Asymmetric Syntheses of Derivatives of β- and γ-Aryl and α-Alkyl Amino Acids Using *n*-BuLi/(−)-Sparteine

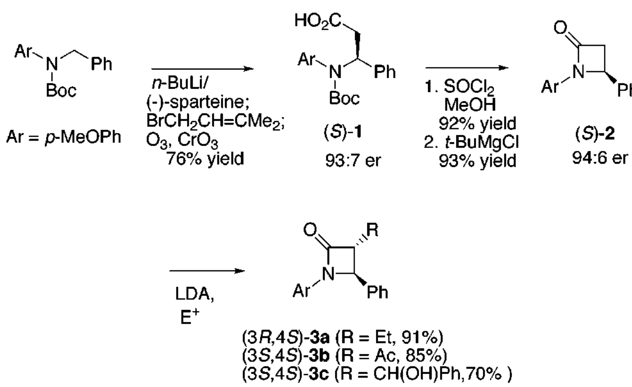
Bong Jin Kim, Yong Sun Park,[1] and Peter Beak*

Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801

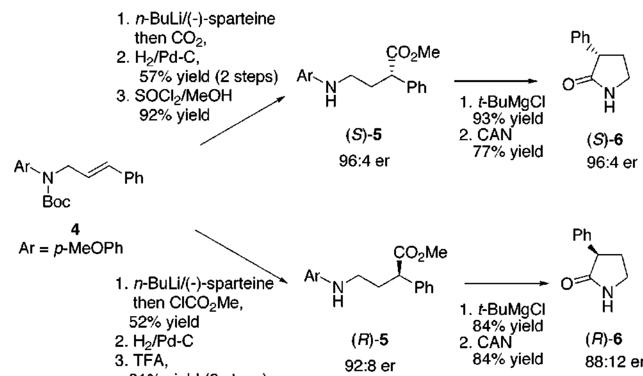
Received August 27, 1998

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 the aymmetric syntheses of α-, β-, and γ-aryl amino acids and esters from *N*-Boc arylmethylamine derivatives by a lithiation−substitution sequence using *n*-BuLi/(−)-sparteine.[3] We report applications of this methodology to enantioselective syntheses of 4-phenyl-β-lactams, 3-phenyl-γ-lactams, and an α-alkyl amino acid.

Highly enantioenriched β-phenyl amino acid derivative (*S*)-**1** can be obtained from the reaction of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine with 4-bromo-2-methyl-2-butene in the presence of *n*-BuLi/(−)-sparteine and subsequent oxidation with O_3 and Jones reagent in 76% overall yield with 93:7 er.[3] When **1** is treated with $SOCl_2$ in MeOH, the methyl ester of **1** is obtained in 92% yield. Cylization of the ester is efficiently carried out with *t*-BuMgCl in THF at −5 °C to provide 4-phenyl β-lactam (*S*)-**2** in 93% yield with 94:6 er.[4] Alkylation of the C-3 position of the lactam ring **2** is performed with LDA and various electrophiles to afford (3*R*,4*S*)-**3a** in 91% yield, (3*S*,4*S*)-**3b** in 85% yield and (3*S*,4*S*)-**3c** in 70% yield.[5]



We have reported that *N*-Boc-*N*-(*p*-methoxyphenyl)-cinnamylamine (**4**) can be selectively deprotonated by *n*-BuLi/(−)-sparteine to form η^3-*N*-Boc-*N*-(*p*-methoxyphenyl)-3-phenylallyllithium·(−)-sparteine. This configurationally stable complex affords products with high enantioenrichments on reactions with different electrophiles.[6] Treatment of **4** with 1.1 equiv of *n*-BuLi/(−)-sparteine and carbon dioxide gives a γ-amino acid which on subsequent hydrogenation and esterification provides (*S*)-**5** in 52% overall yield with 96:4 er. Lithiation of **4** with *n*-BuLi/(−)-sparteine followed by methyl chloroformate, subsequent hydrogenation, and removal of Boc group gives (*R*)-**5** in 41% yield with 92:8 er.[7] Efficient cyclization using *t*-BuMgCl and removal of the *p*-methoxyphenyl group using CAN give 3-phenyl γ-lactam **6** in 72% and 71% overall yields. Thus, either enantiomer of the enantioenriched 3-phenyl γ-lactam **6** can be obtained by this approach.[8]



A further example of the synthetic potential of the methodology for amino acid synthesis is illustrated by the oxidative conversion of (*S*)-**8** to enantioenriched amino acid (*S*)-**9**. The enantioenriched α-methyl-substituted *p*-methoxybenzylamine (*S*)-**8** is produced in 85% yield with 95:5 er by the treatment of **7** with *n*-BuLi/(−)-sparteine complex and MeOTf. For the synthesis of *N*-Boc alanine methyl ester (*S*)-**9**, (*S*)-**8** is treated with CAN to remove the *p*-methoxyphenyl group in 56% yield. The *N*-Boc-α-methyl *p*-methoxybenzylamine is oxidized with RuO_4 for 48 h to the corresponding acid which on esterification and Boc protection gives the methyl ester (*S*)-**9** with 94:6 er in 42% overall yield.[9,10]

In summary, we have demonstrated *n*-BuLi/sparteine complex is effective as a chiral base for the asymmetric syntheses of 3-alkyl-4-phenyl β-lactams, 3-phenyl-γ-lactams, and an α-alkyl amino acid ester. Application of this

(1) Department of Chemistry, Konkuk University, Seoul, Korea, 143-701.

(2) (a) Nozaki, H.; Aratani, T.; Toragata, T.; Noyori, R.; *Tetrahedron*, **1971**, *27*, 905. (b) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422. (c) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S. Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (d) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282 and references therein.

(3) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574.

(4) Holley, R. W.; Holley, A. D. *J. Am. Chem. Soc.* **1949**, *71*, 2124.

(5) The assignment of relative configuration of C-3 and C-4 positions of the lactam ring is based on coupling constant in ^{1}H NMR (J = 2.4 Hz). The ratio of two epimers at hydroxy benzylic position of **3c** is 50:50 based on ^{1}H NMR of **3c** (4.64 and 5.38 ppm)

(6) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. Pippel, D. J.; Weisenburger, G. A.; Wilson, S.; Beak, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2522.

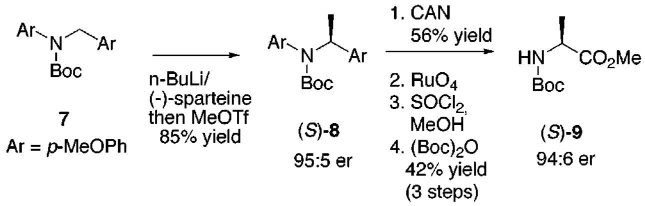
(7) The absolute configuration of **6** is based on comparison to the ureides from (*R*)-1-(1-naphthyl)ethyl isocyanate of previously assigned authentic enantiomers. Pirkle, W. H.; Robertson, M. R.; Hyun, M. H. *J. Org. Chem.* **1984**, *49*, 2433.

(8) We reported that the reaction of the *N*-Boc-*N*-(*p*-methoxyphenyl)-benzylamine lithium intermediate with $ClCO_2Me$ and CO_2 also provided the opposite configuration with $ClCO_2Me$ proceeding through a retentive pathway and CO_2 proceeding through an invertive pathway. Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561.

(9) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless B. *J. Org. Chem.* **1981**, *46*, 3936.

(10) We previously reported that *N*-Boc-α-ethylbenzylamine was oxidized into 2-aminobutyric acid hydrochloride in 41% yield with 97:3 er using RuO_4. Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757.

10.1021/jo9817568 CCC: $18.00
Published on Web 02/06/1999



approach to the syntheses of a variety of enantioenriched natural and unnatural amino acids and their derivatives should be useful. Further work to develop synthetic utilities of this methodology is in progress.

Experimental Section

1-(4-Methoxyphenyl)-4(*S*)-phenylazetidin-2-one (2). (*S*)-1 (604 mg, 1.7 mmol) was stirred at room temperature for 2 h in 15 mL of MeOH containing excess thionyl chloride to give the corresponding Boc-deprotected methyl ester (445 mg, 92% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80 (d, 2H, J = 6.8 Hz), 3.65 (s, 3H), 3.70 (s, 3H), 4.27 (br, 1H), 4.76 (t, 1H, J = 6.8 Hz), 6.52−7.38 (m, 9H). Cyclization of the methyl ester (210 mg, 0.73 mmol) was carried out with *t*-BuMgCl (1.0 equiv) in THF at 0 °C for 1.5 h to give (*S*)-2 as a white solid 173 mg (93% yield) mp 90−92 °C (lit.[11] 94−96 °C racemic); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.89 (dd, 1H, J = 15.0 and 2.4 Hz), 3.50 (dd, 1H, J = 15.0 and 5.7 Hz), 3.69 (s, 3H), 4.93 (dd, 1H, J = 5.7 and 2.4 Hz), 6.75 (d, J = 9.0 Hz, 2H), 7.20−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 46.7, 54.0, 55.3, 114.2, 118.0, 125.8, 128.4, 129.1, 131.3, 138.2, 155.8, 164.0; mass spectrum (70 eV) *m/e* (relative intensity) 253 (M^+, 27), 211 (10), 196 (17), 149 (100), 134 (22). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.91; H, 6.07; N, 5.76.

The enantiomeric ratio of (*S*)-**2** was determined to be 94:6 in favor of the *S*-enantiomer by chiral HPLC analysis using racemic material as a standard (Whelk-O: 15% v/v 2-propanol in hexane; a flow rate of 2.0 mL/min; a detection wavelenth of 254 nm). The *S*- enantiomer (major) had a retention time of 13.8 min, and *R*-enantiomer (minor) had a retention time of 10.0 min.

3(*R*)-Ethyl-1-(4-methoxyphenyl)-4(*S*)-phenylazetidin-2-one (3a). To a solution of (*S*)-**2** (23 mg 0.09 mmol) in THF (1.2 mL) at −78 °C was added LDA (2.0 M in heptane, 1.3 equiv). The reaction mixture was stirred for 30 min at −78 °C, and EtI (4 equiv) was added. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether twice, extraction of the combined diethyl ether extracts with sat. NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration in vacuo. The crude product was further purified by chromatography to give a pure product **3a** as a white solid (23 mg, 90% yield).[12] mp 125−126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (t, J = 5.8 Hz, 3H), 1.83−1.89 (m, 1H), 1.90−2.03 (m, 1H), 3.02−3.05 (m, 1H), 3.73 (s, 3H), 4.62 (d, 1H, J = 2.4 Hz), 6.77 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 7.2 Hz, 2H), 7.25−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.4, 21.9, 55.4, 60.7, 61.9, 114.2, 118.1, 125.8, 128.2, 129.1, 131.3, 138.3, 155.8, 167.2; mass spectrum (70 eV) *m/e* (relative intensity) 281 (M^+, 41), 196 (24), 149 (100), 132 (52), 117 (46). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.69; H, 6.81; N, 4.96.

3(*S*)-Acetyl-1-(4-methoxyphenyl)-4(*S*)-phenylazetidin-2-one (3b). To a solution of (*S*)-**2** (25 mg, 0.1 mmol) in THF (1.5 mL) at −78 °C was added LDA (2.0 M in heptane, 1.3 equiv). The reaction mixture was stirred for 30 min at −78 °C, and methyl acetate (4 equiv) was added. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether twice, extraction of the combined diethyl ether extracts with sat. NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration in vacuo. The crude product was further purified by chromatography to give **3b** as a colorless oil (25 mg, 85% yield).[13] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.37 (s, 3H), 3.73 (s, 3H), 4.12 (d, 1H, J = 2.5 Hz), 5.42 (d, 1H, J = 2.5 Hz), 6.78 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H), 7.25−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 29.8, 55.2, 55.4, 71.6, 114.1, 118.2, 126.0, 128.6, 129.0, 130.5, 136.4, 156.1, 159.5, 199.0 ; mass spectrum (70 eV) *m/e* (relative intensity) 295 (M^+, 30), 252 (7), 196 (15), 149 (100), 134 (23). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.45; H, 5.82; N, 4.52.

3(*S*)-(1′-Hydroxy-1′-phenylmethyl)-1-(4-methoxyphenyl)-4(*S*)- phenylazetidine-2-one (3c). To a solution of (*S*)-**2** (25 mg, 0.1 mmol) in THF (1.5 mL) at −78 °C was added LDA (2.0 M in heptane, 1.3 equiv). The reaction mixture was stirred for 30 min at −78 °C, and then benzaldehyde (4 equiv) was added. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether twice, extraction of the combined diethyl ether extracts with sat. NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration in vacuo. The crude product was further purified by chromatography to give **3c** as a colorless oil (25 mg, 70% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.45 (d, J = 4.0 Hz, 1H), 3.42 (dd, J = 2.4 and 3.8 Hz, 1H), 3.73 (s, 3H), 5.12 (d, 1H, J = 2.0 Hz), 5.39 (dd, 1H, J = 4.0 and 3.8 Hz), 6.78 (d, J = 9.2 Hz, 2H), 6.94 (m, 2H), 7.18−7.23 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.7, 57.7, 66.8, 73.1, 114.3, 118.4, 125.7, 126.7, 128.3, 128.6, 128.8, 129.0, 131.1, 137.6, 141.0, 156.1, 165.1; mass spectrum (70 eV) *m/e* (relative intensity) 359 (M^+, 33), 234 (40), 198 (42), 137 (100), 98 (92). Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.89. Found: C, 76.86; H, 6.14; N, 3.51.

Methyl-*N*-(4-methoxyphenyl)-2-phenyl-4-amino-(*Z*)-butenoate ((*S*)-5). To a solution of (−)-sparteine (0.6 mL, 1.1 equiv) in toluene (15 mL) at −78 °C was added *n*-BuLi (1.6 M in hexane, 1.62 mL, 1.1 equiv). The reaction was stirred for 20 min at −78 °C, and a solution of *N*-Boc-*N*-(4-methoxyphenyl)-3-phenyl-(*E*)-2-propen-1-amine (**4**) (0.802 mg, 2.37 mmol) in toluene (15 mL) was added at −78 °C. The resulting reaction mixture was stirred at −78 °C for 5 h, and carbon dioxide gas was bubbled through the reaction mixture until yellow color disappeared (about 5 min). The reaction mixture was stirred for 30 min at −78 °C and quenched with MeOH before the mixture was allowed to warm to room temperature. Workup procedure consisted of following steps: addition of water (20 mL), extraction of the toluene layer with water (10 mL), extraction of combined the aqueous layer, adjustment of the pH to 4.0 with acetic acid, and extraction of the acidic aqueous solution with diethyl ether. The combined diethyl ether extracts were dried over anhydrous $MgSO_4$. Filtration and concentration in vacuo resulted in a crude residue which was purified by chromatography with 0.03:10:40 AcOH/ethyl acetate/petroleum ether. The product *N*-Boc-*N*-(4-methoxyphenyl)-2(*S*)-phenyl-4-amino-3-butenoic acid was dissolved in 20 mL of ethanol with 10% palladium on activated carbon (54 mg) and hydrogenated under 20 psi hydrogen for 1 h. The resulting mixture was filtered through the Celite pad and washed with ethanol (8 mL) five times. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography with 0.03:10:40 AcOH/petroleum ether/ethyl acetate to give (57% yield, 404 mg) of a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 2.0 (m, 1H), 2.30 (m, 1H), 3.58 (m, 3H), 3.78 (s, 3H), 6.82 (d, J = 8.8 Hz, 2H), 7.03 (m, 2H), 7.22−7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.1, 31.3, 48.7, 55.2, 80.1, 113.9, 127.4, 127.8, 128.5, 134.8, 137.7, 154.9, 157.5, 178.7.; mass spectrum (70 eV) *m/e* (relative intensity) 385 (M^+, 16), 329 (12), 285 (85), 136 (100), 120 (18).

To a solution of *N*-Boc-*N*-(4-methoxyphenyl)-2(*S*)-phenyl-4-aminobutanoic acid (294 mg, 0.763 mmol) in methanol (7 mL) at 0 °C was added thionyl chloride (0.556 mL, 7.63 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was heated to 60 °C for 1 h, cooled to room temperature, and then concentrated under reduced pressure. The residue was dissolved in water and ethyl acetate, and the pH was adjusted to 7−8 with sat. sodium bicarbonate solution in an ice bath. The organic layer was separated, and the aqueous

(11) Kono, S.; Ebato, T., Shiboya, S. *J. Chem. Soc., Perkin Trans. 1*, 1980, 2105. Shu, K.; Mitsuharu, A.; Masaru, Y. *Tetrahedron Lett.* **1995**, *36*, 5773.

(12) (a) Futjieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *Tetrahedron* **1996**, *52*, 2573. (c) Rita, A. Mauro, C.; Franco, C.; Valentina, M.; Olaf, S. *J. Org. Chem.* **1996**, *61*, 8293.

(13) Palomo, C.; Cossio, F. P.; Arrieta, A.; Odriozola, J. M.; Oiatbide, M.; Ontoria, J. M. *J. Org. Chem.* **1989**, *54*, 5736.

layer was extracted with ethyl acetate. The combined organic layer was dried over anhydrous magnesium sulfate and concetrated under reduced pressure. The crude product was purified by chromatography with 4:1 petroleum ether/ethyl acetate to afford 228 mg of **5** (92% yield) as pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.06−2.09 (m, 1H), 2.38−2.42 (m, 1H), 3.06 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H), 3.74 (s, 3H), 3.73 (t, J = 7.5 Hz, 1H), 6.53 (d, J = 9.0 Hz), 6.72 (d, J = 9.0 Hz, 2H), 7.26−7.36 (m, 5H) ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 33.1, 42.9, 49.2, 52.1, 55.8, 114.2, 114.9, 127.4, 127.9, 138.6, 142.2, 152.2, 174.3; mass spectrum (70 eV) *m/e* (relative intensity) 299 (M^+, 40), 268 (5), 136 (100), 121 (15). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 71.71; H, 6.91; N, 4.52.

The enantiomeric ratio of (*S*)-**5** was determined to be 96:4 in favor of the *S*-enantiomer by chiral HPLC analysis using racemic material as a standard (Chiralpak AD: 10% v/v 2-propanol in hexane; a flow rate of 2.0 mL/min; a detection wavelenth of 254 nm) The *S*-enantiomer (major) had a retention time of 9.0 min, and the *R*-enantiomer (minor) had a retention time of 11.4 min.

Methyl *N*-(4-Methoxyphenyl)-2-phenyl-4-aminobutanoate ((*R*)-5). To a solution of (−)-sparteine (0.3 mL, 1.1 equiv) in dry toluene (7.5 mL) at −78 °C was added *n*-BuLi (1.6 M in hexane, 0.81 mL, 1.1 equiv). The reaction was stirred for 20 min at −78 °C, and then a solution of **4** (0.404 mg, 1.18 mmol) in dry toluene (7.5 mL) was added at −78 °C. The resulting reaction mixture was stirred at −78 °C for 1 h, and methyl chloroformate (0.101 mL, 1.3 equiv) was added. The reaction mixture was stirred for 1 h at −78 °C and then quenched with MeOH. This mixture was allowed to slowly warm to room temperature. Workup consisted of addition of water (20 mL), extraction of the aqueous layer with diethyl ether, extraction of the combined diethyl ether extracts with sat. NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration under reduced presssure. The crude mixture was purified by chromatography to give the (52% yield, 246 mg) of the product. ^{1}H NMR (acetone-d_6, 400 MHz); δ 1.41 (s, 9H), 3.43 (s, 3H), 3.80 (s, 3H), 3.99 (d, J = 10.0 Hz, 1H), 5.23 (t, J = 10.0 Hz, 1H), 6.74 (d, J = 10.0 Hz, 1H), 6.82−7.25 (m, 9H). Methyl (*N*-Boc-*N*-(4-methoxyphenyl)-2(*R*)-phenyl-4-amino-3-butenoate (200 mg, 0.503 mmol) was dissolved in 9 mL of ethanol, 10% palladium on activated carbon (20 mg) was added, and the mixture was hydrogenated under 20 psi hydrogen for 1 h. The resulting mixture was filtered through Celite and washed with ethanol (5 mL) five times. The filtrate was evaporated under reduced pressure, and the product was purified by flash chromatography with 9:1 petroleum ether/ethyl acetate to give 195 mg of the (87% yield) of product as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (br, 9H), 2.02 (m, 1H), 2.29 (m, 1H), 3.52 (m, 1H), 3.57 (m, 2H), 3.61 (s, 3H), 3.79 (s, 3H), 6.83 (d, J = 9.0 Hz, 2H), 7.05 (bs, 2H), 7.21−7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 28.3, 31.9, 48.0, 48.9, 52.0, 55.4, 80.3, 114.0, 127.3, 127.8, 128.2, 128.7, 135.1, 138.5, 157.6, 173.9; mass spectrum (70 eV) *m/e* (relative intensity) 399 (M^+, 16), 299 (100), 238 (60), 136 (90).

Methyl *N*-Boc-*N*-(4-methoxyphenyl)-2(*R*)-phenyl-4-aminobutanoate (113 mg, 0.28 m mol) was dissolved in methylene chloride (3.7 mL) in ice bath, and trifluoroacetic acid (0.32 mL, 4.2 mmol) was added. The reaction mixture was stirred for 2 h at room temperature. The resulting solution was concentrated under reduced pressure, 8 mL of water was added, and the pH of the solution was adjusted to 8−9 with saturated sodium bicarbonate solution in an ice bath and then extracted with ethyl acetate. The organic layer was then dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. The product was purified by silica gel chromatography with 20% ethyl acetate in petroleum ether to give 78 mg (93% yield) of (*R*)-**5** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.06−2.09 (m, 1H), 2.38−2.42 (m, 1H), 3.06 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H), 3.74 (s, 3H), 3.73 (t, J = 7.5 Hz, 1H), 6.53 (d, J = 9.0 Hz), 6.72 (d, J = 9.0 Hz, 2H), 7.26−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 33.1, 42.9, 49.2, 52.1, 55.8, 114.2, 114.9, 127.4, 127.9, 138.6, 142.2, 152.2, 174.3.

The enantiomeric ratio of (*R*)-**5** was determined to be 92:8 in favor of the *R*-enantiomer by chiral HPLC analysis using racemic material as a standard (Chiralpak AD: 5% v/v 2-propanol in hexane; a flow rate of 2.0 mL/min; a detection wavelenth of 254 nm). The *R*-enantiomer (major) had a retention time of 11.6 min, and the *S*-enantiomer (minor) had a retention time of 9.34 min.

3-Phenyl-2-pyrrolidone ((*S*)-6). A solution of (*S*)-**5** (102 mg, 0.341 mmol) in dry tetrahydrofuran (3 mL) was cooled to −10 °C, and *tert*-butylmagnesium chloride (1 M in hexane, 0.341 mL, 0.341 mmol) was added under nitrogen. The reaction mixture was stirred for 1.5 h at same temperature. The resulting solution was quenched with water (10 mL) and extracted with ethyl acetate (15 mL) three times. The extract was dried with anhydrous magnesium sulfate, concentrated under reduced pressure, and purified by flash chromatography with 20% ethyl acetate in petroleum ether to afford 85 mg (93% yield) of the product as a white solid. mp: 113−114 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.27 (m, 1H), 2.63 (m, 1H), 3.80 (s, 3H), 3.88 (m, 3H), 6.91 (d, 2H, J = 9.2 Hz), 7.25−7.36 (m, 5H), 7.58(d, J = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 27.7, 47.1, 49.4, 55.4, 114.0, 121.5, 128.0, 127.1, 137.8, 139.4, 156.6, 173.7; mass spectrum (70 eV) *m/e* (ralative intensity) 267 (M^+, 100), 150 (35), 136 (45), 120 (32). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.18; H, 6.34 N, 5.26.

The enantiomeric ratio of the product was determined to be 96:4 in favor of the *S*-enantiomer by chiral HPLC analysis, using racemic material as a standard (Chiakpak AD: 30% v/v 2-propanol in hexane; a flow rate of 1.0 mL/min; a detection wavelenth of 254 nm. The *S*-enantiomer (major) had a retention time of 27.9 min, and the *R*-enantiomer (minor) had a retention time of 14.9 min.

Ammonium cerium(IV) nitrate (0.974 mg, 1.616 mmol) was dissolved in water (1.2 mL) and slowly added to ice cooled solution of 3(*S*)-phenyl-1-(4-methoxyphenyl)-2-pyrrolidone (158.6 mg, 0.592 mmol) in acetonitrile (1.2 mL). The reaction mixture was stirred for 30 min, and the resulting solution was concentrated under reduced pressure at a 35 °C bath temperature. The residue was triturated with ethyl acetate (20 mL). Filtration, concentration, and purification by chromatography on silica gel with 3:1 petroleum ether/ethyl acetate gave 3(*S*)-phenyl-2-pyrrolidone. mp 104−105 °C (lit.[14] 84−85 °C racemic) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.25 (m, 1H), 2.60 (m, 1H), 3.46 (t, J = 9.0 Hz), 6.9 (br, 1H), 7.25−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 30.7, 40.6, 127.1, 128.0, 139.3, 179.0; mass spectrum (70 eV) *m/e* (relative intensity) 161 (M^+, 81), 117 (100), 103 (23), 91 (32). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.36; H, 6.89 N, 8.55.

For determination of absolute configuration, **6** was converted to *N*-[(*S*)-1-(naphthyl)ethyl]-3(*S*)-phenyl-2-pyrrolidone-1-carboxamide. A solution of 3(*S*)-phenyl-2-pyrrolidone (35 mg, 0.217 mmol) and (*R*)-(−)-(1-naphthyl)ethyl isocyanate (44.4 mg, 0.225 mmol) in 3.0 mL of dry benzene was refluxed for 24 h, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 10% ethyl acetate in petroleum ether. The major diastereomer eluted first (high R_f diasteriomer), and the minor diastereomer eluted next (low R_f diastereomer). The major diastereomeric ureides were isolated; 70 mg (90% yield). Major diastereomer (high R_f): mp 146−147 °C (lit.[7] 147−148 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.66 (d, J = 7.0 Hz, 3H), 2.15−2.24 (m, 1H), 2.47−2.53 (m, 1H), 3.79−3.91 (m, 2H), 4.03−4.08 (m, 1H), 5.79−5.94 (overlapping quartets, 1H), 7.11−8.11 (m, 12H), 8.89 (d, J = 7.0 Hz, 1H); mass spectrum (70 eV) *m/e* (relative intensity) 358 (M^+, 38), 343 (22), 270 (20), 197 (29), 182 (14), 171 (14), 170 (100), 163 (21), 161 (12), 118 (12), 107 (49). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.09; H, 6.15; N, 7.82. Found: C, 76.84; H, 6.38; N, 7.46. The absolute configuration was assigned by comparism of preparative HPLC retention times to reference data. The first eluted diastereomer was reported to have (*S*)-configuration.[7]

3-Phenyl-2-pyrrolidone ((*R*)-6). From methyl *N*-(4-methoxyphenyl)-2(*R*)-phenyl-4-aminobutanoate (113.4 mg, 0.38 mmol) was obtained *N*-(4-methoxyphenyl)-3(*R*)-phenyl-2-pyrrolidone (85 mg, 84%) as a white solid. mp: 113−114 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.27 (m, 1H), 2.63 (m, 1H), 3.80 (s, 3H), 3.88 (m, 3H), 6.91 (d, 2H, J = 9.2 Hz), 7.25−7.36 (m, 5H), 7.58 (d, J = 9.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 27.7, 47.1, 49.4, 55.4, 114.0, 121.5, 128.0, 127.1, 137.8, 139.4, 156.6, 173.7.

The enantiomeric ratio of the product was determined to be 88:12 in favor of the *S*-enantiomer by chiral HPLC analysis using

(14) Clark, R. D.; Jahanger, *Tetrahedron* **1993**, *49*, 1351.

racemic material as a standard (Chiakpak AD: 30% v/v 2-propanol in hexane; a flow rate of 1.0 mL/min; a detection wavelenth of 254 nm. The *S*-enantiomer (major) had a retention time of 14.7 min, and the *R*-enantiomer (minor) had a retention time of 27.4 min.

From 79 mg (0.30 mmol) of *N*-(4-methoxylphenyl)-3(*R*)-phenyl-2-pyrrolidone was obtained 40 mg (84%) of 3(*R*)-phenyl-2-pyrrolidone as a solid. mp 104−105 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.25 (m, 1H), 2.60 (m, 1H), 3.46 (t, J = 9.0 Hz), 6.9 (br, 1H), 7.25−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125.5 MHz) δ 30.7, 40.6, 127.1, 128.0, 139.3, 179.0.

For determination of the absolute configuration, **6** was converted to *N*-[(*S*)-1-(naphthyl)ethyl]-3(*S*)-phenyl-2-pyrrolidone-1-carboxamide. From 40 mg (0.25 mmol) of 3(*R*)-phenyl-2-pyrrolidone was obtained *N*-[(*S*)-1-(naphthyl)ethyl]-3(*R*)-phenyl-2-pyrrolidone-1-carboxamide as 76 mg of a colorless oil (86% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.66 (d, J = 7.0 Hz), 2.15−2.24 (m, 1H), 2.47−2.53 (m, 1H), 3.79−3.91 (m, 2H), 4.03−4.08 (m, 1H), 5.79−5.94 (overlapping quartets, 1H), 7.11−8.11 (m, 12H), 8.89 (d, J = 7.0 Hz, 1H); mass spectrum (70 eV) *m*/*e* (relative intensity) 358 (M^+, 38), 343 (22), 270 (20), 197 (29), 182 (14), 171 (14), 170 (100), 163 (21), 161 (12), 118 (12), 107 (49). Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.09; H, 6.15; N, 7.82. Found: C, 76.84; H, 6.38; N, 7.46. The absolute configuration was assigned comparism of preparative HPLC retention time to reference data. The second eluted diastereomer was reported to have (*R*)-configuration.[7]

***N*-Boc-*N*-(4-methoxyphenyl)-*p*-methoxybenzylamine (7).** From the reaction of N-Boc-*p*-anisidine (1.92 g, 8.6 mmol) and p-methoxybenzyl chloride (1.28 mL, 1.1 equiv) with NaH (1.1 equiv) in THF (25 mL) was obtained **7**: 2.95 g, 86% yield. ^{1}H NMR($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 3.76 (s, 3H), 3.78 (s, 3H), 4.69(s, 2H), 7.14−6.76 (m, 8H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 28.2, 53.3, 55.1, 55.2, 80.0, 113.5, 113.6, 128.1, 129.0, 130.6, 135.3, 155.0, 157.4, 158.5; HRMS calcd for $C_{20}H_{25}NO_4$: 343.1784; found: 343.1777.

***N*-Boc-*N*-(4-methoxyphenyl)-α-methyl-*p*-methoxybenzylamine ((*S*)-8).** To a solution of (−)-sparteine (0.33 mL, 1.2 equiv) in toluene (14 mL) at −78 °C was added *n*-BuLi (1.1 equiv). The reaction mixture was stirred for 30 min at −78 °C, and a solution of **7** (440 mg, 1.0 equiv) in toluene (7 mL) was transferred to the above solution at −78 °C. The resulting reaction mixture was stirred at −78 °C for 4 h, and methyl triflate (0.18 mL, 1.2 equiv) in toluene (14 mL) was added after precooling. After stirring for 3 h at −78 °C, this mixture was allowed to slowly warm to room temperature. Workup consisted of addition of water, extraction of the aqueous layer with diethyl ether, extraction of the combined diethyl ether extracts with sat. NH_4Cl solution, drying over anhydrous $MgSO_4$, filtration, and concentration in vacuo. The crude mixture was purified by chromatography to give of (*S*)-**8** as a colorless oil in (389 mg 85% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (m, 12H), 3.75 (s, 3H), 3.79 (s, 3H), 5.65 (br, 1H), 7.15−6.70 (m, 8H); ^{13}C NMR ($CHCl_3$, 100.5 MHz) δ 18.0, 28.2, 55.05, 55.12, 79.8, 113.1, 128.6, 130.8, 131.2, 134.3, 155.3, 157.9, 158.5; HRMS calcd for $C_{21}H_{27}NO_4$: 357.1940; found: 357.1940.

***N*-Boc-alanine Methyl Ester ((*S*)-9).** To **8** (283 mg, 0.79 mmol) dissolved in CH_3CN-H_2O (4:1; ca.0.05 M) was added CAN (ceric ammonium nitrate, 954 mg, 2.2 equiv) at 0 °C. After stirring at 0 °C for 0.5 h, the mixture was diluted with diethyl ether, poured into water, and extracted with diethyl ether. The extracts were combined, dried over $MgSO_4$, filtered through a pad of Celite, and concentrated in vacuo. The crude mixture was further purified by chromatography to give the product, 111 mg, 56% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 12H), 3.79 (s, 3H), 4.73 (br, 2H), 6.85 (d, J = 9.2 Hz, 2H), 7.22 (d, J = 9.2 Hz, 2H). To a solution of above product (30 mg, 0.12 mmol) in 0.5 mL of CCl_4, 1.1 mL of MeCN, and 1.1 mL of H_2O were added $NaIO_4$ (387 mg, 15 equiv) and $RuCl_3$ H_2O (2.5 mg). After stirring for 48 h at room temperature, the reaction mixture was diluted with CH_2Cl_2/H_2O mixture and extracted twice with CH_2Cl_2. The extract was dried and concentrated in vacuo. The resulting crude product was treated with $SOCl_2$/MeOH for 2 h and concentrated in vacuo, and then excess $(Boc)_2O$ in CH_2Cl_2 was added. Washing of the solution with sat. $NaHCO_3$ solution and brine, drying, evaporation, and flash column chromatography gave (*S*)-**9** (10 mg) in 42% overall yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (d, J = 7.2 Hz, 3H), 1.44 (s, 9H), 3.74 (s, 3H), 4.30 (s, 1H), 5.02 (br, 1H). The absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*S*)-alanine.

Acknowledgment. We are grateful to the National Institute of Health (GM-18874) and the National Science Foundation (CHE-9526355) for support of this work. B.J.K. thanks KRICT, and Y.S.P. thanks Konkuk University, for the support of this work.

JO9817568