H), 7.29 (m, 2H), 7.22 (m, 1H), 6.66 (d, J = 15.8 Hz, 1H), 6.26 (dt, J = 15.8, 6.5 Hz, 1H), 4.45 (dd, J = 6.56, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 167.9, 136.1, 133.9, 133.7, 132.1, 128.5, 127.8, 126.4, 123.2, 122.6, 39.6. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.52; H, 5.06; N, 5.34.

To a solution of *N*-cinnamyl pthalamide (24.20 g, 91.9 mmol) in EtOH (360 mL) was added aqueous H_2NNH_2 (55%, 6.40 mL, 109.8 mmol), and the resulting solution was refluxed for 6.5 h. Upon heating the solution turned a clear yellow color followed by formation of a white precipitate. After the reaction was cooled to room temperature, the reaction mixture was poured over concentrated HCl (aqueous, 100 mL), and the resulting solid was filtered off and washed with 10% (v/v, 50 mL). The filtrant was then made basic by the addition of 40% KOH (wt/wt, 200 mL), and the aqueous layer was extracted with Et_2O (5 times, 100 mL). The combined ether extracts were treated with a solution of $(Boc)_2O$ (24.5 g, 112.3 mmol) in Et_2O (25.0 mL). The solution was then stirred at room temperature for 14 h, and then the Et_2O solution was washed with H_3PO_4 (0.5 M, 2 times, 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was concentrated in vacuo to afford the crude product as an off-white solid. The material was recrystallized from hexane (2 times, 100 mL) to afford *N*-Boc-cinnamylamine as white crystalline solid (17.53 g, 82%): mp 87−88 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 2H), 7.29 (m, 2H), 7.22 (m, 1H), 6.47 (d, J = 15.9 Hz, 1H), 6.17 (m, 1H), 4.86 (s, br, 1H), 3.89 (s, br, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.7, 136.5, 131.2, 128.4, 127.4, 126.2, 79.2, 42.6, 28.3. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H,8.21; N, 6.00. Found: C, 72.18;, H, 8.22; N, 6.05.

To a solution of *N*-Boc-cinnamylamine (11.94 g, 51.2 mmol) and NaH (60% dispersion in mineral oil, 2.90 g, 72.5 mmol) in THF (250 mL) under nitrogen was added 1-bromo-4-chlorobutane (12.65 g, 8.50 mL), 73.8 mmol). The resulting solution was refluxed for 7.25 h. The solution was allowed to cool to room temperature, and the solution was treated with H_2O. The material was partitioned between the layers, and the organic layer was separated. The aqueous layer was extracted with Et_2O (4 times, 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford the crude product as a yellow oil which was purified by flash column chromatography to afford **9** as a clear, colorless oil (10.00 g, 60%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (m, 2H), 7.31 (m, 2H), 7.23 (m, 1H), 6.46 (d, br, J = 15.9 Hz, 1H), 6.17 (s, br, 1H), 3.97 (s, br, 2H), 3.55 (t, J = 6.2 Hz, 2H), 3.27 (s, br, 2H), 1.80−1.53 (m, 4H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 155.6, 136.8, 132.2 and 131.7 (rotamers), 128.7, 127.7, 126.5, 125.8, 79.8, 49.2 and 48.8 (rotamers), 45.7, 44.8, 29.9, 28.6, 25.7. Anal. Calcd for $C_{18}H_{27}NO_2Cl$: C, 66.76; H, 8.09; N, 4.32. Found: C, 66.68; H, 8.17; N, 4.59.

Synthesis of (*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(*trans*-β-styryl)piperidine (10). To a solution of the chlorocarbamate **9** (0.4540 g, 1.40 mmol) in Et_2O (14.0 mL) cooled to −78 °C was added a pre-cooled solution of (−)-sparteine (0.66 mL, 2.87 mmol)/*n*-BuLi (1.75 M, 1.60 mL, 2.80 mmol) in Et_2O (14.0 mmol) at −78 °C. The resulting yellow solution was allowed to stir at −78 °C for 6.5 h and then allowed to warm to room temperature. After the treatment of the reaction mixture with water (10 mL), the aqueous layer was extracted with EtOAc (5 times, 10 mL). The combined organic extracts were washed successively with H_3PO_4 (0.5 M, 2 times, 15 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated to give the crude product as a yellow oil. Preparative HPLC purification (2.5% EtOAc/hexane) afforded (*S*)-**10** as a white solid (0.320 g, 55%): mp 60−62 °C; ^{1}H NMR ($CDCl_3$) δ 7.37−7.20 (m, 5 H), 6.37 (dd, J = 16.1, 1.8 Hz, 1H), 6.17 (dd, J = 16.1, 4.8 Hz, 1H), 4.95 (br, s, 1H), 3.99 (d, br, J = 2.2 Hz, 1H), 2.90 (d, J = 13.1 Hz, 1H), 1.46 (s, 9H), 1.81−1.41 (br, m, 6H); ^{13}C NMR ($CDCl_3$) δ 156.1, 137.7, 131.4, 129.3, 129.2, 128.2, 128.0, 126.9, 80.1, 78.2, 52.9, 40.5, 30.2, 29.2, 26.2, 20.4. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.23; H, 8.77; 4.87. Found: C, 75.28; H, 8.66; N, 4.96. The enantiomeric ratio (*S*:*R*) was determined to be 82:18 by CSP−HPLC (1.75 mL/min, 2.5% 2-propanol/hexane) (R_f of major peak, 9.8 min; R_f minor peak, 4.6 min).

Determination of Absolute Configuration of (*S*)-*N*-(*tert*-Butoxycarbonyl)-2-(*trans*-β-styryl)piperidine (10). To a stirred solution of (*S*)-**10** (0.117 g, 0.41 mmol, 84:16 er) and 0.0024 g of $RuCl_3 \cdot xH_2O$ (0.012 mmol) in water (1.2 mL)/CCl_4 (0.8 mL)/CH_3CN (0.8 mL) was added $NaIO_4$ (0.400 g, 1.87 mmol). The biphasic reaction mixture was stirred at room temperature rapidly for 5 h. After 5 h, water (5 mL) and CH_2Cl_2 (5 mL) were added, and the material was partitioned between the layers. The aqueous layer was extracted with CH_2Cl_2 (5 times, 5 mL), and the combined organic extracts were dried over $MgSO_4$. The crude product was isolated by concentration in vacuo and purified by flash column using 1% AcOH/20% EtOAc/hexane to afford (*S*)-*N*-Boc-pipecolic acid. Using standard DCC coupling procedure, (*S*)-*N*-Boc-pipecolic acid (0.0460 g, 0.20 mmol), DCC (0.0458 g, 0.22 mmol), HOBT (0.0291 g, 0.22 mmol), and 3,5-dimethylaniline (0.03 mL, 0.24 mmol) in CH_2Cl_2 (8.0 mL) were stirred at room temperature for 18 h and then worked up by filtering through a plug of silica gel using 100% EtOAc as the eluent. The product was purified by flash column (20% EtOAc/hexane) and then by preparatory HPLC (5% EtOAc/hexane) to afford the anilide was a sticky oil (0.0514 g, 78%): ^{1}H NMR was in agreement with the racemic product. The product was obtained in an er of 84:16 using the Whelk-O column (5% 2-propanol/hexane, 1.50 mL/min; R_f (*R*)-enantiomer (11.3 min, minor); R_f (*S*)-enantiomer (13.3 min, major).

Preparation of *N*-(*tert*-Butoxycarbonyl)-*N*-(3-oxa-3-butenyl)benzylamine (11). To a solution of *N*-Boc-*N*-(3-butenyl)benzylamine (50 mg) in 5 mL of methylene chloride was added mCPBA (2.2 equiv), and the resulting solution was stirred for 10 h at room temperature. saturated $NaHCO_3$ solution (10 mL) was added and the aqueous layer was extracted with methylene chloride. The combined organic phase was dried, filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatograghy to give **11** (41 mg, 78% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.33−7.23 (m, 5 H), 4.43 (br, 2H), 3.36 (br, 2H), 2.89 (br, 1H), 2.72 (t, 1H, J = 4.9 Hz), 2.42 (br, 1H), 1.65 (m, 2H), 1.44 (br, 9H); ^{13}C NMR ($CDCl_3$) δ 155.5, 138.3, 128.5, 127.7, 127.2, 79.8, 50.8, 50.2, 46.9, 43.7, 31.4, 28.7; HRMS calcd for $C_{16}H_{24}NO_3$ (M^+ + 1) 278.1756, found 278.1747.

***N*-(*tert*-Butoxycarbonyl)-2-Phenyl-3-(hydroxymethyl)-pyrrolidine (13).** The procedure identical with the synthesis of **10** was used to produce **13**. From 20 mg of **11**, 13 mg (67% yield) of an inseparable 50:50 mixture of two diastereomers was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) less polar product 7.31−7.05 (m, 5H), 4.90 (d, J = 7.7 Hz, 1H), 3.84 (m, 1H), 3.51 (m, 1H), 3.24 (m, 2H), 2.69 (m, 1H), 1.97 (m, 1H), 1.81 (m, 1H), 1.56 (brs, 9H); more polar product 7.96−7.05 (m, 5H), 4.52 (br, 1H), 3.72 (m, 4H), 2.35 (m, 1H), 2.06 (m, 1H), 1.77 (m, 1H), 1.56 (s, br, 9H); CIMS m/z 278 (M^+ + 1); HRMS calcd for $C_{16}H_{24}NO_3$ (M^+ + 1) 278.1756, found 278.1749. The enantiomeric ratio of the less polar product **13** was determined to be 97:3 by chiral HPLC using racemic material as a standard (Whelk-O column; 10% 2-propanol in hexane; 1.5 mL/min; the major enantiomer had a retention time of 7.6 min, and the minor enantiomer had a retention time of 6.6 min). The enantiomeric ratio of the more polar product **13** was determined to be 95:5 by chiral HPLC using racemic material as a standard (Whelk-O column; 10% 2-propanol in hexane; 1.5 mL/min; the major enantiomer had a retention time of 15.4 min, and the minor enantiomer had a retention time of 9.1 min).

Preparation of *N*-(*tert*-Butoxycarbonyl)-*N*-(4-oxa-4-pentenyl)benzylamine (12). The procedure identical with the synthesis of **11** was used to produce **12** (80% yield). The ^{1}H NMR of product was identical to those of the authentic material reported previously:[11] ^{1}H NMR ($CDCl_3$) δ 7.33−7.23

(m, 5 H), 4.20 (br, 2H), 3.20 (br, 2H), 2.89 (br, 1H), 2.72 (t, 1H, J = 4.3 Hz), 2.43 (br, 1H), 1.60 (m, 4H), 1.45 (br, 9H).

***N*-(*tert*-Butoxycarbonyl)-2-Phenyl-3-(hydroxymethyl)-piperidine (14).** The procedure identical with the synthesis of **10** was used to produce **14**. From 208 mg of **12**, 60 mg (29% yield) of an inseparable 86:14 mixture of two diastereomers was obtained as a colorless oil. The ^{1}H NMR of product was identical to those of the authentic material reported previously.[11] The enantiomeric ratio of major diastereomer was determined to be 81:19 by chiral HPLC using racemic material as a standard (Whelk-O column; 5% 2-propanol in hexane; 1.5 mL/min; the major enantiomer had a retention time of 17.4 min, and the minor enantiomer had a retention time of 12.3 min). The enantiomeric ratio of minor diastereomer was determined to be 86:14 by chiral HPLC using racemic material as a standard (Whelk-O column; 5% 2-propanol in hexane; 1.5 mL/min; the major enantiomer had a retention time of 8.3 min, and the minor enantiomer had a retention time of 7.4 min).

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