Synthesis of Quaternary α-Methyl α-Amino Acids by Asymmetric Alkylation of Pseudoephenamine Alaninamide Pivaldimine

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Supporting Information

For reference, compounds not numbered in the manuscript are numbered in the order they appear in the Supplemental Information.

General experimental procedures: All reactions were performed in flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 35 °C at 40 mmHg. Analytical thin-layer chromatography (TLC) was performed using glass plates precoated with silica gel (0.25-mm, 60-Å pore size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$) or ceric ammonium molybdate solution (CAM), and were developed by heating with a heat gun. Flash column chromatography was performed as described by Still et al.,[1] employing silica gel (60 Å, standard grade) purchased from Dynamic Adsorbents. Flash column chromatography using deactivated silica gel was performed by preparing the silica gel slurry with triethylamine (10% v/v in corresponding eluent mixture) and flushing column with the eluent prior to loading the compound on the column.

Materials: Commercial solvents and reagents were used as received, with the following exceptions. *N,N*-diisopropylamine, dichloromethane, ethyl ether, and tetrahydrofuran were purified by the method of Pangborn et al.[2] Lithium chloride was dried at 150 °C under vacuum (0.1 mmHg) for 12 h and stored in a drying oven at 150 °C (760 mmHg); the hot, dried solid was flame dried under vacuum (0.1 mmHg) for 2–3 min immediately prior to use. 4 Å molecular sieves were stored in a drying oven at 150 °C (760 mmHg) and flame dried under vacuum (0.1 mmHg) for 2-3 min immediately prior to use. Benzyl bromide, *tert*-butyl bromoacetate, 3-methoxybenzyl bromide, ethyl iodide, and allyl bromide were filtered neat through a column of oven-dried basic alumina immediately prior to use. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[3]

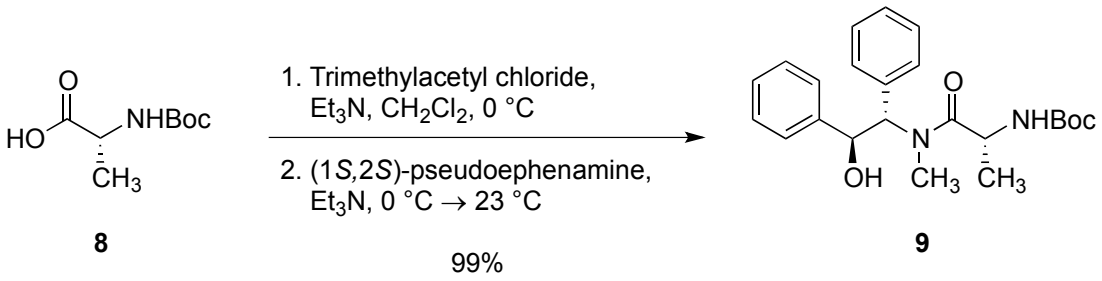
Instrumentation: Proton nuclear magnetic resonance spectra (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian INOVA 600 (600 MHz/150 MHz), Varian INOVA 500 (500 MHz/125 MHz) or Varian 400 (400 MHz/100 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, HDO: δ 4.79, CD_2HOD: δ 4.87, THF-d_8: δ 3.58). Carbon chemical shifts are

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
[3] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.2, CD_3OD: δ 49.0, THF-d_8: δ 67.6). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, dq= doublet of quartets, dquint = doublet of quintets, sxt = sextet, m = multiplet, br = broad), integration, and coupling constant (J) in Hertz (Hz). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s = strong, m = medium, br = broad). HPLC retention times were acquired using a Beckman System Gold instrument equipped with a Phenomenex Chirex 3126 (D)-penicillamine column (5 µm particle size, 4.6 mm x 50 mm). Melting points were determined using a Thomas Scientific capillary melting point apparatus. High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility. X-ray crystallographic analysis was performed at the Harvard University X-Ray Crystallographic Laboratory by Dr. Shao-Liang Zheng.

1 Synthesis of Pseudoephenamine Alaninamide Pivaldimines

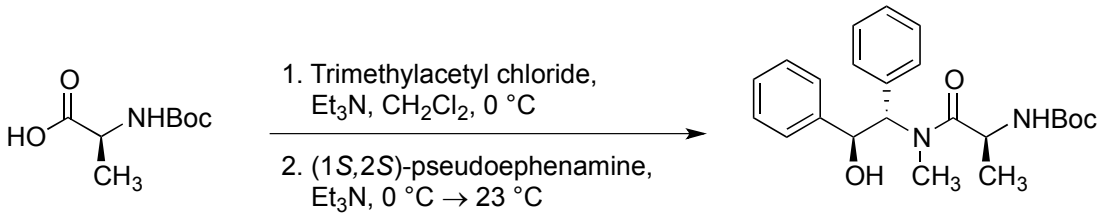
1.1 Synthesis of Pseudoephenamine Alaninamide Pivaldimines via Pivaldehyde Condensation



8 **9**

***Tert*-butyl ((*R*)-1-(((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)(methyl)amino)-1-oxopropan-2-yl)carbamate (9)**

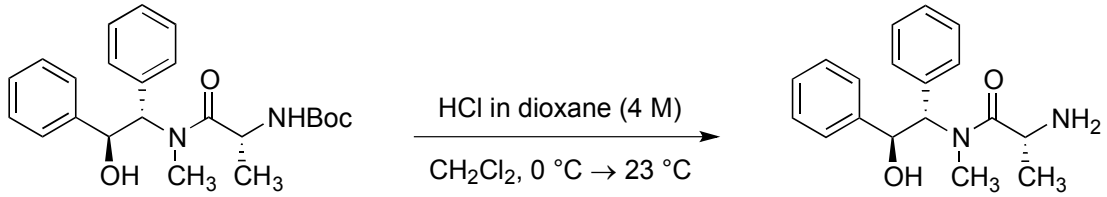
Trimethylacetyl chloride (4.22 mL, 34.3 mmol, 2.60 equiv) was added dropwise to a stirring solution of *N*-(*tert*-butoxycarbonyl)-D-alanine (6.49 g, 34.3 mmol, 2.60 equiv) and triethylamine (4.42 mL, 31.7 mmol, 2.40 equiv) in dichloromethane (88.0 mL) at 0 °C. A white precipitate gradually formed; after 30 min, a second portion of triethylamine (4.42 mL, 31.7 mmol, 2.40 equiv) was added to the reaction mixture, followed by a single portion of (1*S*,2*S*)-pseudoephenamine (**26**) (3.00 g, 13.2 mmol, 1.00 equiv). Stirring was continued, and, after 12 h, saturated aqueous sodium bicarbonate solution (150 mL) was added. The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 100 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (30→50% ethyl acetate-hexanes) to provide amide **9** as a white foam (5.26 g, 99%). TLC (40% ethyl acetate-hexanes): R_f = 0.55 (UV, $KMnO_4$). ^{1}H NMR (6:1 rotamer ratio, asterisk denotes minor rotamer peaks, 600 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.34 – 7.22 (m, 6H), 7.24 – 7.15 (m, 2H), 5.49 (d, *J* = 7.8 Hz, 1H), 5.39* (d, *J* = 7.2 Hz, 1H), 5.36 (d, *J* = 7.6 Hz, 1H), 5.27* (d, *J* = 8.7 Hz, 1H), 4.87 – 4.77* (m, 1H), 4.58 – 4.50 (m, 1H), 2.90 (s, 3H), 2.88* (s, 3H), 1.42 (s, 9H), 1.38* (s, 9H), 1.10 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.08, 155.50, 141.62, 136.47, 128.88, 128.64, 128.46, 128.25, 127.81, 127.75, 127.33, 126.75, 79.87, 73.49, 67.13, 47.12, 34.70, 28.48, 18.25. FTIR (neat), cm^{-1}: 2980 (m), 1705 (s), 1635 (s), 1454 (s), 1367 (m), 1166 (s). HRMS (ESI): Calcd for $(C_{23}H_{30}N_2O_4 + H)^+$: 399.2286. Found: 399.2312.



10 **11**

***Tert*-butyl ((*S*)-1-(((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)(methyl)amino)-1-oxopropan-2-yl)-carbamate (11)**

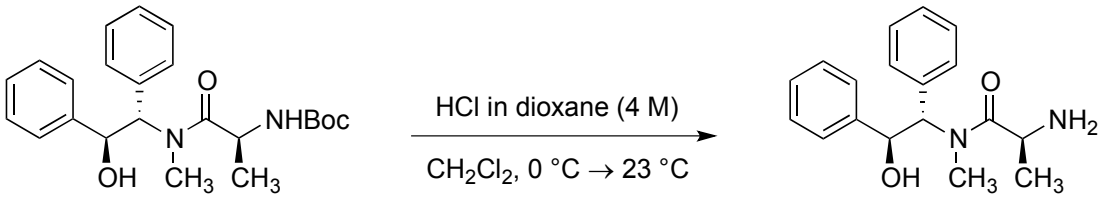
Trimethylacetyl chloride (9.85 mL, 80.0 mmol, 2.60 equiv) was added dropwise to a stirring solution of *N*-(*tert*-butoxycarbonyl)-L-alanine (15.2 g, 80.0 mmol, 2.60 equiv) and triethylamine (10.3 mL, 74.0 mmol, 2.40 equiv) in dichloromethane (200 mL) at 0 °C. A white precipitate gradually formed; after 30 min, a second portion of triethylamine (10.3 mL, 74.0 mmol, 2.40 equiv) was added to the reaction mixture, followed by a single portion of (1*S*,2*S*)-pseudoephenamine (**26**) (7.00 g, 30.8 mmol, 1.00 equiv). Stirring was continued, and, after 12 h, saturated aqueous sodium bicarbonate solution (200 mL) was added. The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 100 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (30→50% ethyl acetate-hexanes) to provide amide **11** as a white foam (12.3 g, 99%). TLC (40% ethyl acetate-hexanes): R_f = 0.55 (UV, $KMnO_4$). ^{1}H NMR (4:1 rotamer ratio, asterisk denotes minor rotamer peaks, 600 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H), 7.33 – 7.17 (m, 8H), 5.74 (d, *J* = 7.4 Hz, 1H), 5.45 (d, *J* = 7.5 Hz, 1H), 5.43* (d, *J* = 8.6 Hz, 1H), 5.24* (d, *J* = 9.0 Hz, 1H), 4.91* (p, *J* = 6.9 Hz, 1H), 4.54 (p, *J* = 7.1 Hz, 1H), 2.98* (s, 3H), 2.96 (s, 3H), 1.45* (s, 9H), 1.43 (s, 9H), 1.33* (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (4:1 rotamer ratio, asterisk denotes minor rotamer peaks, 100 MHz, $CDCl_3$) δ 174.63, 155.34, 141.44, 136.82, 128.77*, 128.72*, 128.68, 128.51, 128.41, 128.16*, 128.08*, 127.95, 127.78, 127.26*, 126.71, 79.68, 73.66, 73.12*, 66.00*, 64.48, 47.06, 45.78*, 33.48, 29.35*, 28.48, 19.00*, 18.59. FTIR (neat), cm^{-1}: 2980 (m), 1699 (s), 1633 (s), 1494 (s), 1410 (m), 1166 (s). HRMS (ESI): Calcd for $(C_{23}H_{30}N_2O_4 + H)^+$: 399.2286. Found: 399.2306.



9 **12**

(*R*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (12)

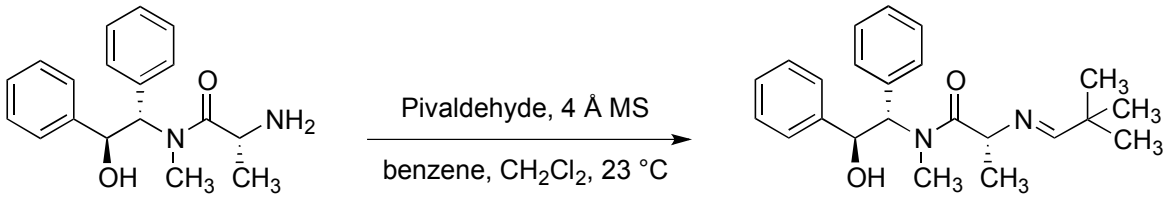
A solution of hydrogen chloride in dioxane (4 M, 14.4 mL, 57.6 mmol, 4.40 equiv) was added dropwise to a stirring solution of amide **9** (5.20 g, 13.1 mmol, 1.00 equiv) in dichloromethane (29.0 mL) at 0 °C over 2 min. After 5 min, the reaction mixture was allowed to warm to 23 °C. A white precipitate gradually formed, and the resulting suspension was stirred at 23 °C for 2 h, after which time the reaction mixture was brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. Saturated aqueous sodium chloride solution (40 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (8% methanol-dichloromethane, triethylamine pretreated silica gel) to provide amide **12** as a white solid (3.21 g, 82%). TLC (10% methanol-dichloromethane): R_f = 0.29 (UV, $KMnO_4$). ^{1}H NMR (10:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.35 – 7.29 (m, 6H), 7.29 – 7.23 (m, 2H), 5.73 (d, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 8.1 Hz, 1H), 5.38 – 5.37* (m, 1H), 5.17* (d, *J* = 8.0 Hz, 1H), 3.85* (q, *J* = 6.8 Hz, 1H), 3.78 (q, *J* = 6.8 Hz, 1H), 3.09* (s, 3H), 2.93 (s, 3H), 2.39 (br s, 2H), 1.36 – 1.28* (m, 3H), 1.15 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.12, 141.87, 137.04, 128.58, 128.45, 128.41, 127.81, 127.67, 126.91, 73.35, 65.38, 47.61, 33.32, 20.79. FTIR (neat), cm^{-1}: 3030 (m), 2974 (m), 1627 (s), 1452 (m), 1273 (m), 1062 (s). HRMS (ESI): Calcd for $(C_{18}H_{22}N_2O_2 + H)^+$: 299.1761. Found: 299.1755.



11 **13**

(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (13)

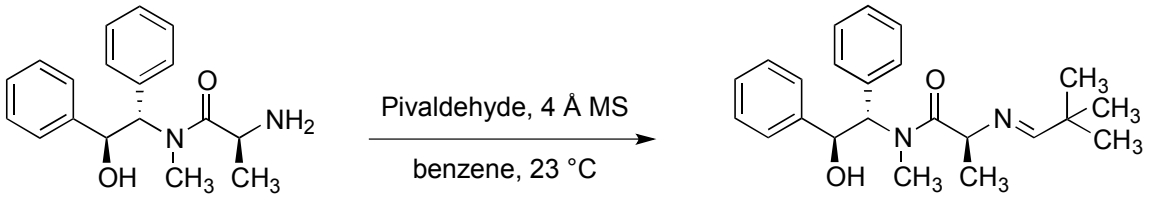
A solution of hydrogen chloride in dioxane (4 M, 34.2 mL, 137 mmol, 4.40 equiv) was added dropwise to a stirring solution of amide **11** (12.3 g, 30.8 mmol, 1.00 equiv) in dichloromethane (70.0 mL) at 0 °C over 2 min. After 5 min, the reaction mixture was allowed to warm to 23 °C. A white precipitate gradually formed, and the resulting suspension was stirred at 23 °C for 1.5 h, after which time the reaction mixture was brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. Saturated aqueous sodium chloride solution (50 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (7% methanol-dichloromethane, triethylamine pretreated silica gel) to provide amide **13** as a white foam (7.40 g, 81%). TLC (10% methanol-dichloromethane): R_f = 0.38 (UV, $KMnO_4$). ^{1}H NMR (4:3 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.35 – 7.20 (m, 8H), 5.75 (d, *J* = 7.7 Hz, 1H), 5.42 (d, *J* = 7.7 Hz, 1H), 5.37 – 5.29* (m, 2H), 3.94* (q, *J* = 6.5 Hz, 1H), 3.73 (q, *J* = 6.8 Hz, 1H), 2.91 (s, 3H), 1.86 (br s, 2H), 1.37* (d, *J* = 6.5 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (4:3 rotamer ratio, asterisk denotes minor rotamer peaks, 126 MHz, $CDCl_3$) δ 177.49, 175.89*, 142.09*, 141.85, 137.13, 136.37*, 128.74, 128.66, 128.60, 128.58, 128.53, 128.46, 128.37, 127.99, 127.96, 127.73, 127.63, 127.24, 126.74, 73.39, 72.47*, 65.19, 64.15*, 47.46, 46.78*, 32.85, 29.85*, 21.36*, 20.63. FTIR (neat), cm^{-1}: 3030 (m), 2976 (m), 1627 (s), 1494 (m), 1450 (m). HRMS (ESI): Calcd for ($C_{18}H_{22}N_2O_2$ + H)$^+$: 299.1761. Found: 299.1770.



12 **1**

(*R*)-2-((*E*)-(2,2-dimethylpropylidene)amino)-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (1)

A 25 mL pear-shaped flask charged with a teflon-coated magnetic stirring bar and 4 Å molecular sieves (20 mg) was flame-dried in vacuo for 3 min. After cooling under vacuum, amide **12** (100 mg, 0.335 mmol, 1.00 equiv), dry benzene (1.20 mL) and dichloromethane (1.00 mL) were added to the flask. Pivaldehyde (74.0 μL, 0.670 mmol, 2.00 equiv) was added to the solution by syringe, and stirring of the reaction mixture was continued at 23 °C for 50 min. The solvent was then evaporated under reduced pressure (ca. 80 mmHg) and the white residue was dried under high vacuum in an oil bath (35 °C) overnight to remove excess pivaldehyde. The *tert*-butyl imine product **1** (123 mg, ≥99%) was used in subsequent alkylation reactions without further purification. ^{1}H NMR (1:1 rotamer ratio, asterisk denotes rotamer peaks, 600 MHz, THF-d_8) δ 7.60 (s, 1H), 7.53 – 7.49 (m, 3H), 7.42 – 7.36 (m, 4H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.13 (m, 7H), 7.11 (t, *J* = 7.3 Hz, 2H), 5.89 (d, *J* = 8.3 Hz, 1H), 5.45 (d, *J* = 5.5 Hz, 1H), 5.31* (d, *J* = 8.3 Hz, 1H), 5.26* (d, *J* = 5.5 Hz, 1H), 4.90 (br s, 1H), 4.75* (br s, 1H), 4.33 (q, *J* = 6.6 Hz, 1H), 4.04* (q, *J* = 6.4 Hz, 1H), 2.94 (s, 3H), 2.75* (s, 3H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.02 (s, 9H), 0.97* (s, 9H), 0.92* (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (1:1 rotamer ratio, asterisk denotes rotamer peaks, 126 MHz, THF) δ 173.12, 172.63, 172.34*, 144.84*, 144.57, 139.85, 139.57*, 130.13, 129.71, 129.18, 128.85, 128.76, 128.42, 128.26, 127.94, 127.76, 74.18, 73.60*, 64.43*, 64.19, 62.23, 37.21, 27.35, 27.15*, 19.27, 18.96*. FTIR (neat), cm^{-1}: 2962 (m), 2235 (s), 2081 (s), 1645 (m), 1099 (s), 1045 (s). HRMS (ESI): Calcd for $(C_{23}H_{30}N_2O_2 + H)^+$: 367.2380. Found: 367.2402.

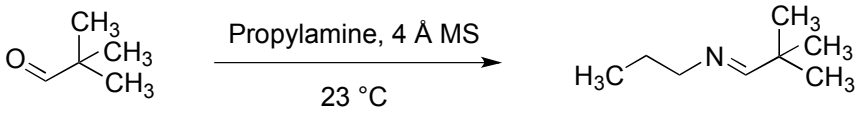


(*S*)-2-((*E*)-(2,2-dimethylpropylidene)amino)-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (2)

A 25 mL pear-shaped flask charged with a teflon-coated magnetic stirring bar and 4 Å molecular sieves (20 mg) was flame-dried in vacuo for 3 min. After cooling under vacuum, amide **13** (100 mg, 0.335 mmol, 1.00 equiv) and dry benzene (2.20 mL) were added to the flask. Pivaldehyde (74.0 μL, 0.670 mmol, 2.00 equiv) was added to the solution by syringe, and stirring of the reaction mixture was continued at 23 °C for 30 min, during which time a white precipitate formed. The solvent was then evaporated under reduced pressure (ca. 80 mmHg) and the white residue was dried under high vacuum in an oil bath (35 °C) overnight to remove excess pivaldehyde. The *tert*-butyl imine product **2** (123 mg, ≥99%) was used in subsequent alkylation reactions without further purification. ^{1}H NMR (4:1 rotamer ratio, asterisk denotes minor rotamer peaks, 600 MHz, THF-d_8) δ 7.65 (s, 1H), 7.41 – 7.37 (m, 2H), 7.37 – 7.31 (m, 2H), 7.24 – 7.14 (m, 4H), 7.14 – 7.07 (m, 2H), 5.97 (d, *J* = 7.5 Hz, 1H), 5.57* (d, *J* = 9.3 Hz, 1H), 5.37 (d, *J* = 7.5 Hz, 1H), 5.21* (d, *J* = 9.1 Hz, 1H), 4.92* (br s, 1H), 4.73 (br s, 1H), 4.70 – 4.64* (m, 1H), 4.37 (q, *J* = 6.6 Hz, 1H), 2.95 (s, 3H), 1.24* (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.07* (s, 9H), 0.91 (s, 9H). ^{13}C NMR (126 MHz, THF-d_8) δ 172.85, 172.06, 144.59, 140.15, 129.63, 128.82, 128.70, 128.10, 127.89, 127.66, 73.60, 62.99, 62.77, 37.08, 32.24, 27.20, 19.01. FTIR (neat), cm^{-1}: 2962 (m), 2237 (m), 2083 (m), 1645 (s), 1099 (s), 1045 (s). HRMS (ESI): Calcd for $(C_{23}H_{30}N_2O_2 + H)^+$: 367.2380. Found: 367.2384.

1.2 Synthesis of Pseudoephenamine Alaninamide Pivaldimines via Transimination

1.2.1 Synthesis of Transimination Reagent

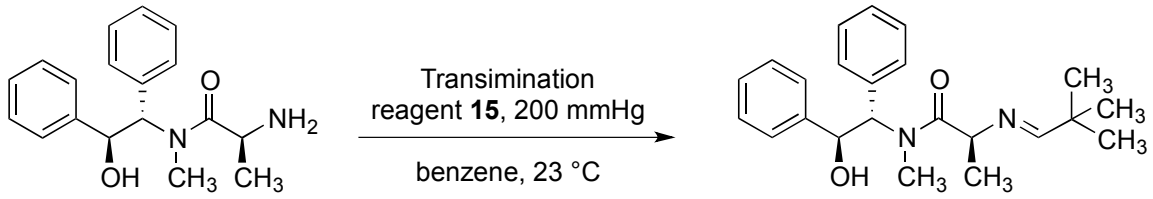


14 **15**

(*E*)-*N*-(2,2-dimethylpropylidene)propan-1-amine (15)

A 50 mL round-bottom flask charged with a teflon-coated magnetic stirring bar and 4 Å molecular sieves (10.0 g) was flame-dried in vacuo for 3 min. After cooling under vacuum, pivaldehyde (12.0 mL, 110 mmol, 1.00 equiv) was added. The mixture was cooled to 0 °C, propylamine (18.2 mL, 221 mmol, 2.00 equiv) was added, and, after 5 min, the reaction mixture was allowed to warm to 23 °C for 1 h. The transimination reagent **15** was directly distilled from the reaction flask (58-62 °C, 100 mmHg) to provide a colorless liquid (13.5 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (t, *J* = 1.2 Hz, 1H), 3.32 (td, *J* = 6.9, 1.2 Hz, 2H), 1.59 (h, *J* = 7.3 Hz, 2H), 1.06 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.87, 63.14, 35.97, 27.02, 23.89, 11.58. FTIR (neat), cm^{-1}: 2964 (s), 2931 (m), 1668 (m), 1629 (s), 1284 (m). HRMS (ESI): Calcd for $(C_8H_{17}N + H)^+$: 128.1441 Found: 128.1439.

1.2.2 Pivaldimine Synthesis via Transimination



13 **2**

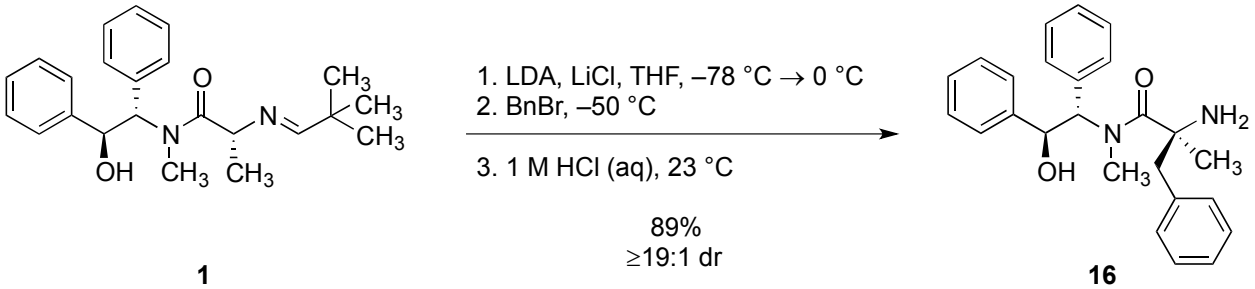
(*S*)-2-((*E*)-(2,2-dimethylpropylidene)amino)-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylpropanamide (2)

Transimination reagent **15** (305 μL, 1.68 mmol, 5.00 equiv) was added to a stirring solution of amide **13** (100 mg, 0.335 mmol, 1.00 equiv) in dry benzene (3.35 mL). The mixture was stirred under reduced pressure (200 mmHg) at 23 °C for 30 min, during which time gas was observed to evolve from the reaction mixture. The solvent was then evaporated under reduced pressure (ca. 80 mmHg) and the white

residue was dried under high vacuum in an oil bath (35 °C) overnight to remove excess transimination reagent. The characterization data were in agreement with values for the same *tert*-butyl imine **2** prepared by direct condensation of pivaldehyde with amide **13**, as reported above.

2 Alkylations of Pseudoephenamine Alaninamide Pivaldimine

2.1 Matched Case

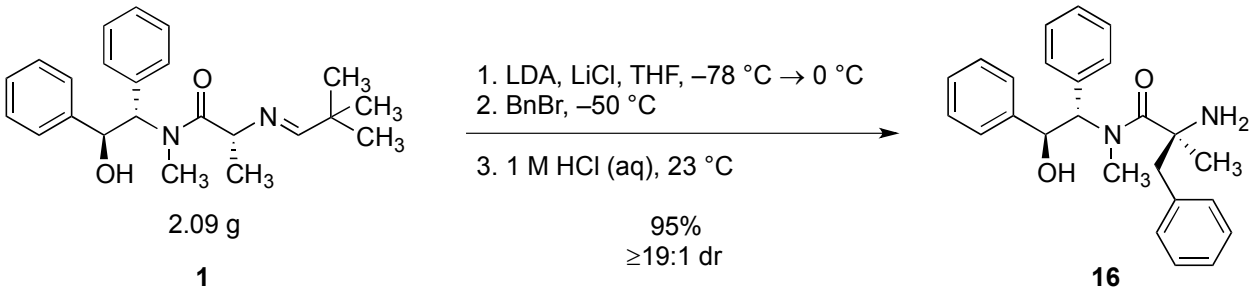


1 **16**

(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenylpropanamide (16)

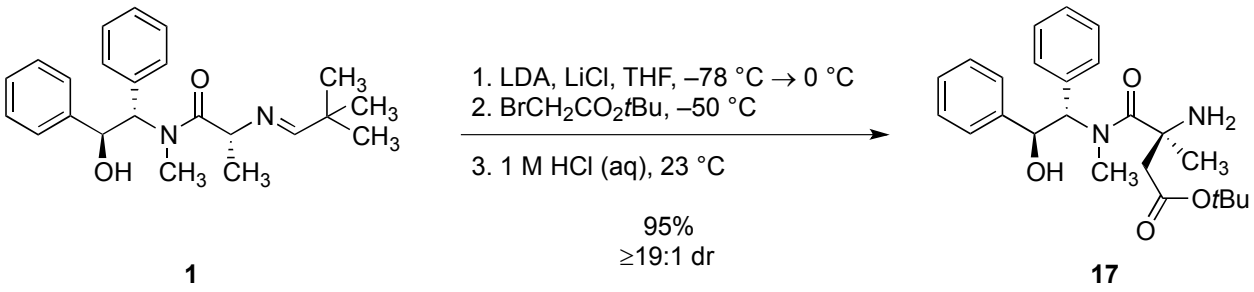
A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, benzyl bromide (100 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 3.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 3 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (2→4% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **16** as a white solid (116 mg, 89%, mp = 111-113 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.47 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 6H), 7.13 – 7.05 (m, 2H), 7.04 – 6.98 (m, 2H), 5.79 (d, *J* = 7.6 Hz, 1H), 3.93 (d, *J* = 7.6 Hz, 1H), 3.12 (d, *J* = 13.3 Hz, 1H), 2.85 (d, *J* = 13.3 Hz, 1H), 2.25 (s, 3H), 1.91 (br s, 2H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.04, 138.35,

137.60, 136.26, 130.20, 128.55, 128.42, 128.23, 128.12, 128.01, 127.77, 127.11, 126.96, 80.62, 69.33, 58.85, 46.72, 34.47, 29.80, 26.30. FTIR (neat), cm^{-1}: 2926 (m), 2852 (m), 1732 (s), 1602 (m), 1454 (s). HRMS (ESI): Calcd for $(C_{25}H_{28}N_2O_2 + H)^+$: 389.2231. Found: 389.2234.



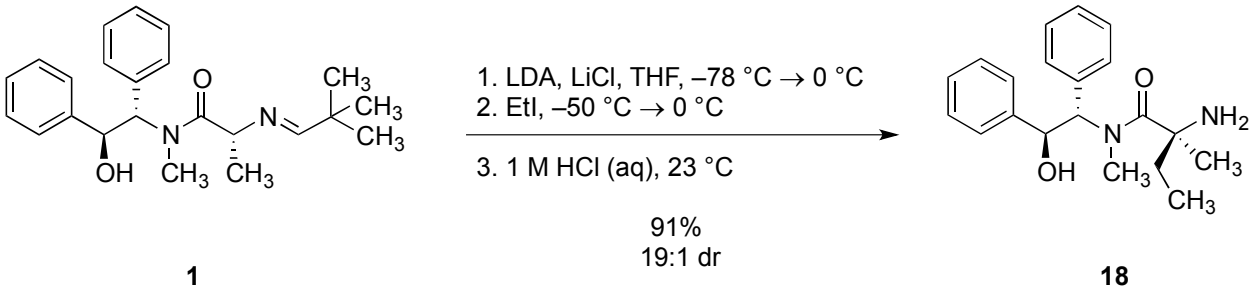
Larger scale synthesis of (*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenylpropanamide (16)

A solution of *tert*-butyl imine **1** (2.09 g, 5.70 mmol, 1.00 equiv) in tetrahydrofuran (24.0 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (1.45 g, 34.2 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 7.00 mL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 12.5 μL, 12.5 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask by cannula, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, benzyl bromide (1.69 mL, 14.2 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 3.5 h, after which time 1 M aqueous hydrochloric acid solution (100 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 3 h. Ethyl acetate (20 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 30 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 100 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **16** as a white solid (2.11 g, 95%). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. The characterization data were in agreement with the values for α,α-disubstituted amide **16** prepared on a smaller scale, as reported above.



(*S*)-*tert*-butyl 3-amino-4-(((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)(methyl)amino)-3-methyl-4-oxobutanoate (17)

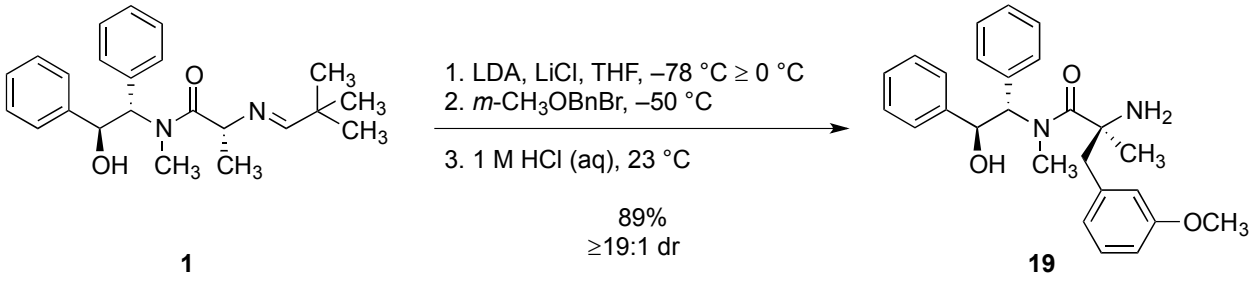
A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, *tert*-butyl bromoacetate (124 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 2.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (1→2.5% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **17** as a white solid (132 mg, 95%, mp = 83-84 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (8% methanol-dichloromethane): R_f = 0.45 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.11 (m, 6H), 7.09 – 7.03 (m, 2H), 7.02 – 6.96 (m, 2H), 5.82 (d, *J* = 8.5 Hz, 1H), 3.90 (d, *J* = 8.5 Hz, 1H), 3.00 (d, *J* = 16.6 Hz, 1H), 2.55 (d, *J* = 16.5 Hz, 1H), 2.24 (s, 3H), 2.01 (br s, 2H), 1.46 (s, 9H), 1.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.35, 170.88, 138.64, 137.62, 128.77, 128.09, 127.98, 127.97, 127.63, 127.35, 81.76, 80.97, 69.90, 56.10, 45.63, 34.47, 28.21, 27.02. FTIR (neat), cm^{-1}: 2976 (m), 2793 (m), 1734 (s), 1367 (m), 1153 (s). HRMS (ESI): Calcd for $(C_{24}H_{32}N_2O_4 + H)^+$: 413.2442. Found: 413.2440.



1 **18**

(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylbutanamide (18)

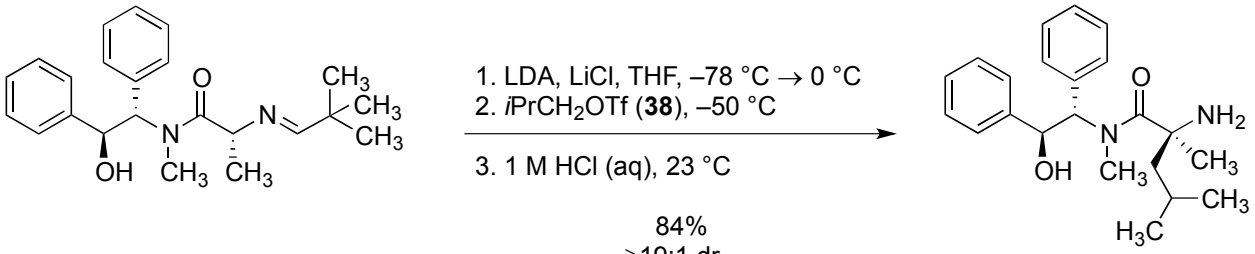
A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, ethyl iodide (67.8 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 30 min, and then was warmed to 0 °C for 3.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **18** as a white solid (100 mg, 91%, mp = 57-58 °C). The diastereomeric ratio of the crude material was determined to be 19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.40 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 6H), 7.11 – 7.07 (m, 2H), 7.06 – 7.02 (m, 2H), 5.77 (d, *J* = 7.8 Hz, 1H), 3.93 (d, *J* = 7.8 Hz, 1H), 2.27 (s, 3H), 1.95 (br s, 2H), 1.87 – 1.76 (m, 1H), 1.72 – 1.62 (m, 1H), 1.32 (s, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.69, 138.54, 137.87, 128.52, 128.18, 128.08, 127.99, 127.68, 127.11, 80.48, 69.62, 58.35, 34.52, 33.79, 25.82, 8.52. FTIR (neat), cm^{-1}: 2970 (m), 1732 (s), 1226 (m), 1136 (s), 908 (s). HRMS (ESI): Calcd for $(C_{20}H_{26}N_2O_2 + H)^+$: 327.2074. Found: 327.2075.



(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-3-(3-methoxyphenyl)-*N*,2-dimethylpropanamide (19)

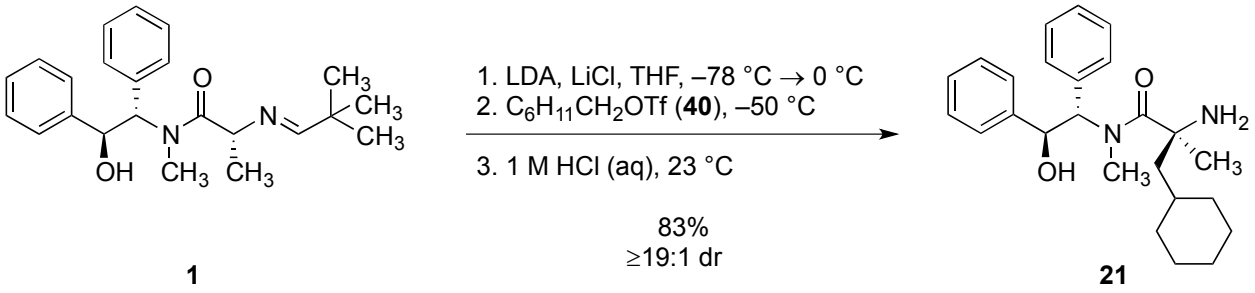
A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, 3-methoxybenzyl bromide (117 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 3 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 2 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (2→4% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **19** as a white solid (125 mg, 89%, mp = 52-53 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.53 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 7H), 7.10 – 7.04 (m, 2H), 7.01 – 6.95 (m, 2H), 6.76 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.71 – 6.70 (m, 1H), 6.70 – 6.65 (m, 1H), 5.78 (d, *J* = 7.6 Hz, 1H), 3.92 (d, *J* = 7.7 Hz, 1H), 3.71 (s, 3H), 3.12 (d, *J* = 13.3 Hz, 1H), 2.82 (d, *J* = 13.3 Hz, 1H), 2.25 (s, 3H), 1.84 (br s, 2H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.15, 159.59, 138.54, 137.89,

137.64, 129.41, 128.55, 128.19, 128.10, 127.98, 127.73, 127.06, 122.48, 115.56, 112.76, 80.66, 69.48, 58.88, 55.20, 46.87, 34.55, 26.55. FTIR (neat), cm^{-1}: 2926 (m), 1732 (m), 1601 (m), 1454 (m), 1263 (m). HRMS (ESI): Calcd for $(C_{26}H_{30}N_2O_3 + H)^+$: 419.2329. Found: 419.2345.



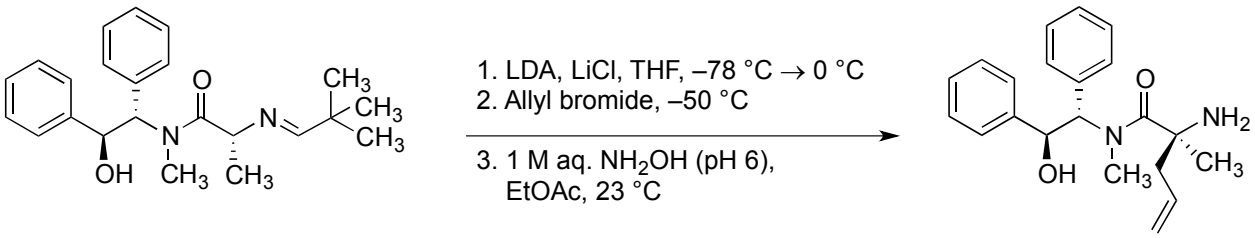
(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2,4-trimethylpentanamide (20)

A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, isobutyl trifluoromethanesulfonate (**38**) (173 mg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 1.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 4 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **20** as a white solid (100 mg, 84%, mp = 59-60 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.52 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.14 (m, 6H), 7.11 – 7.05 (m, 2H), 7.04 – 6.99 (m, 2H), 5.73 (d, *J* = 7.9 Hz, 1H), 3.92 (d, *J* = 8.0 Hz, 1H), 2.28 (s, 3H), 1.78 – 1.67 (m, 1H), 1.64 – 1.54 (m, 2H), 1.31 (s, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.43, 138.56, 137.79, 128.62, 128.17, 128.06, 128.01, 127.69, 127.22, 80.77, 69.63, 57.84, 49.35, 34.54, 27.66, 24.70, 24.53, 23.61. FTIR (neat), cm^{-1}: 2955 (m), 1724 (s), 1454 (m), 1207 (m), 1138 (s). HRMS (ESI): Calcd for $(C_{22}H_{30}N_2O_2 + H)^+$: 355.2380. Found: 355.2382.



(*S*)-2-amino-3-cyclohexyl-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylpropanamide (21)

A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, cyclohexylmethyl trifluoromethanesulfonate (**42**) (207 mg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 3 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 12 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **21** as a white solid (110 mg, 83%, mp = 83-84 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.52 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 6H), 7.10 – 7.07 (m, 2H), 7.05 – 7.00 (m, 2H), 5.74 (d, *J* = 7.8 Hz, 1H), 3.93 (d, *J* = 7.8 Hz, 1H), 2.28 (s, 3H), 1.71 (dd, *J* = 14.1, 6.8 Hz, 1H), 1.65 – 1.57 (m, 7H), 1.54 (dd, *J* = 14.1, 5.2 Hz, 1H), 1.36 (s, 1H), 1.29 (s, 3H), 1.21 – 1.05 (m, 3H), 0.97 – 0.93 (m, 1H), 0.86 – 0.77 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.51, 138.68, 137.79, 128.63, 128.17, 128.06, 128.01, 127.68, 127.27, 80.74, 69.61, 57.74, 48.20, 35.12, 34.57, 34.15, 34.12, 27.75, 26.48, 26.40, 26.27. FTIR (neat), cm^{-1}: 2926 (m), 1730 (s), 1454 (m), 1136 (m), 906 (s). HRMS (ESI): Calcd for $(C_{25}H_{34}N_2O_2 + H)^+$: 395.2700. Found: 395.2720.



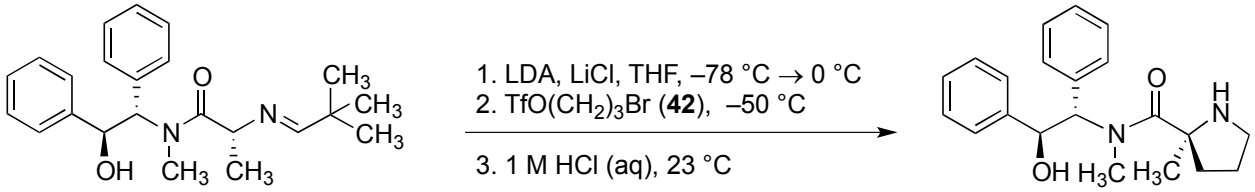
(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylpent-4-enamide (22)

A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, allyl bromide (72.6 μg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 3 h, after which time water (8 mL) and dichloromethane (10 mL) were added. The layers were separated, the aqueous layer was rapidly extracted with dichloromethane (3 x 20 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in ethyl acetate (2 mL) and a stock solution of hydroxylamine hydrochloride in water[4] (5 mL) was added. The biphasic mixture was stirred vigorously at 23 °C for 1.5 h, after which time the aqueous layer was carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 40 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **22** as a white solid (91.0 mg, 80%, mp = 62-63 °C). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (10% methanol-dichloromethane): R_f = 0.50 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 6H), 7.13 – 7.05 (m, 2H), 7.06 – 7.01 (m, 2H), 5.78 (d, *J* = 7.9 Hz, 1H), 5.73 – 5.64 (m, 1H), 5.17 – 5.13 (m, 1H), 5.13 – 5.11 (m, 1H), 3.92 (d, *J* = 8.0 Hz, 1H), 2.59 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.33 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.26 (s, 3H), 1.94 (br s, 2H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$)

[4] Prepared by dissolving hydroxylamine hydrochloride (1.39 g) in water (10.0 mL), followed by adjustment of the pH to 6 by the addition of saturated aqueous sodium bicarbonate solution (10.0 mL).

δ 176.31, 138.44, 137.72, 132.99, 128.55, 128.23, 128.11, 128.07, 127.74, 127.16, 119.52, 80.71, 69.63, 57.62, 45.15, 34.44, 26.21. FTIR (neat), cm^{-1}: 2976 (m), 2793 (m), 1732 (s), 1205 (m), 1136 (s). HRMS (ESI): Calcd for $(C_{21}H_{26}N_2O_2 + H)^+$: 339.2074. Found: 339.2081.

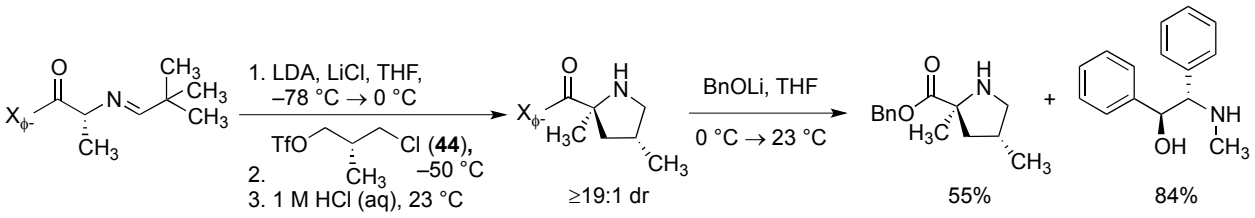
2.1.1 Cyclic Products



1 **23**

(*S*)-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylpyrrolidine-2-carboxamide (23)

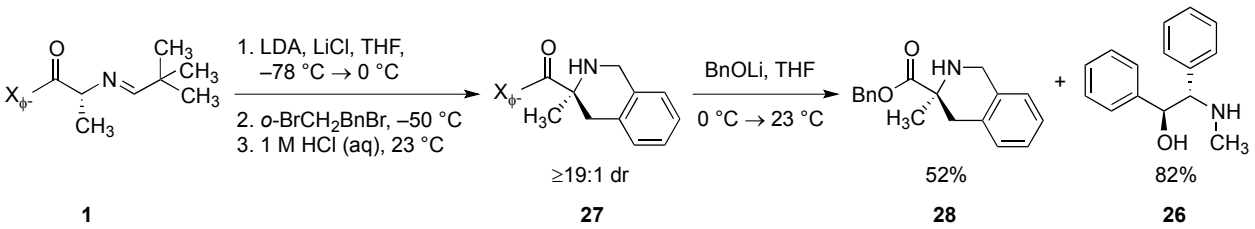
A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, 3-bromopropyl trifluoromethanesulfonate (**42**) (227 mg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 1.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 2 h. The mixture was cooled in an ice bath, and the aqueous layer was carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 40 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3→4% methanol-dichloromethane, triethylamine pretreated silica gel) to provide cyclic α,α-disubstituted amide **23** as a colorless oil (90.0 mg, 79%). The diastereomeric ratio of the crude material was determined to be ≥19:1 by ^{1}H NMR integration. TLC (8% methanol-dichloromethane): R_f = 0.31 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.12 (m, 6H), 7.11 – 7.06 (m, 2H), 7.06 – 7.01 (m, 2H), 5.78 (d, *J* = 7.9 Hz, 1H), 3.92 (d, *J* = 7.7 Hz, 1H), 3.02 – 2.90 (m, 2H), 2.27 (s, 3H), 2.26 – 2.21 (m, 1H), 1.90 – 1.79 (m, 1H), 1.79 – 1.66 (m, 2H), 1.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.42, 138.55, 137.77, 128.52, 128.20, 128.12, 128.10, 128.03, 127.71, 127.09, 80.49, 69.68, 65.90, 46.55, 36.94, 34.53, 26.06, 25.27. . FTIR (neat), cm^{-1}: 2976 (m), 1728 (m), 1454 (m), 1170 (m), 1116 (m). HRMS (ESI): Calcd for ($C_{21}H_{26}N_2O_2$ + H)$^+$: 339.2074. Found: 339.2089.



(2*S*,4*R*)-benzyl 2,4-dimethylpyrrolidine-2-carboxylate (25)

A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, triflate **44** (202 mg, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 2 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 2 h. The mixture was cooled in an ice bath and the aqueous layer was carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 30 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (2.60 mL), the resulting solution was cooled to 0 °C, and a freshly prepared solution of lithium phenylmethanolate in tetrahydrofuran (1 M, 670 μL, 0.670 mmol, 2.00 equiv) was added dropwise to the crude mixture.[5] The solution was warmed to 23 °C for 3 h, after which time water (5 mL) and saturated aqueous sodium chloride solution (5 mL) were added. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (10% diethyl ether-dichloromethane, then 2→10% methanol-dichloromethane) to provide (1*S*,2*S*)-pseudoephenamine (**26**) (64.0 mg, 84%) and benzyl ester **25** as a colorless oil (43.0 mg, 55%). The characterization data for the recovered auxiliary were in agreement with values previously reported.[6] Benzyl ester **25**: The diastereomeric ratio of the crude material prior to cleavage of the auxiliary was determined to be ≥19:1 by ^{1}H NMR

integration, and the relative stereochemistry of the ester product was determined by NOE correlations. TLC (10% methanol-dichloromethane): R_f = 0.54 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 5.15 (s, 2H), 3.17 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.52 (dd, *J* = 10.3, 8.1 Hz, 1H), 2.43 (dd, *J* = 12.8, 7.4 Hz, 1H), 2.17 – 2.02 (m, 2H), 1.42 (s, 3H), 1.30 (dd, *J* = 12.8, 10.1 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.60, 136.12, 128.72, 128.36, 128.03, 66.96, 66.68, 54.07, 45.98, 34.17, 26.60, 18.78. FTIR (neat), cm^{-1}: 2960 (m), 2872 (m), 1726 (s), 1163 (s), 1126 (s). HRMS (ESI): Calcd for $(C_{14}H_{19}NO_2 + H)^+$: 234.1496 Found: 234.1503.



(2*S*,4*S*)-benzyl 2,4-dimethylpyrrolidine-2-carboxylate (28)

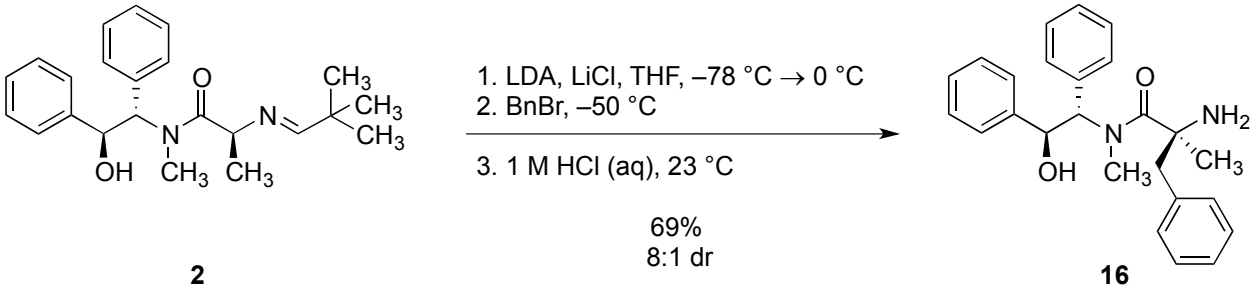
A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, 1,2-bis(bromomethyl)benzene (2 M solution in tetrahydrofuran, 168 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 2.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 3 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (2.60 mL), the resulting solution was cooled to 0 °C, and a freshly prepared solution of lithium phenylmethanolate in tetrahydrofuran (1 M, 670 μL, 0.670 mmol, 2.00 equiv) was added dropwise to the crude mixture.[5] The solution was warmed to 23 °C for 3 h, after which time water (5 mL) and saturated aqueous sodium chloride solution (5 mL) were added. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (10% diethyl ether-dichloromethane, then 1→10% methanol-dichloromethane) to provide (1*S*,2*S*)-pseudoephenamine (**26**) (62.0 mg, 82%) and benzyl ester **28** as a colorless oil (49.0 mg, 52%). The characterization data for the

[5] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

recovered auxiliary were in agreement with values previously reported.[6] Benzyl ester **28**: The diastereomeric ratio of the crude material prior to cleavage of the auxiliary was determined to be ≥19:1 by ^{1}H NMR integration. TLC (1% methanol-dichloromethane): R_f = 0.29 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 3H), 7.18 – 7.11 (m, 4H), 7.11 – 7.06 (m, 1H), 7.02 – 6.98 (m, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 5.07 (d, *J* = 12.5 Hz, 1H), 4.13 (d, *J* = 15.9 Hz, 1H), 4.02 (d, *J* = 16.0 Hz, 1H), 3.30 (d, *J* = 16.0 Hz, 1H), 2.82 (d, *J* = 16.0 Hz, 1H), 1.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.91, 135.99, 133.78, 133.20, 129.03, 128.64, 128.24, 127.90, 126.31, 126.27, 126.11, 66.76, 58.22, 45.15, 37.89, 26.40. FTIR (neat), cm^{-1}: 2958 (m), 1728 (s), 1288 (m), 1178 (s), 1105 (s). HRMS (ESI): Calcd for $(C_{18}H_{19}NO_2 + H)^+$: 282.1496. Found: 282.1506.

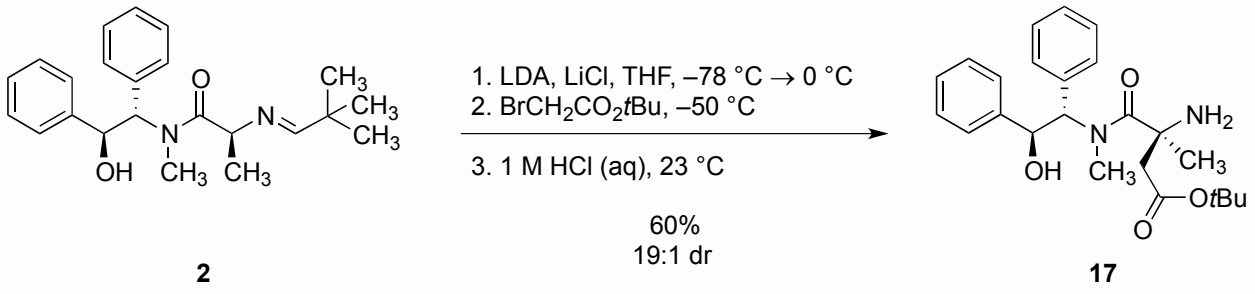
[6] Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568.

2.2 Mismatched Case



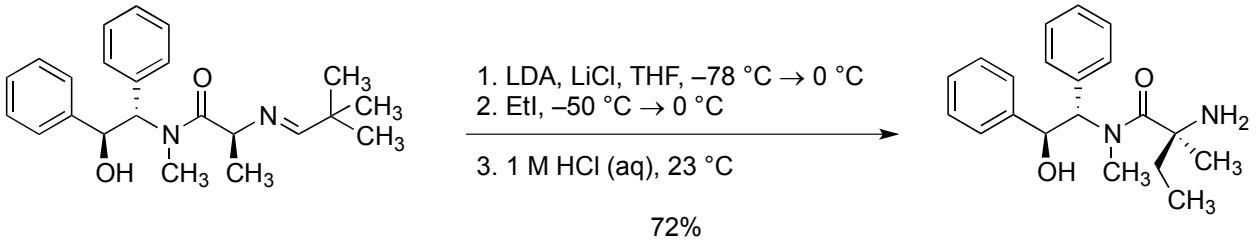
(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenylpropanamide (16)

A solution of *tert*-butyl imine **2** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, benzyl bromide (100 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 3.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 3 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The diastereomeric ratio of the crude material was determined to be 8:1 by ^{1}H NMR integration. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide a 9:1 diastereomeric mixture of α,α-disubstituted amides **16** and **28** (90 mg, 69%). The characterization data for the major and minor diastereomers were consistent with the values for α,α-disubstituted amides **16** and **28**, respectively.



(*S*)-*tert*-butyl 3-amino-4-(((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)(methyl)amino)-3-methyl-4-oxobutanoate (17)

A solution of *tert*-butyl imine **2** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, *tert*-butyl bromoacetate (124 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 2.5 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The diastereomeric ratio of the crude material was determined to be 19:1 by ^{1}H NMR integration. The residue was purified by flash chromatography (1→2.5% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **17** as a white solid (83 mg, 60%). The characterization data were in agreement with values for the same α,α-disubstituted amide **17** reported above.

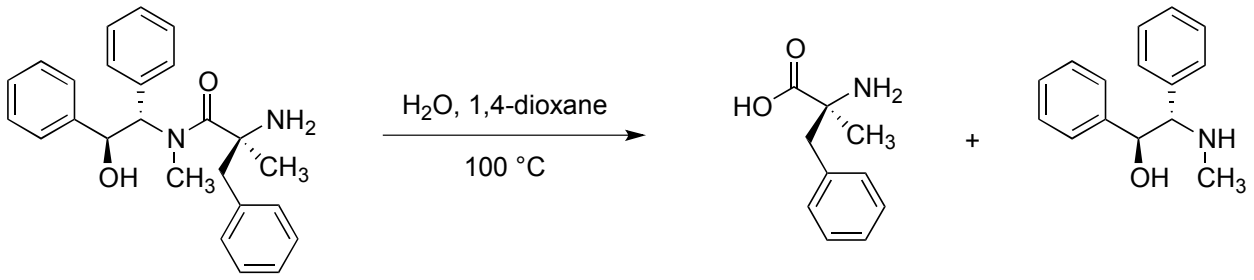


2 **18**

(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylbutanamide (18)

A solution of *tert*-butyl imine **2** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, ethyl iodide (67.8 μL, 0.839 mmol, 2.50 equiv) was added by syringe. The mixture was stirred at −50 °C for 30 min, and then was warmed to 0 °C for 4 h, after which time 1 M aqueous hydrochloric acid solution (8 mL) was added. The biphasic mixture was warmed to 23 °C and stirred vigorously for 1 h. Ethyl acetate (10 mL) was added, and the layers were separated. The organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL). The aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 50 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The diastereomeric ratio of the crude material was determined to be 13:1 by ^{1}H NMR integration. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide a 17:1 diastereomeric mixture of α,α-disubstituted amide **18** and **30** (79 mg, 72%). The characterization data for the major and minor diastereomers were consistent with the values for α,α-disubstituted amides **18** and **30**, respectively.

3 Hydrolysis of α-methyl α-amino amides



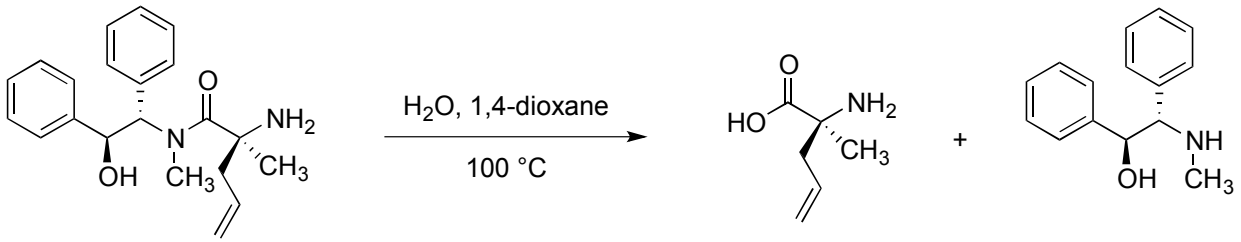
16 **29** **26**

≥99%, 98% ee ≥99%

(*S*)-2-amino-2-methyl-3-phenylpropanoic acid (29)

α,α-disubstituted amide **16** (1.00 g, 2.57 mmol, 1.00 equiv) was dissolved in 1,4-dioxane (12.9 mL) and water (12.9 mL) was added. The mixture was refluxed at 100 °C for 3 h, after which time it was cooled to 23 °C and diluted with dichloromethane (30 mL). The layers were separated, and the aqueous solution was extracted with dichloromethane (4 x 30 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide (1*S*,2*S*)-pseudoephenamine (**26**) (583 mg, ≥99%). The aqueous layer was concentrated in vacuo to provide α,α-disubstituted amino acid **29** as a white solid (460 mg, ≥99%). The characterization data for the recovered auxiliary were in agreement with values previously reported.[6] Chiral HPLC analysis (Phenomenex Chirex 3126 (D)-penicillamine, 95:5 aqueous 2 mM copper (II) sulfate solution:*i*-PrOH, 0.5 mL/min, λ = 240 nm, t_R (major, amino acid **29**) = 25.7 min, t_R(minor, amino acid ***ent*-29**) = 39.9 min) of amino acid **29** established that **31** was of 98% ee. The characterization data for α,α-disubstituted amino acid **29** were in agreement with values previously reported[7]: ^{1}H NMR (500 MHz, D_2O) δ 7.43 – 7.34 (m, 3H), 7.29 – 7.24 (m, 2H), 3.30 (d, *J* = 14.2 Hz, 1H), 2.98 (d, *J* = 14.3 Hz, 1H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, D_2O) δ 176.31, 134.31, 130.06, 129.06, 127.93, 62.26, 42.78, 22.48. FTIR (neat), cm^{-1}: 3331 (s), 2945 (s), 2833 (s), 1448 (m), 1022 (s). HRMS (ESI): Calcd for $(C_{10}H_{13}NO_2 + H)^+$: 180.1026. Found: 180.1024.

[7] Green, J. E.; Bender, D. M.; Jackson, S.; O'Donnell, M. J.; McCarthy, J. R. *Org. Lett.* **2009**, *11*, 807.



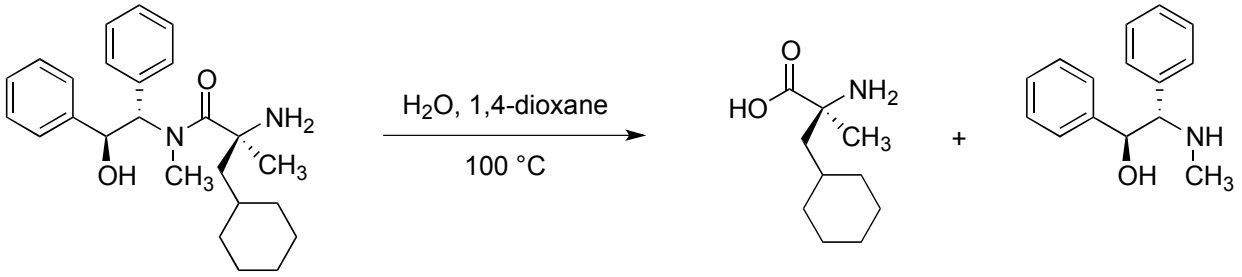
22 **30** **26**

97%, 98% ee 94%

(*S*)-2-amino-2-methylpent-4-enoic acid (30)

α,α-disubstituted amide **22** (70.0 mg, 0.207 mmol, 1.00 equiv) was dissolved in 1,4-dioxane (1.03 mL) and water (1.03 mL) was added. The mixture was refluxed at 100 °C for 1 h, after which time it was cooled to 23 °C and diluted with dichloromethane (3 mL). The layers were separated, and the aqueous solution was extracted with dichloromethane (4 x 7 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide (1*S*,2*S*)-pseudoephenamine (**26**) (44.0 mg, 94%). The aqueous layer was concentrated in vacuo to provide α,α-disubstituted amino acid **30** as a white solid (26.0 mg, 97%). The characterization data for the recovered auxiliary were in agreement with values previously reported.[6] Chiral HPLC analysis (Phenomenex Chirex 3126 (D)-penicillamine, 99:1 aqueous 2 mM copper (II) sulfate solution:*i*-PrOH, 0.5 mL/min, λ = 240 nm, t_R (major, amino acid **30**) = 11.3 min, t_R(minor, amino acid ***ent*-30**) = 15.4 min) of amino acid **30** established that **30** was of 98% ee. The characterization data for α,α-disubstituted amino acid **30** were in agreement with values previously reported[8]: ^{1}H NMR (500 MHz, D_2O) δ 5.81 – 5.68 (m, 1H), 5.34 – 5.22 (m, 2H), 2.65 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.45 (dd, *J* = 14.4, 8.4 Hz, 1H), 1.48 (s, 3H). ^{13}C NMR (126 MHz, D_2O) δ 176.59, 130.80, 121.46, 61.13, 41.57, 22.12. FTIR (neat), cm^{-1}: 3365 (s), 2839 (m), 2501 (s), 1444 (m), 1014 (s). HRMS (ESI): Calcd for $(C_6H_{11}NO_2 + Na)^+$: 152.0682. Found: 152.0680.

[8] Lu, T. J.; Lin, C. K. *J. Org. Chem.* **2011**, *76*, 1621.



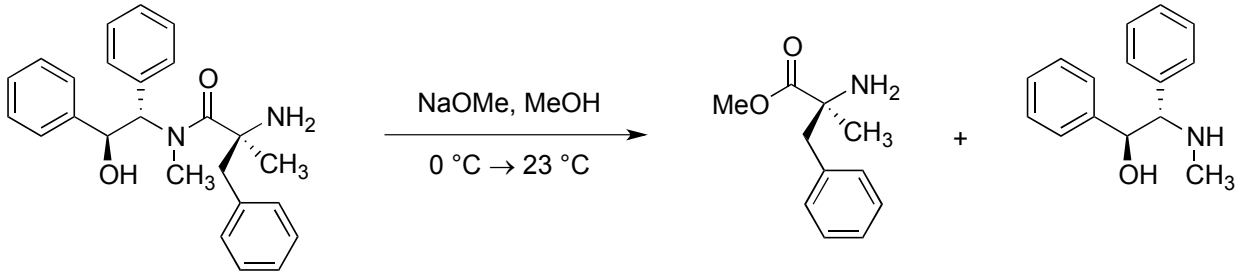
21 **31** **26**

99% 98%

(*S*)-2-amino-3-cyclohexyl-2-methylpropanoic acid (31)

α,α-disubstituted amide **21** (71.0 mg, 0.180 mol, 1.00 equiv) was dissolved in 1,4-dioxane (900 μL) and water (900 μL) was added. The mixture was refluxed at 100 °C for 2 h, after which time it was cooled to 23 °C and diluted with dichloromethane (3 mL). The layers were separated, and the aqueous solution was extracted with dichloromethane (4 x 7 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide (1*S*,2*S*)-pseudoephenamine (**26**) (40.0 mg, 98%). The aqueous layer was concentrated in vacuo to provide α,α-disubstituted amino acid **31** as a white solid (33.0 mg, 99%). The characterization data for the recovered auxiliary were in agreement with values previously reported.[6] α,α-disubstituted amino acid **31**: ^{1}H NMR (500 MHz, CD_3OD) δ 1.90 – 1.82 (m, 2H), 1.74 – 1.60 (m, 4H), 1.54 (dd, *J* = 14.6, 4.4 Hz, 1H), 1.51 – 1.43 (m, 1H), 1.42 (s, 3H), 1.38 – 1.22 (m, 2H), 1.22 – 1.10 (m, 1H), 1.08 – 0.92 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 176.85, 61.91, 46.56, 36.17, 34.66, 34.47, 27.40, 27.22, 27.17, 25.02. FTIR (neat), cm^{-1}: 3331 (s), 2945 (m), 2833 (s), 1415 (m), 1024 (s). HRMS (ESI): Calcd for $(C_{10}H_{19}NO_2 + H)^+$: 186.1496. Found: 186.1504.

4 Esterification of α-methyl α-amino amides

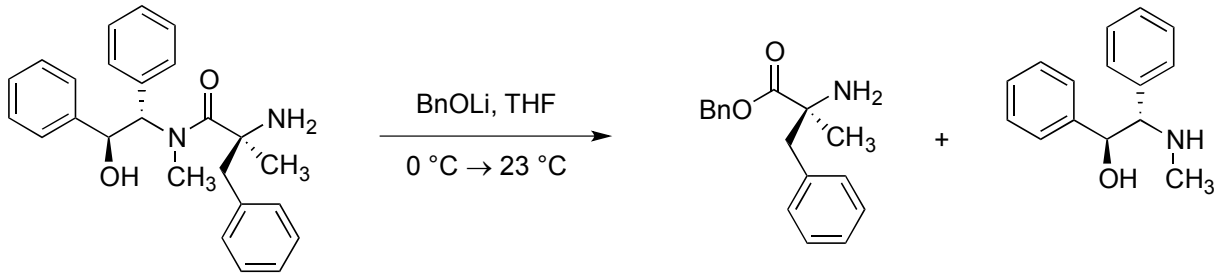


16 **32** 88% **26** 91%

(*S*)-methyl 2-amino-2-methyl-3-phenylpropanoate (32)

Sodium methoxide (0.5 M solution in methanol, 772 μL, 0.386 mmol, 1.00 equiv) was added to a cooled (0 °C) solution of α,α-disubstituted amide **16** (150 mg, 0.386 mmol, 1.00 equiv) in anhydrous methanol (2.40 mL).[9] The mixture was stirred at 23 °C for 3 h, after which time water (4 mL) and saturated aqueous sodium chloride solution (4 mL) were added. The aqueous layer was extracted with dichloromethane (3 x 20 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude residue was purified by flash chromatography (3→10% methanol-dichloromethane) to provide (1*S*,2*S*)-pseudoephenamine (**26**) (80.0 mg, 91%) and methyl ester **32** as a colorless oil (66.0 mg, 88%). The characterization data for the recovered auxiliary were in agreement with values previously reported.[6] The characterization data for methyl ester **32** were in agreement with values previously reported[10]: TLC (10% methanol-dichloromethane): R_f = 0.56 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 3H), 7.19 – 7.13 (m, 2H), 3.72 (s, 3H), 3.15 (d, *J* = 13.2 Hz, 1H), 2.81 (d, *J* = 13.2 Hz, 1H), 1.58 (br s, 2H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.67, 136.68, 130.06, 128.47, 127.07, 58.97, 52.23, 47.07, 26.79. FTIR (neat), cm^{-1}: 3030 (m), 2951 (m), 1732 (s), 1454 (m), 1197 (s). HRMS (ESI): Calcd for $(C_{11}H_{15}NO_2 + H)^+$: 194.1176 Found: 194.1172.

[9] Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron* **2001**, *57*, 6615.
[10] Smith, N. D.; Wohlrab, A. M.; Goodman, M. *Org. Lett.* **2005**, *7*, 255.



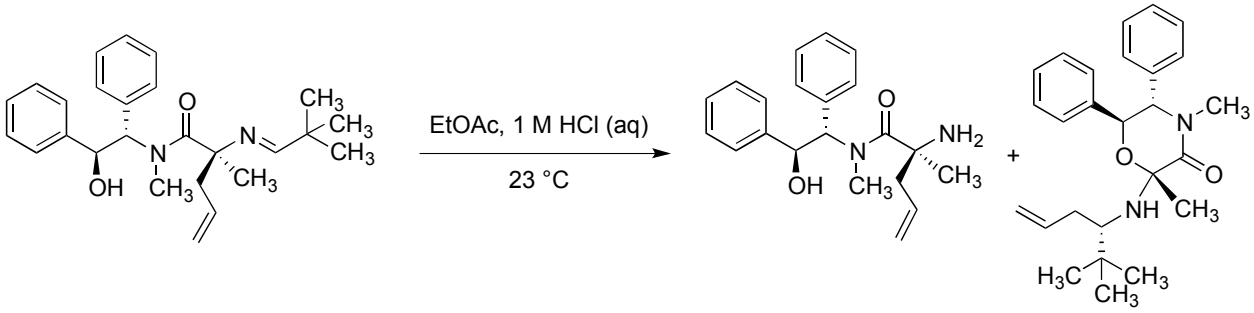
16 **33** **26**

84% 83%

(*S*)-benzyl 2-amino-2-methyl-3-phenylpropanoate (33)

A freshly titrated solution of *n*-butyllithium in hexanes (2.39 M, 113 μL, 1.50 equiv) was added to a cooled (0 °C) solution of benzyl alcohol (37.3 μL, 0.360 mmol, 2.00 equiv) in tetrahydrofuran (200 μL).[5] A solution of α,α-disubstituted amide **16** (70.0 mg, 0.180 mmol, 1.00 equiv) in tetrahydrofuran (800 μL) was transferred to the cold benzyl alkoxide solution via syringe and the transfer was quantitated with tetrahydrofuran (2 x 400 μL). The reaction mixture was stirred at 0 °C for 1 h and then at 23 °C for 1.5 h, after which time water (5 mL) and dichloromethane (5 mL) were added. The layers were separated, the aqueous layer was extracted with dichloromethane (3 x 15 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude residue was purified by flash chromatography (10% diethyl ether-dichloromethane, then 10% methanol-dichloromethane) to provide (1*S*,2*S*)-pseudoephenamine (**26**) (36.0 mg, 88%) and benzyl ester **33** as a colorless oil (41.0 mg, 84%). The characterization data for the recovered auxiliary were in agreement with values previously reported.[6] Benzyl ester **33**: TLC (40% ethyl acetate-hexanes): R_f = 0.30 (UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 7.22 (dd, *J* = 4.8, 1.9 Hz, 3H), 7.12 – 7.06 (m, 2H), 5.13 (s, 2H), 3.15 (d, *J* = 13.2 Hz, 1H), 2.81 (d, *J* = 13.2 Hz, 1H), 1.62 (br s, 2H), 1.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.02, 136.56, 135.78, 130.10, 128.72, 128.50, 128.47, 128.44, 127.01, 67.01, 58.97, 46.95, 26.80. FTIR (neat), cm^{-1}: 3032 (m), 1728 (s), 1496 (m), 1170 (s), 906 (s). HRMS (ESI): Calcd for $(C_{17}H_{19}NO_2 + H)^+$: 270.1489 Found: 270.1497.

5 Aza-Cope Rearrangement of α-methyl α-allyl pivaldimine



34 **22** **35**

33%
≥19:1 dr

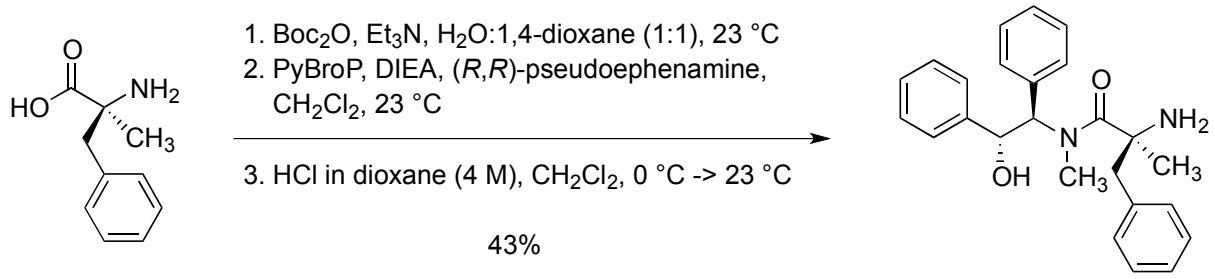
50%
7:1 dr

(*S*)-2-amino-*N*-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethylpent-4-enamide (22) and **(2*R*,5*S*,6*S*)-2-(((*S*)-2,2-dimethylhex-5-en-3-yl)amino)-2,4-dimethyl-5,6-diphenylmorpholin-3-one (35)**

Crude allylated imine **34** was obtained via alkylation of *tert*-butyl imine **1** with allyl bromide, similar to the synthesis of α,α-disubstituted amide **22**, with the omission of the final imine hydrolysis step using aqueous hydroxylamine solution. 1 M aqueous hydrochloric acid solution (7 mL) was added to a solution of crude allylated imine **34** (65.0 mg, 0.160 mmol, 1.00 equiv) in ethyl acetate (1.50 mL). The biphasic mixture was stirred vigorously at 23 °C for 3h, after which time ethyl acetate (8 mL) was added. The layers were separated, the organic layer was extracted with 1 M aqueous hydrochloric acid solution (3 x 10 mL), followed by saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The crude residue was purified by flash chromatography (10% ethyl acetate-hexanes) to provide morpholinone **35** (33.0 mg, 50%) as a colorless solid. The diastereomeric ratio of the crude material was determined to be 7:1 by ^{1}H NMR integration. Morpholinone **35**: TLC (20% ethyl acetate-hexanes): R_f = 0.37 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 3H), 7.22 – 7.13 (m, 3H), 7.01 – 6.96 (m, 2H), 6.96 – 6.91 (m, 2H), 5.95 – 5.86 (m, 1H), 5.27 (d, *J* = 9.7 Hz, 1H), 4.79 – 4.74 (m, 1H), 4.72 (d, *J* = 10.2 Hz, 1H), 4.48 (d, *J* = 9.8 Hz, 1H), 2.77 (t, *J* = 4.7 Hz, 1H), 2.67 (s, 3H), 2.25 – 2.19 (m, 1H), 2.17 – 2.11 (m, 1H), 2.01 (s, 1H), 1.67 (s, 3H), 0.98 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.02, 138.13, 137.66, 136.46, 128.76, 128.42, 128.25, 128.10, 128.04, 127.80, 114.91, 89.61, 74.51, 70.61, 59.20, 37.54, 35.67, 32.86, 27.59, 24.04. FTIR (neat), cm^{-1}: 2957 (m), 1651 (s), 1477 (m), 1396 (m), 1101 (s). HRMS (ESI): Calcd for $(C_{26}H_{34}N_2O_2 + H)^+$: 407.2693. Found: 407.2707.

The acidic aqueous extracts were combined, cooled in an ice bath, and carefully brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The basic aqueous solution was extracted with dichloromethane (3 x 40 mL), and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (3% methanol-dichloromethane, triethylamine pretreated silica gel) to provide α,α-disubstituted amide **22** as a white solid (18.0 mg, 33%). The diastereomeric ratio of the crude material was determined to be $\geq$19:1 by ^{1}H NMR integration and the characterization data were in agreement with values for the same α,α-disubstituted amide **22** reported above.

6 Synthesis of (*S*)-2-amino-*N*-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenylpropanamide for spectroscopic comparison



31 **36**

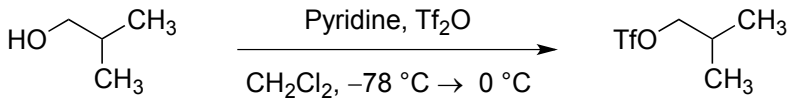
(*S*)-2-amino-*N*-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-*N*,2-dimethyl-3-phenylpropanamide (36)

A solution of commercially available L-α-methylphenylalanine (50.0 mg, 0.279 mmol, 1.00 equiv) in water (1.10 mL) and 1,4-dioxane (1.10 mL) was treated with triethylamine (156 μL, 1.12 mmol, 4.00 equiv) and di-*tert*-butyl dicarbonate (130 μL, 0.558 mmol, 2.00 equiv).[11] The mixture was stirred at 23 °C for 12 h, after which time 1 M aqueous hydrochloric acid solution (2 mL) and ethyl acetate (10 mL) were added. The layers were separated and the organic phase was extracted with saturated aqueous sodium chloride solution (10 mL). The organic layer was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated to provide *N*-(*tert*-butoxycarbonyl)-L-α-methylphenylalanine as a white foam. In the following step, (1*R*,2*R*)-pseudoephenamine (22.4 mg, 0.098 mmol, 1.10 equiv), bromotripyrrolidinophosphonium hexafluorophosphate (28.7 mg, 0.089 mmol, 1.00 equiv) and *N*,*N*-diisopropylethylamine (39.1 μL, 0.224 mmol, 2.50 equiv) were added to a solution of the crude *N*-(*tert*-butoxycarbonyl)-L-α-methylphenylalanine (25.0 mg, 0.089 mmol, 1.00 equiv) in dichloromethane (360 μL).[12,13] The cloudy mixture was stirred at 23 °C for 15 h, after which time dichloromethane (10 mL) and saturated aqueous sodium chloride solution (10 mL) were added. The layers were separated and the organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide a colorless oil. A solution of hydrogen chloride in dioxane (4 M, 100 μL, 0.400 mmol, 4.49 equiv) was added dropwise to a solution of this oil in dichloromethane (200 μL) at 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. The mixture was stirred at 23 °C for 1.5 h,

[11] Costanzo, M. J.; Almond, H. R.; Hecker, L. R.; Schott, M. R.; Yabut, S. C.; Zhang, H. C.; Andrade-Gordon, P.; Corcoran, T. W.; Giardino, E. C.; Kauffman, J. A.; Lewis, J. M.; de Garavilla, L.; Haertlein, B. J.; Maryanoff, B. E. *J. Med. Chem.* **2005**, *48*, 1984.
[12] Coste, J.; Frerot, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437.
[13] Frerot, E.; Coste, J.; Pantaloni, A.; Dufour, M. N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259.

after which time the reaction mixture was brought to pH 14 by the addition of 2 M aqueous sodium hydroxide solution. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 7 mL). The combined organic extracts were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (5% methanol-dichloromethane) to provide α,α-disubstituted amide **36** as a white foam (15.0 mg, 43%). The ^{1}H NMR, ^{13}C NMR and MS data obtained for α,α-disubstituted amide **36** were consistent with the values for the opposite diastereomer of α,α-disubstituted amide **16** reported above. TLC (10% methanol-dichloromethane): R_f = 0.51 (UV, $KMnO_4$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 9H), 7.11 – 7.06 (m, 2H), 7.05 – 6.98 (m, 2H), 6.98 – 6.93 (m, 2H), 5.84 (d, *J* = 8.0 Hz, 1H), 3.93 (d, *J* = 8.0 Hz, 1H), 3.08 (d, *J* = 13.3 Hz, 1H), 2.80 (d, *J* = 13.3 Hz, 1H), 2.24 (s, 3H), 1.65 (br s, 2H), 1.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.13, 138.45, 137.31, 130.21, 128.58, 128.33, 128.17, 128.13, 127.71, 127.67, 126.91, 80.44, 69.20, 58.86, 46.59, 34.43, 26.77. FTIR (neat), cm^{-1}: 3030 (m), 2935 (m), 1720 (s), 1454 (s), 1168 (s). HRMS (ESI): Calcd for $(C_{25}H_{28}N_2O_2 + H)^+$: 389.2231. Found: 389.2234.

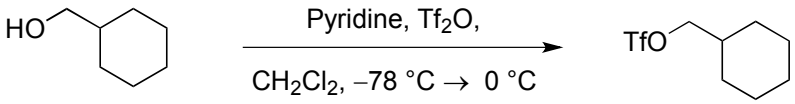
7 Preparation of Alkyl Triflate Reagents



37 77% **38**

Isobutyl trifluoromethanesulfonate (38)

Pyridine (421 μL, 5.20 mmol, 1.20 equiv) was added to a stirring solution of isobutanol (400 μL, 4.33 mmol, 1.00 equiv) in dichloromethane (4.33 mL) at −78 °C.[14] Trifluormethanesulfonic anhydride (739 μL, 4.38 mmol, 1.01 equiv) was added dropwise over 1 min, and stirring was continued at −78 °C for 5 min. The solution was then warmed to 0 °C for 25 min, after which time the mixture was diluted with pentane (10 mL) and cold (0 °C) 1 M aqueous sulfuric acid solution (10 mL). The layers were separated, the organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the colorless liquid was dried under high vacuum for 30 sec. Triflate **38** (689 mg, 77%) was used in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, *J* = 6.4 Hz, 2H), 2.18 – 2.08 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 6H).



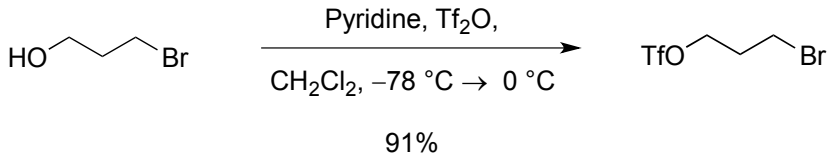
39 97% **40**

Cyclohexylmethyl trifluoromethanesulfonate (40)

Pyridine (394 μL, 4.88 mmol, 1.20 equiv) was added to a stirring solution of cyclohexanemethanol (500 μL, 4.06 mmol, 1.00 equiv) in dichloromethane (4.06 mL) at −78 °C.[14] Trifluormethanesulfonic anhydride (693 μL, 4.10 mmol, 1.01 equiv) was added dropwise over 1 min, and stirring was continued at −78 °C for 5 min. The solution was then warmed to 0 °C for 25 min, after which time the mixture was diluted with pentane (10 mL) and cold (0 °C) 1 M aqueous sulfuric acid solution (10 mL). The layers were separated, the organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the light yellow liquid was dried under high vacuum for 30 sec. Triflate **40** (969 mg,

[14] Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Welch, M. J. *J. Org. Chem.* **1987**, *52*, 658.

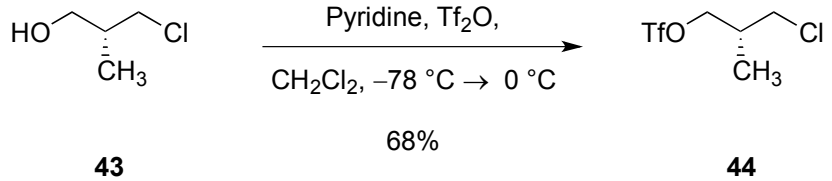
97%) was used in subsequent reactions without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.33 (d, *J* = 6.1 Hz, 2H), 1.84 – 1.75 (m, 5H), 1.74 – 1.68 (m, 1H), 1.33 – 1.13 (m, 3H), 1.09 – 0.98 (m, 2H).



41 **42**

3-Bromopropyl trifluoromethanesulfonate (42)

Pyridine (268 μL, 3.32 mmol, 1.20 equiv) was added to a stirring solution of 3-bromopropan-1-ol (250 μL, 2.76 mmol, 1.00 equiv) in dichloromethane (2.77 mL) at −78 °C.[14] Trifluormethanesulfonic anhydride (472 μL, 2.79 mmol, 1.01 equiv) was added dropwise over 1 min, and stirring was continued at −78 °C for 5 min. The solution was then warmed to 0 °C for 40 min, after which time the mixture was diluted with pentane (10 mL) and cold (0 °C) 1 M aqueous sulfuric acid solution (10 mL). The layers were separated, the organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the colorless liquid was dried under high vacuum for 30 sec. Triflate **42** (680 mg, 91%) was used in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (t, *J* = 5.8 Hz, 2H), 3.51 (t, *J* = 6.2 Hz, 2H), 2.36 (tt, *J* = 6.1 Hz, *J* = 6.2 Hz, 2H).



43 **44**

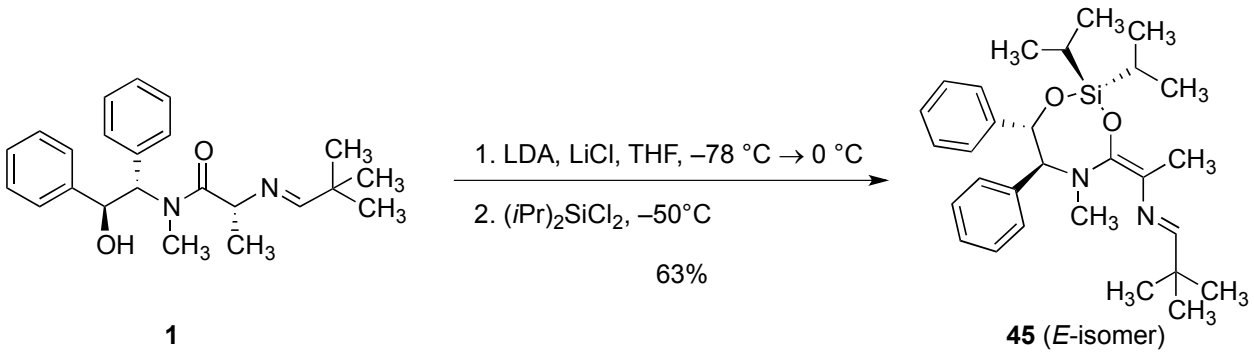
(*R*)-3-Chloro-2-methylpropyl trifluoromethanesulfonate (44)

Pyridine (156 μL, 1.93 mmol, 1.20 equiv) was added to a stirring solution of (*R*)-3-chloro-2-methylpropan-1-ol[15] (175 mg, 1.61 mmol, 1.00 equiv) in dichloromethane (1.61 mL) at −78 °C.[14] Trifluormethanesulfonic anhydride (275 μL, 1.63 mmol, 1.01 equiv) was added dropwise over 1 min, and stirring was continued at −78 °C for 5 min. The solution was then warmed to 0 °C for 30 min, after which time the mixture was diluted with pentane (10 mL) and cold (0 °C) 1 M aqueous sulfuric acid solution (10 mL). The layers were separated, the organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the light brown liquid was dried under high vacuum for

[15] Gaucher, A.; Ollivier, J.; Marguerite, J.; Paugam, R.; Salaun, J. *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **1994**, *72*, 1312.

30 sec. Triflate **44** (265 mg, 68%) was used in subsequent reactions without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (d, *J* = 5.7 Hz, 2H), 3.63 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.54 (dd, *J* = 11.4, 6.2 Hz, 1H), 2.43 – 2.33 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H).

8 Pseudoephenamine Alaninamide Pivaldimine Enolate Trapping Experiment



1 **45** (*E*-isomer)

Cyclic siloxane (*E*-isomer) 45

A solution of *tert*-butyl imine **1** (123 mg, 0.336 mmol, 1.00 equiv) in tetrahydrofuran (1.20 mL) was transferred via cannula to a flask containing flame-dried lithium chloride (85.0 mg, 2.01 mmol, 6.00 equiv). The transfer was quantitated with tetrahydrofuran (2 x 500 μL). The resulting slurry was cooled to −78 °C, after which a freshly prepared solution of lithium diisopropylamide (1 M, 738 μL, 0.738 mmol, 2.20 equiv) precooled to 0 °C was added slowly to the inner edge of the reaction flask, such that the solution was cooled before reaching the reaction mixture. The yellow slurry was stirred for 5 min at −78 °C, and then was warmed to 0 °C for 10 min. The slurry was then cooled to −50 °C. After 10 min, distilled dichlorodiisopropylsilane (84.8 μL, 0.470 mmol, 1.20 equiv) was added by syringe. The mixture was stirred at −50 °C for 2.5 h, then was first concentrated by rotary evaporation (~40 mmHg) at 23 °C, afterwards with a vacuum manifold (1 mmHg) for 30 min at 23 °C. Dry benzene (2 mL) was added to the residue and the resulting suspension was filtered through oven-dried basic alumina, rinsing with additional benzene (5 x 2 mL). The filtrate was concentrated to provide cyclic siloxane **47** as a pale-yellow oil (101 mg, 63%). The *E*-geometry of the product was confirmed by a NOE correlation between the protons of the *N*-methyl and *tert*-butyl group. TLC (10% ethyl acetate-hexanes): R_f = 0.42 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, C_6D_6) δ 7.21 – 7.14 (m, 4H), 7.06 – 6.87 (m, 7H), 5.49 (d, *J* = 10.3 Hz, 1H), 4.00 (d, *J* = 10.3 Hz, 1H), 2.95 (s, 3H), 2.07 (s, 3H), 1.34 – 1.13 (m, 14H), 0.87 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 157.97, 150.31, 141.85, 138.18, 129.76, 128.59, 128.35, 128.16, 127.97, 127.66, 127.32, 114.24, 78.02, 75.78, 43.21, 36.63, 27.76, 17.75, 17.57, 17.52, 17.33, 13.78, 13.66, 11.03. FTIR (neat), cm^{-1}: 3036 (m), 1815 (m), 1479 (s), 1035 (m), 812 (m). HRMS (ESI): Calcd for $(C_{29}H_{42}N_2O_2Si + H)^+$: 479.3096. Found: 479.3095.

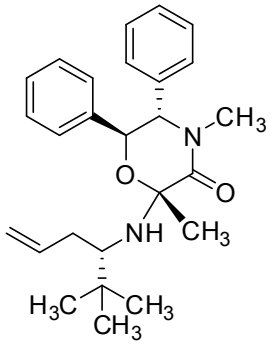
9 X-ray data

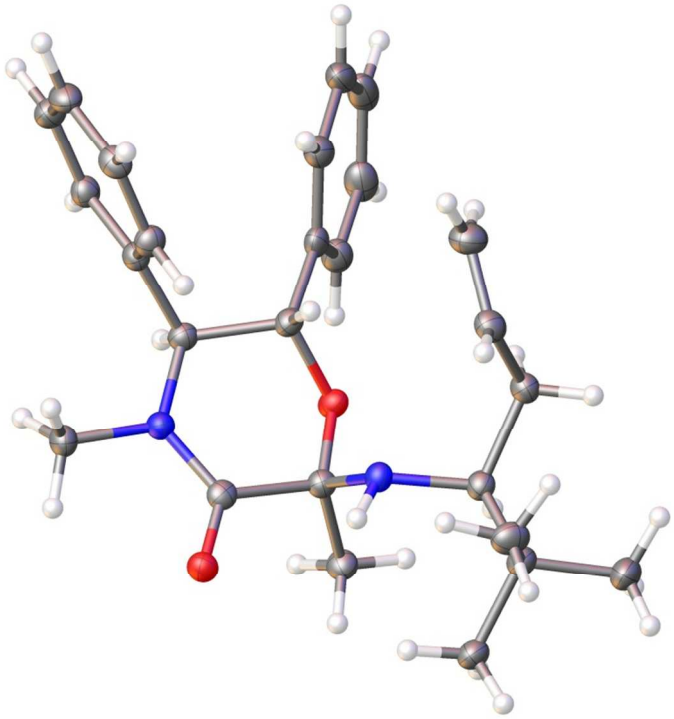
X-ray Crystallographic Laboratory

Harvard University

Structure Report

Shao-Liang Zheng





X-Ray Crystallography: Data was collected at 180 K from a crystal mounted on a diffractometer. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer ($Cu_{K\alpha}$ radiation, λ=1.54178 Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in ω at 30°, 55°, 80° and 115° in 2θ. Data integration down to 0.84 Å resolution was carried out using SAINT V7.46 A (Bruker diffractometer, 2009)[16] with reflection spot size optimization. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods again F^2 using SHELXS-97 and SHELXL-97 (Sheldrick, 2008).[17,18] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, and geometric parameters are shown in Table 2. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).[19]

Table 1. Experimental details

	(39lpEE)
Crystal data	
Chemical formula	$C_{26}H_{34}N_2O_2$
M_r	406.55
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	100
a, *b*, *c* (Å)	9.0583 (2), 14.4124 (4), 17.2685 (4)
V (Å^3)	2254.43 (10)
Z	4
Radiation type	Cu *K*α
μ (mm^{-1})	0.59
Crystal size (mm)	0.20 × 0.18 × 0.14
Data collection	

[16] Bruker AXS APEX II, Bruker AXS, Madison, Wisconsin, 2009.
[17] G. M. Sheldrick, Acta Cryst. 2008, A64, 112-122.
[18] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann J. Appl. Cryst. 2009, 42, 339-341.
[19] Accelrys DS Visualizer v2.0.1, Accelrys Software. Inc., 2007.

Diffractometer	Bruker D8 goniometer with CCD area detector diffractometer
Absorption correction	Multi-scan *SADABS*
T_{min}, T_{max}	0.892, 0.922
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	33748, 3915, 3894
R_{int}	0.034
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.594
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.027, 0.069, 1.09
No. of reflections	3915
No. of parameters	280
No. of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.12, -0.19
Absolute structure	Flack H D (1983), Acta Cryst. A39, 876-881
Flack parameter	0.06 (15)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL* (Sheldrick, 2008).

Table 2. Geometric parameters (Å, º)

C1—O1	1.2309 (15)	C12—H12A	0.9800
C1—N1	1.3450 (15)	C12—H12B	0.9800
C1—C2	1.5425 (16)	C12—H12C	0.9800
C2—O2	1.4257 (14)	C13—H13A	0.9800
C2—N2	1.4610 (15)	C13—H13B	0.9800
C2—C5	1.5308 (16)	C13—H13C	0.9800
C3—O2	1.4268 (14)	C14—C19	1.3922 (19)
C3—C14	1.5088 (17)	C14—C15	1.3940 (18)
C3—C4	1.5378 (16)	C15—C16	1.396 (2)
C3—H3	1.0000	C15—H15	0.9500
C4—N1	1.4786 (15)	C16—C17	1.382 (2)
C4—C20	1.5139 (16)	C16—H16	0.9500
C4—H4	1.0000	C17—C18	1.382 (2)
C5—H5A	0.9800	C17—H17	0.9500

C5—H5B	0.9800	C18—C19	1.3863 (19)
C5—H5C	0.9800	C18—H18	0.9500
C6—N2	1.4774 (15)	C19—H19	0.9500
C6—C7	1.5473 (16)	C20—C25	1.3894 (16)
C6—C10	1.5592 (16)	C20—C21	1.3950 (17)
C6—H6	1.0000	C21—C22	1.3831 (18)
C7—C8	1.5031 (17)	C21—H21	0.9500
C7—H7A	0.9900	C22—C23	1.3887 (18)
C7—H7B	0.9900	C22—H22	0.9500
C8—C9	1.3189 (19)	C23—C24	1.3889 (19)
C8—H8	0.9500	C23—H23	0.9500
C9—H9A	0.9500	C24—C25	1.3907 (17)
C9—H9B	0.9500	C24—H24	0.9500
C10—C12	1.5336 (18)	C25—H25	0.9500
C10—C13	1.5377 (17)	C26—N1	1.4642 (15)
C10—C11	1.5420 (17)	C26—H26A	0.9800
C11—H11A	0.9800	C26—H26B	0.9800
C11—H11B	0.9800	C26—H26C	0.9800
C11—H11C	0.9800	N2—H2	0.887 (16)
O1—C1—N1	122.98 (11)	H12A—C12—H12B	109.5
O1—C1—C2	118.09 (10)	C10—C12—H12C	109.5
N1—C1—C2	118.92 (10)	H12A—C12—H12C	109.5
O2—C2—N2	110.74 (9)	H12B—C12—H12C	109.5
O2—C2—C5	103.72 (9)	C10—C13—H13A	109.5
N2—C2—C5	117.14 (10)	C10—C13—H13B	109.5
O2—C2—C1	113.13 (9)	H13A—C13—H13B	109.5
N2—C2—C1	103.61 (9)	C10—C13—H13C	109.5
C5—C2—C1	108.80 (9)	H13A—C13—H13C	109.5
O2—C3—C14	107.78 (10)	H13B—C13—H13C	109.5
O2—C3—C4	108.86 (9)	C19—C14—C15	118.89 (12)
C14—C3—C4	110.85 (9)	C19—C14—C3	120.16 (11)
O2—C3—H3	109.8	C15—C14—C3	120.91 (12)
C14—C3—H3	109.8	C14—C15—C16	119.83 (13)
C4—C3—H3	109.8	C14—C15—H15	120.1
N1—C4—C20	111.62 (9)	C16—C15—H15	120.1

N1—C4—C3	109.16 (9)	C17—C16—C15	120.63 (13)
C20—C4—C3	109.20 (9)	C17—C16—H16	119.7
N1—C4—H4	108.9	C15—C16—H16	119.7
C20—C4—H4	108.9	C18—C17—C16	119.64 (12)
C3—C4—H4	108.9	C18—C17—H17	120.2
C2—C5—H5A	109.5	C16—C17—H17	120.2
C2—C5—H5B	109.5	C17—C18—C19	120.13 (14)
H5A—C5—H5B	109.5	C17—C18—H18	119.9
C2—C5—H5C	109.5	C19—C18—H18	119.9
H5A—C5—H5C	109.5	C18—C19—C14	120.86 (13)
H5B—C5—H5C	109.5	C18—C19—H19	119.6
N2—C6—C7	109.23 (9)	C14—C19—H19	119.6
N2—C6—C10	111.88 (10)	C25—C20—C21	119.19 (11)
C7—C6—C10	116.12 (10)	C25—C20—C4	120.79 (10)
N2—C6—H6	106.3	C21—C20—C4	119.80 (11)
C7—C6—H6	106.3	C22—C21—C20	120.73 (11)
C10—C6—H6	106.3	C22—C21—H21	119.6
C8—C7—C6	116.29 (10)	C20—C21—H21	119.6
C8—C7—H7A	108.2	C21—C22—C23	119.85 (11)
C6—C7—H7A	108.2	C21—C22—H22	120.1
C8—C7—H7B	108.2	C23—C22—H22	120.1
C6—C7—H7B	108.2	C22—C23—C24	119.87 (12)
H7A—C7—H7B	107.4	C22—C23—H23	120.1
C9—C8—C7	124.15 (13)	C24—C23—H23	120.1
C9—C8—H8	117.9	C23—C24—C25	120.18 (11)
C7—C8—H8	117.9	C23—C24—H24	119.9
C8—C9—H9A	120.0	C25—C24—H24	119.9
C8—C9—H9B	120.0	C20—C25—C24	120.17 (11)
H9A—C9—H9B	120.0	C20—C25—H25	119.9
C12—C10—C13	108.94 (11)	C24—C25—H25	119.9
C12—C10—C11	108.40 (10)	N1—C26—H26A	109.5
C13—C10—C11	107.18 (10)	N1—C26—H26B	109.5
C12—C10—C6	114.14 (10)	H26A—C26—H26B	109.5
C13—C10—C6	109.03 (10)	N1—C26—H26C	109.5
C11—C10—C6	108.92 (10)	H26A—C26—H26C	109.5
C10—C11—H11A	109.5	H26B—C26—H26C	109.5

C10—C11—H11B	109.5	C1—N1—C26	118.40 (10)
H11A—C11—H11B	109.5	C1—N1—C4	124.12 (9)
C10—C11—H11C	109.5	C26—N1—C4	117.39 (9)
H11A—C11—H11C	109.5	C2—N2—C6	118.46 (9)
H11B—C11—H11C	109.5	C2—N2—H2	107.5 (10)
C10—C12—H12A	109.5	C6—N2—H2	111.2 (10)
C10—C12—H12B	109.5	C2—O2—C3	113.81 (9)
O1—C1—C2—O2	173.10 (9)	N1—C4—C20—C25	-129.88 (11)
N1—C1—C2—O2	-7.06 (15)	C3—C4—C20—C25	109.33 (12)
O1—C1—C2—N2	-66.92 (12)	N1—C4—C20—C21	55.47 (14)
N1—C1—C2—N2	112.91 (11)	C3—C4—C20—C21	-65.32 (14)
O1—C1—C2—C5	58.40 (13)	C25—C20—C21—C22	-1.21 (18)
N1—C1—C2—C5	-121.77 (11)	C4—C20—C21—C22	173.52 (11)
O2—C3—C4—N1	51.95 (12)	C20—C21—C22—C23	0.67 (18)
C14—C3—C4—N1	170.33 (10)	C21—C22—C23—C24	0.17 (19)
O2—C3—C4—C20	174.23 (9)	C22—C23—C24—C25	-0.44 (19)
C14—C3—C4—C20	-67.39 (12)	C21—C20—C25—C24	0.93 (17)
N2—C6—C7—C8	45.82 (14)	C4—C20—C25—C24	-173.76 (10)
C10—C6—C7—C8	-81.81 (13)	C23—C24—C25—C20	-0.11 (18)
C6—C7—C8—C9	-134.83 (13)	O1—C1—N1—C26	-6.81 (16)
N2—C6—C10—C12	-64.59 (13)	C2—C1—N1—C26	173.36 (10)
C7—C6—C10—C12	61.72 (14)	O1—C1—N1—C4	176.83 (11)
N2—C6—C10—C13	173.35 (10)	C2—C1—N1—C4	-2.99 (16)
C7—C6—C10—C13	-60.34 (13)	C20—C4—N1—C1	-140.09 (11)
N2—C6—C10—C11	56.70 (12)	C3—C4—N1—C1	-19.28 (15)
C7—C6—C10—C11	-176.99 (10)	C20—C4—N1—C26	43.52 (13)
O2—C3—C14—C19	29.45 (14)	C3—C4—N1—C26	164.33 (10)
C4—C3—C14—C19	-89.58 (13)	O2—C2—N2—C6	-70.80 (12)
O2—C3—C14—C15	-152.85 (10)	C5—C2—N2—C6	47.83 (15)
C4—C3—C14—C15	88.12 (13)	C1—C2—N2—C6	167.61 (9)
C19—C14—C15—C16	0.28 (18)	C7—C6—N2—C2	102.53 (12)
C3—C14—C15—C16	-177.46 (11)	C10—C6—N2—C2	-127.49 (11)
C14—C15—C16—C17	-1.58 (19)	N2—C2—O2—C3	-73.16 (11)
C15—C16—C17—C18	1.29 (19)	C5—C2—O2—C3	160.36 (9)
C16—C17—C18—C19	0.3 (2)	C1—C2—O2—C3	42.64 (13)

C17—C18—C19—C14	-1.60 (19)	C14—C3—O2—C2	173.26 (9)
C15—C14—C19—C18	1.30 (18)	C4—C3—O2—C2	-66.44 (12)
C3—C14—C19—C18	179.05 (12)		

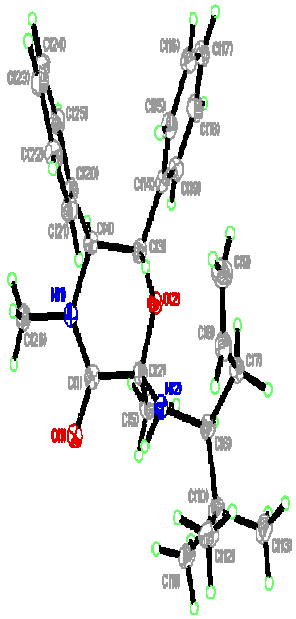


Figure 1. Perspective views showing 50% probability displacement.

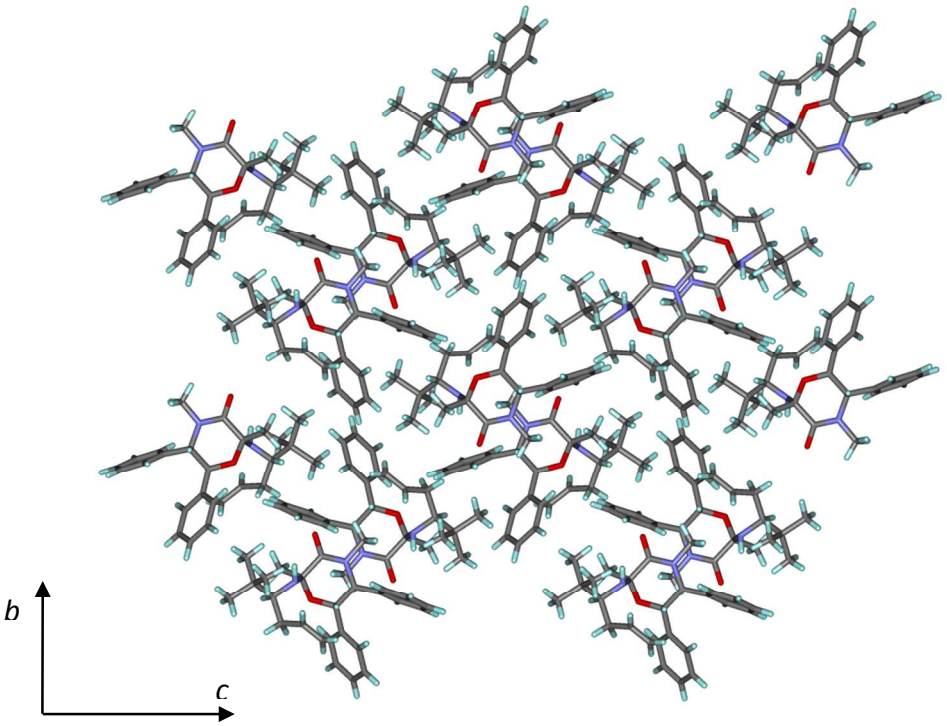
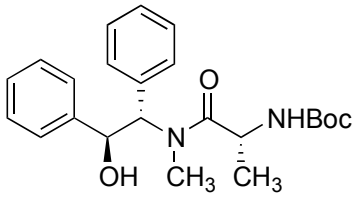


Figure 2. Three-dimensional supramolecular architecture viewed along the *a*-axis direction.

10 ^{1}H and ^{13}C NMR Spectra



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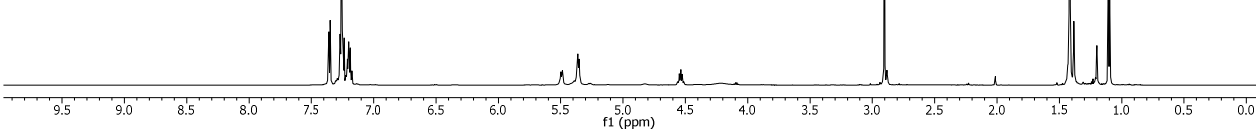

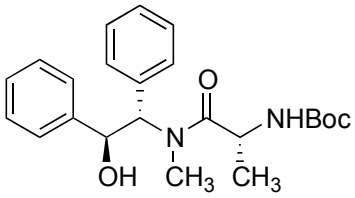

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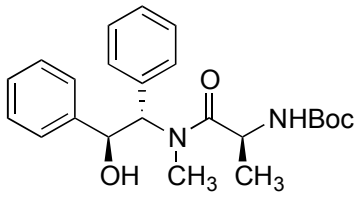
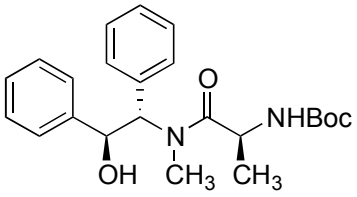

O
NHBoc
N
OH
CH3
CH3

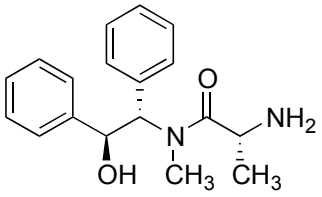
11

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
NHBoc
N
OH
CH3
CH3

11

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
NH2
N
OH
CH3
CH3

12

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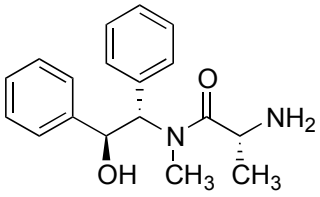
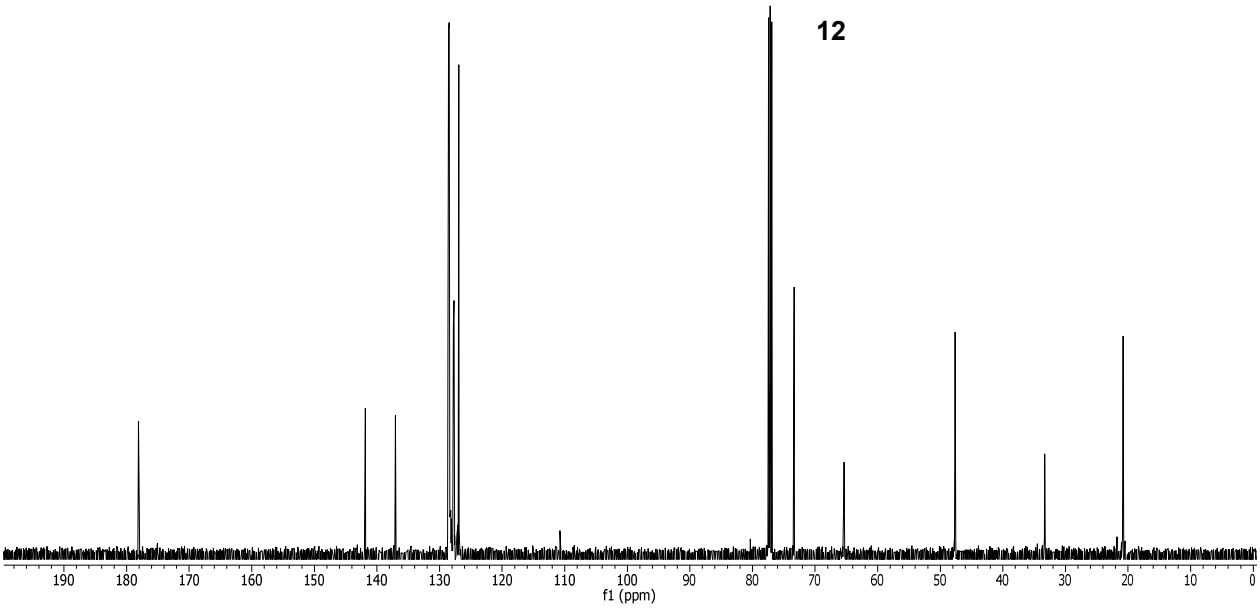
f1 (ppm)


O
NH2
N
OH
CH3
CH3

12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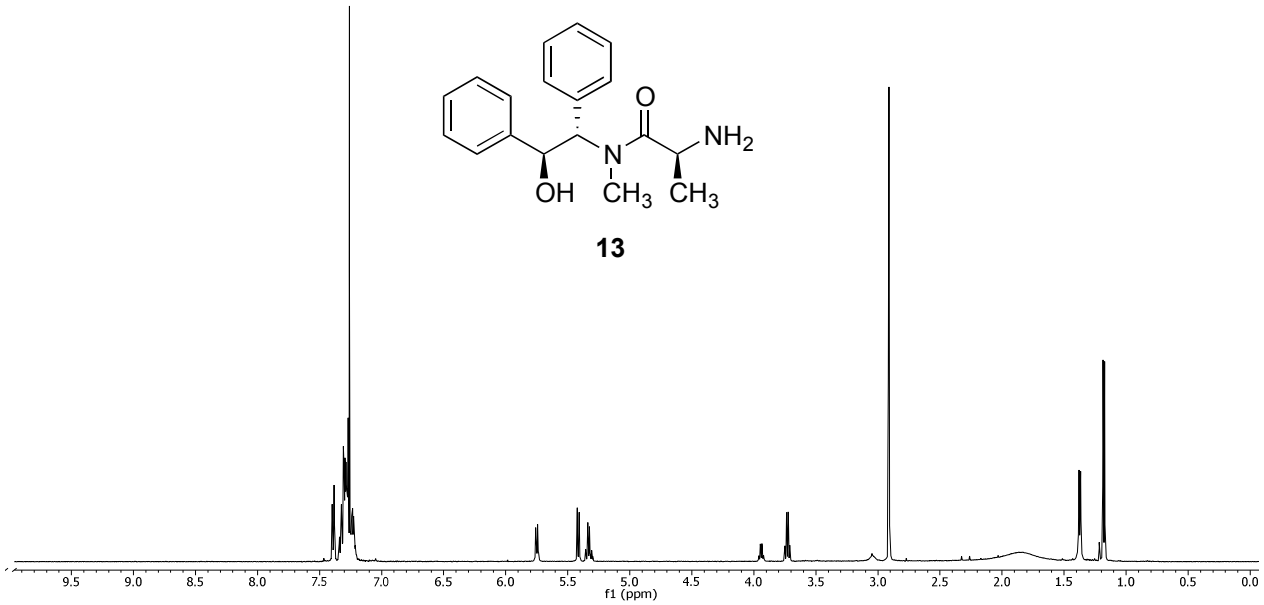
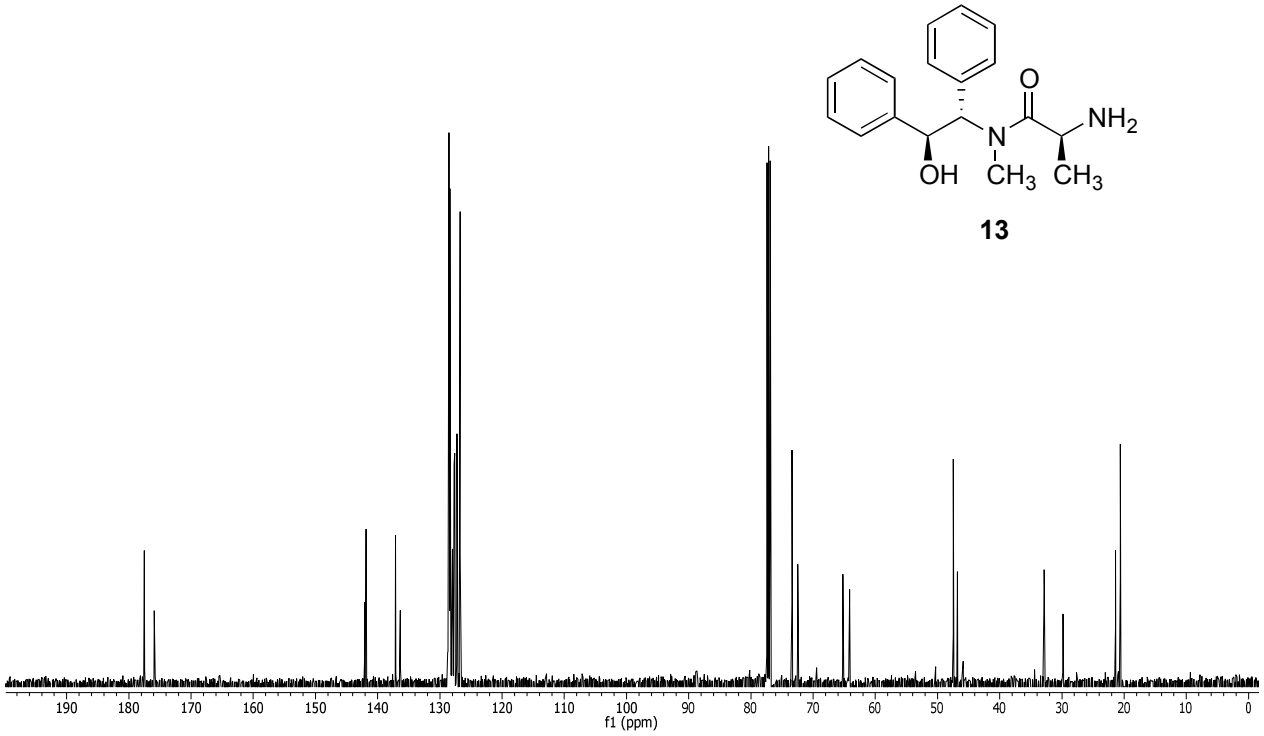
f1 (ppm)


O
NH2
N
OH
CH3
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

13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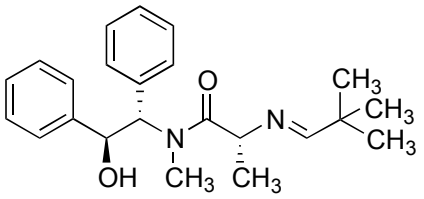
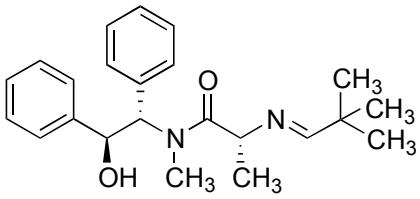
NH2
N
OH
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

13


O
CH3
CH3
CH3
N
N
OH
CH3
CH3

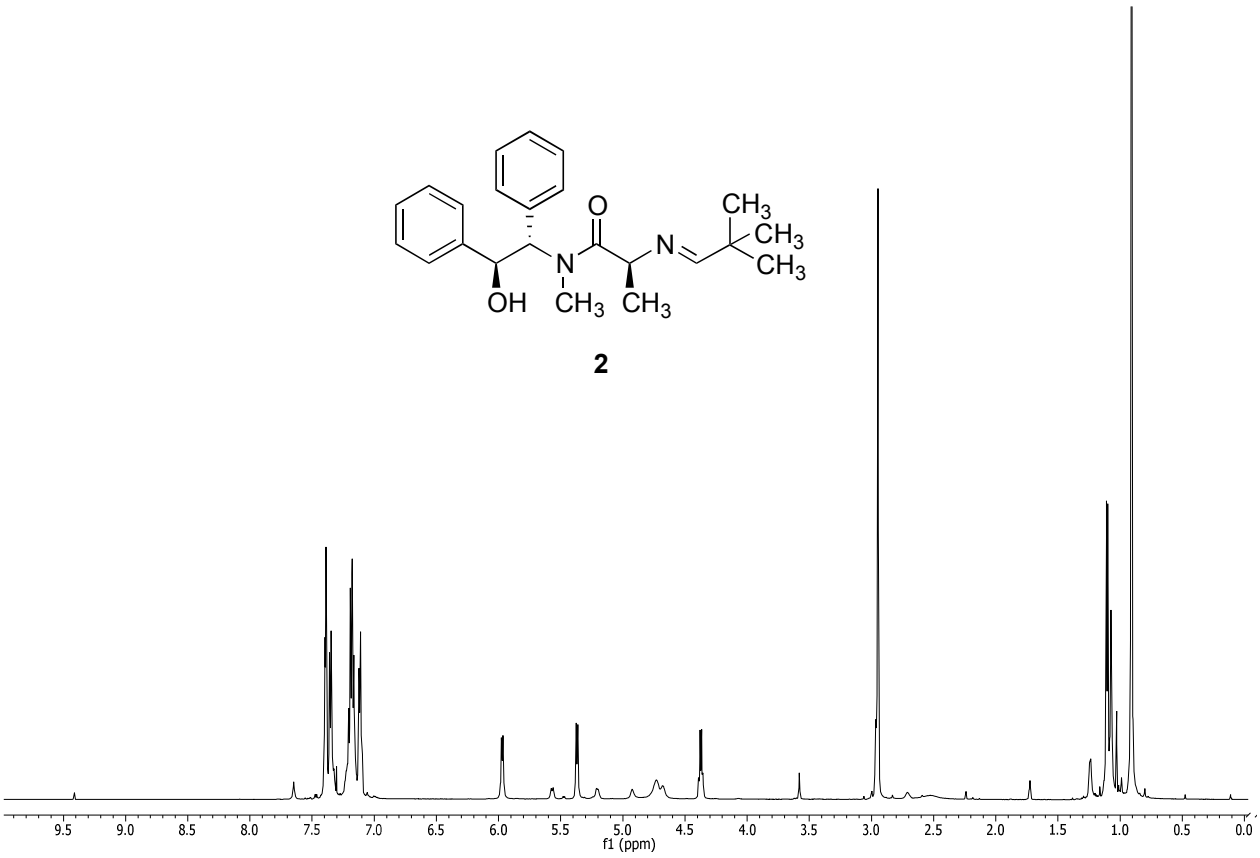
1

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


O
CH3
CH3
CH3
N
N
OH
CH3
CH3

1

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
CH3
CH3
CH3
N
OH
CH3
CH3
9.5
9.0
8.5
8.0
7.5
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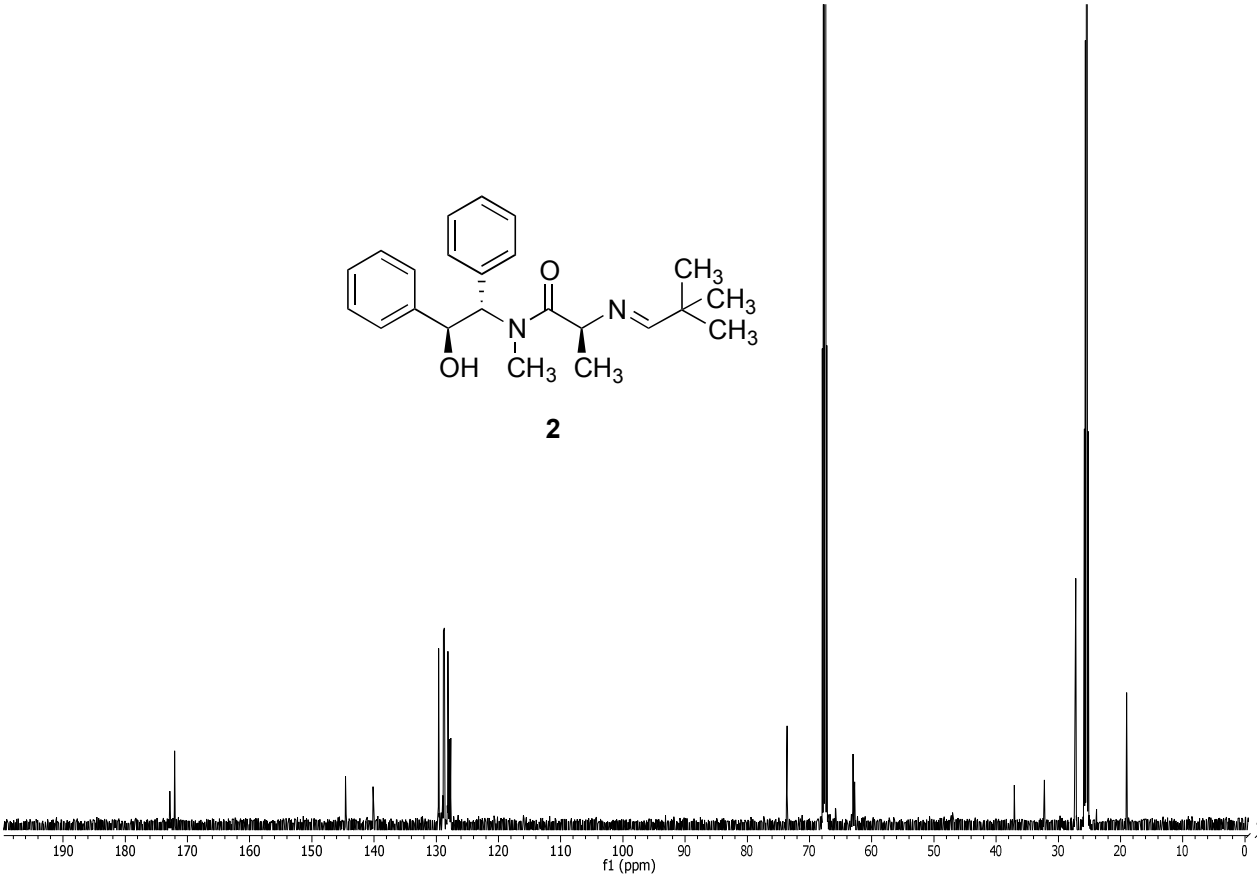
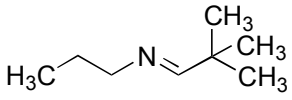
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

2


O
N
CH3
CH3
CH3
N
OH
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

2



15

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6.5
6.0
5.5
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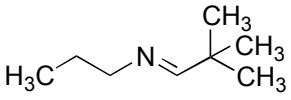
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



15

190
180
170
160
150
140
130
120
110
100
90
80
70
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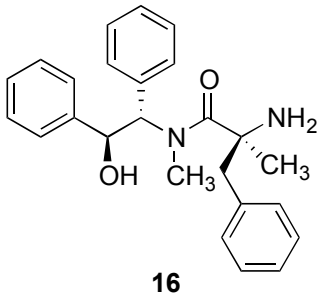
50
40
30
20
10
0
f1 (ppm)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NH2
N
CH3
OH
CH3

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5.5
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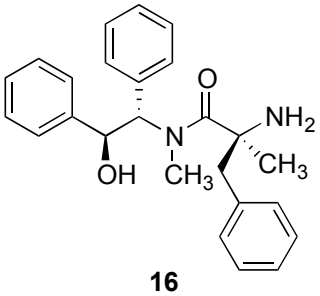
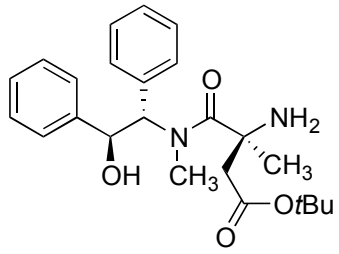
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
NH2
N
CH3
OH
CH3

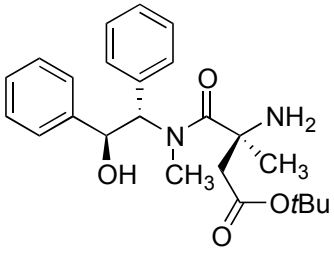
16

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
NH2
N
CH3
OH
CH3
OtBu
O

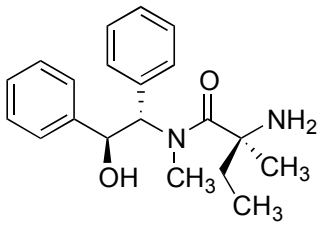
17

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

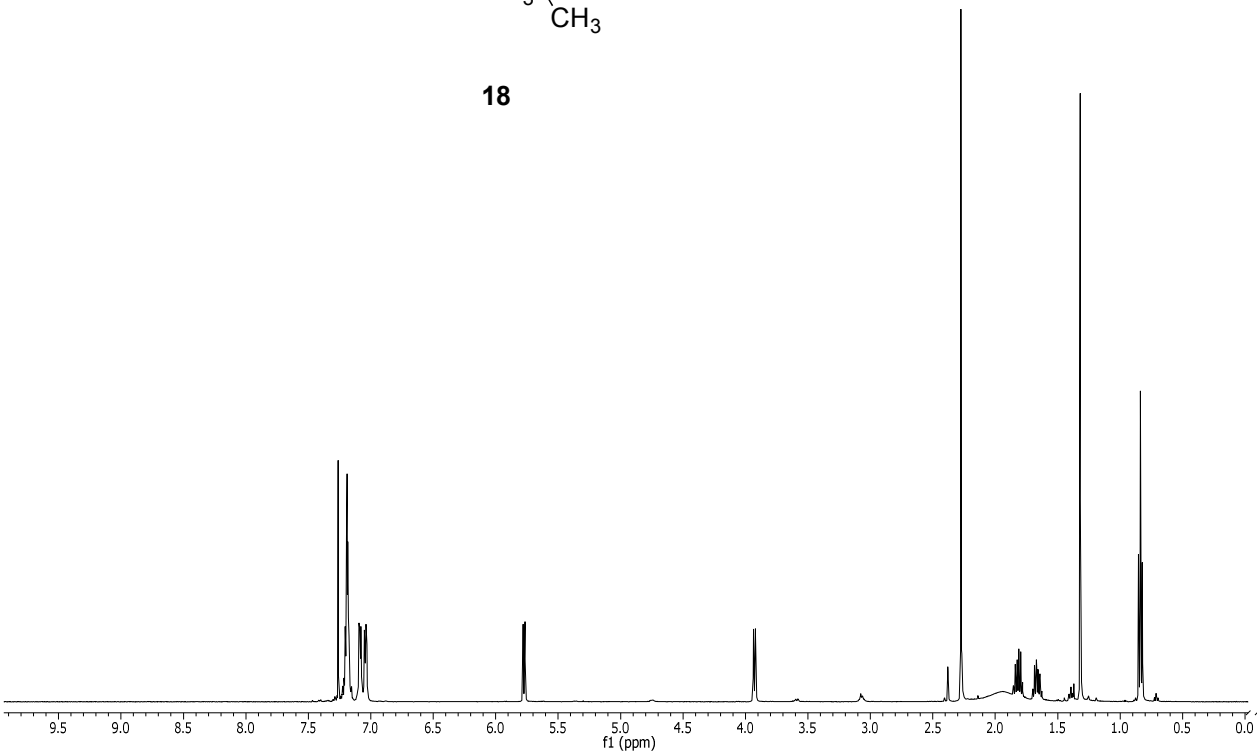

O
NH2
N
CH3
OH
CH3
OtBu
O

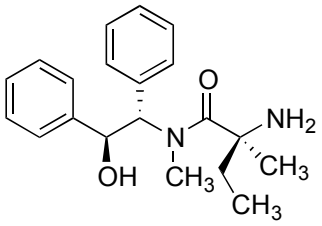
17

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

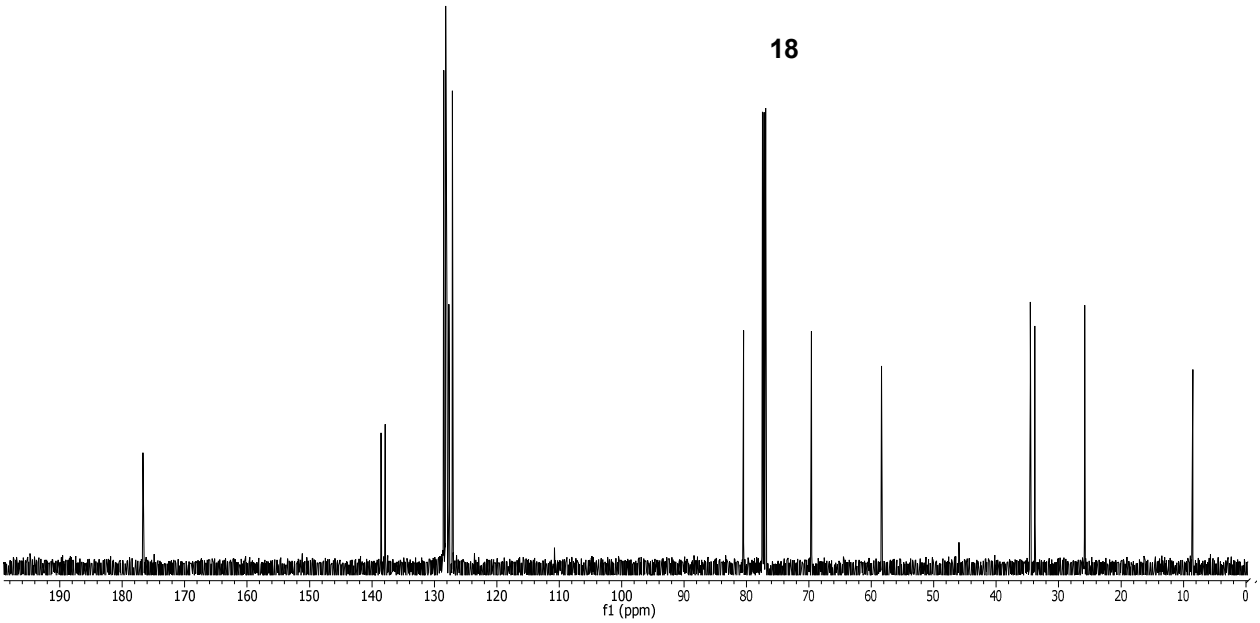

O
NH2
N
OH
CH3
CH3
CH3

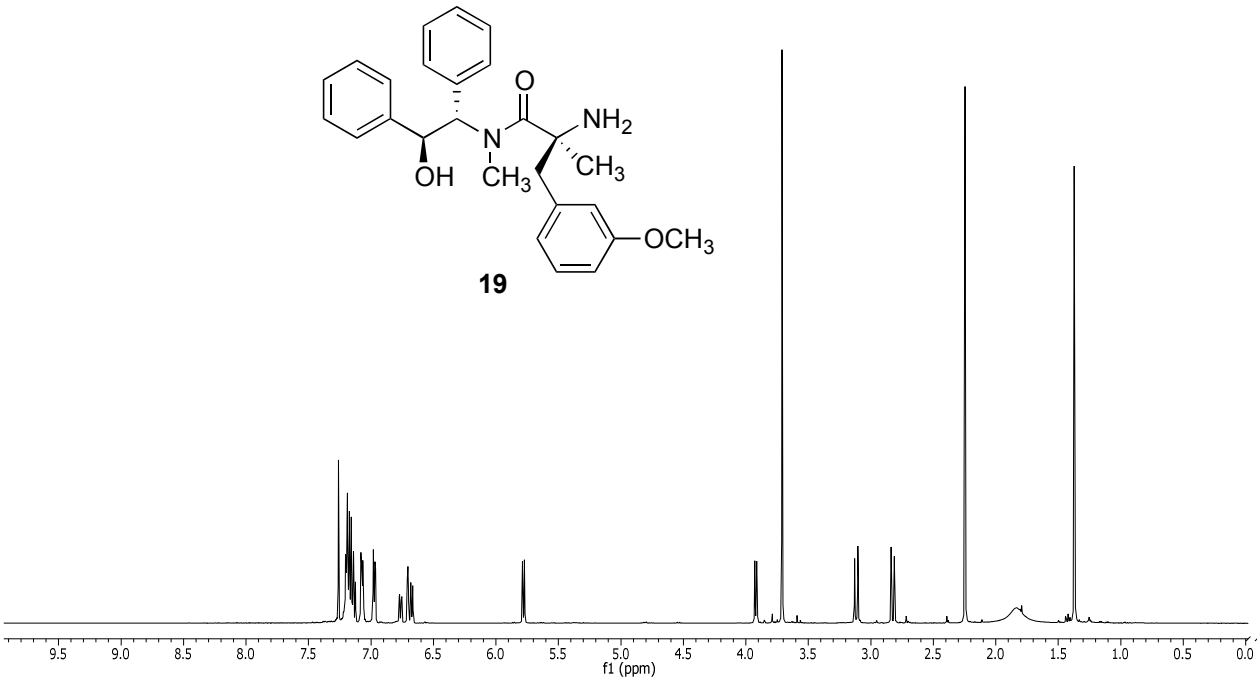
18


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

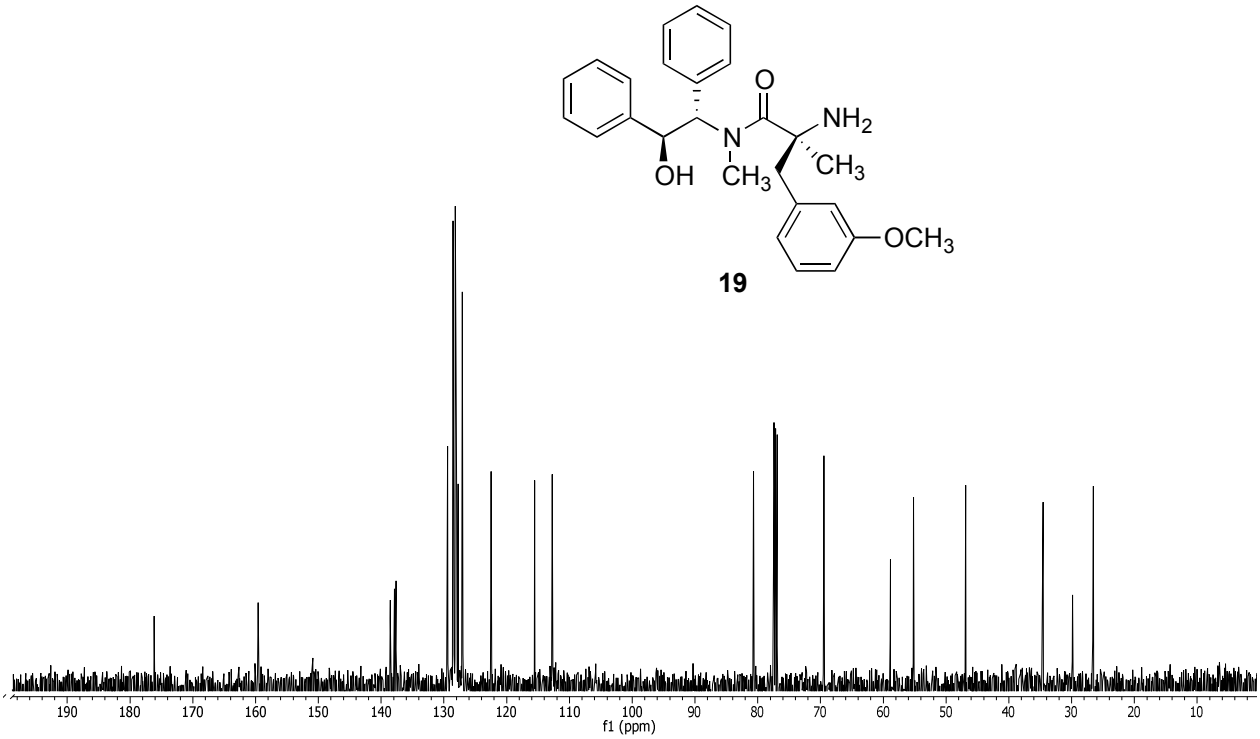

O
NH2
N
OH
CH3
CH3
CH3

18

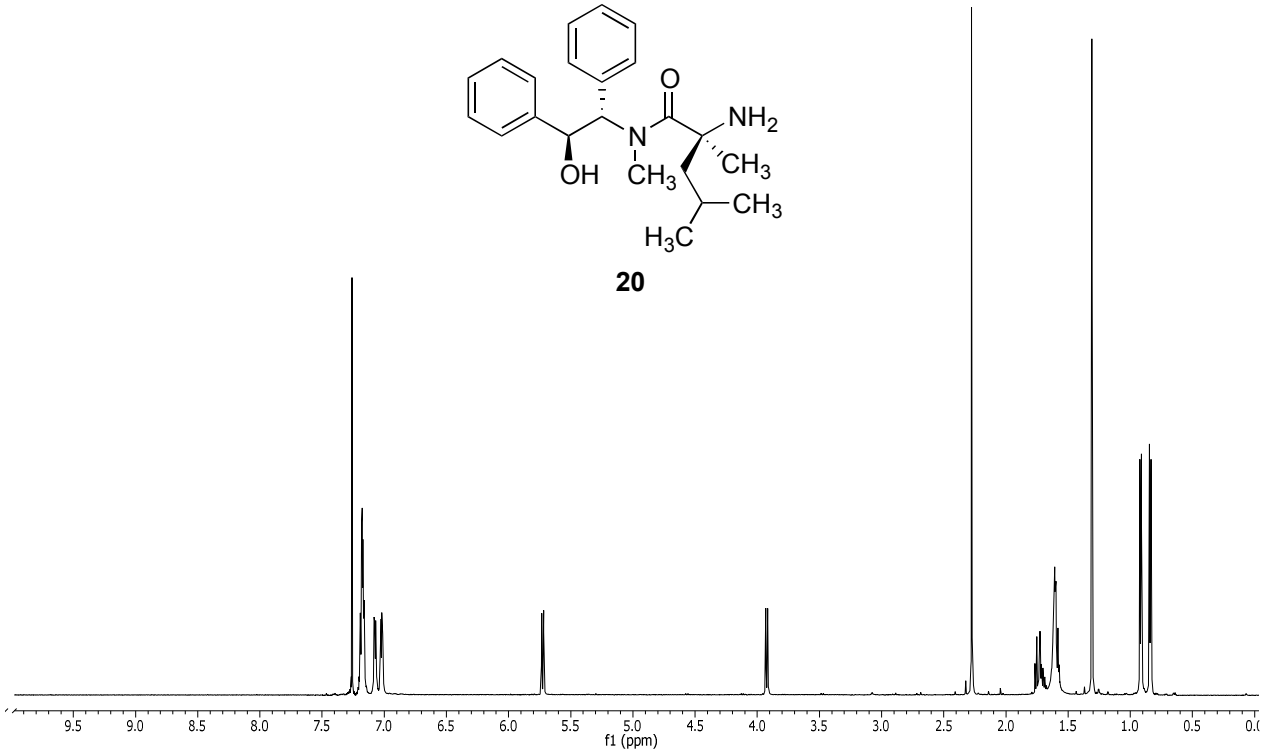

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
NH2
N
OH
CH3
CH3
OCH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

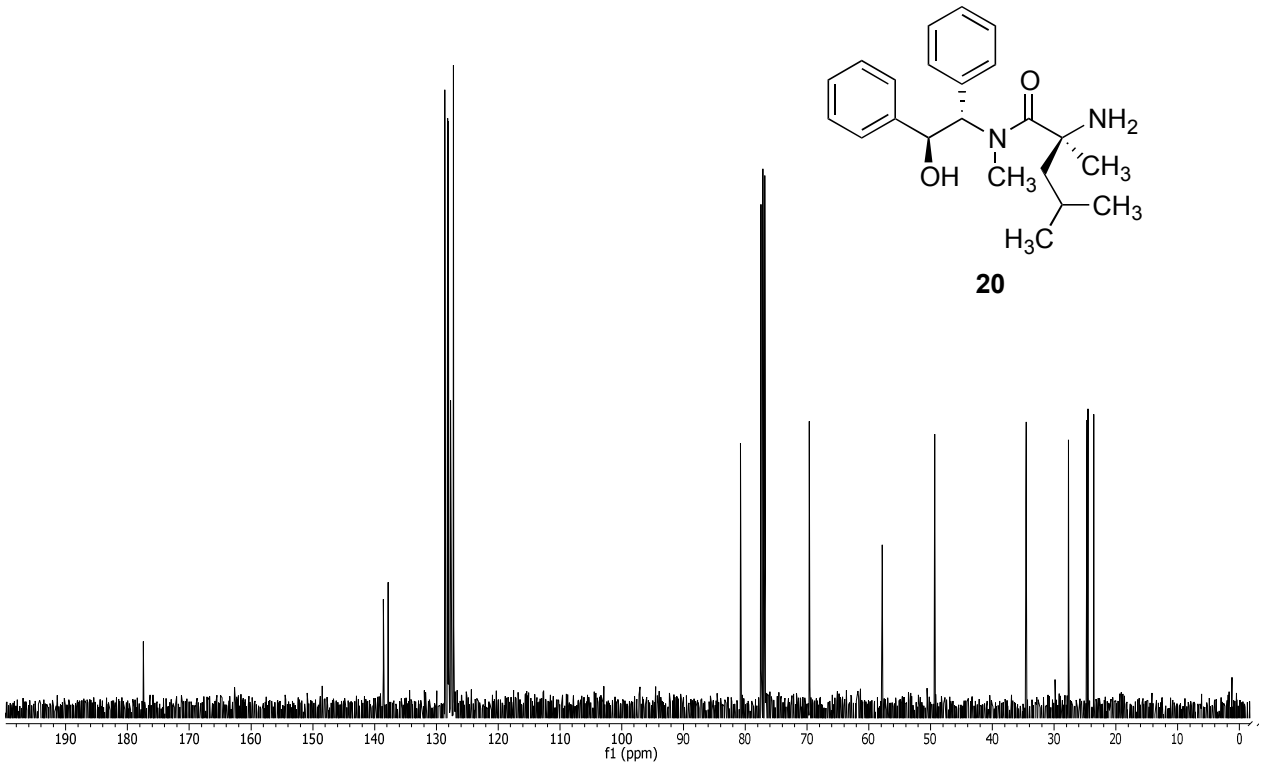
19


O
NH2
N
OH
CH3
CH3
OCH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

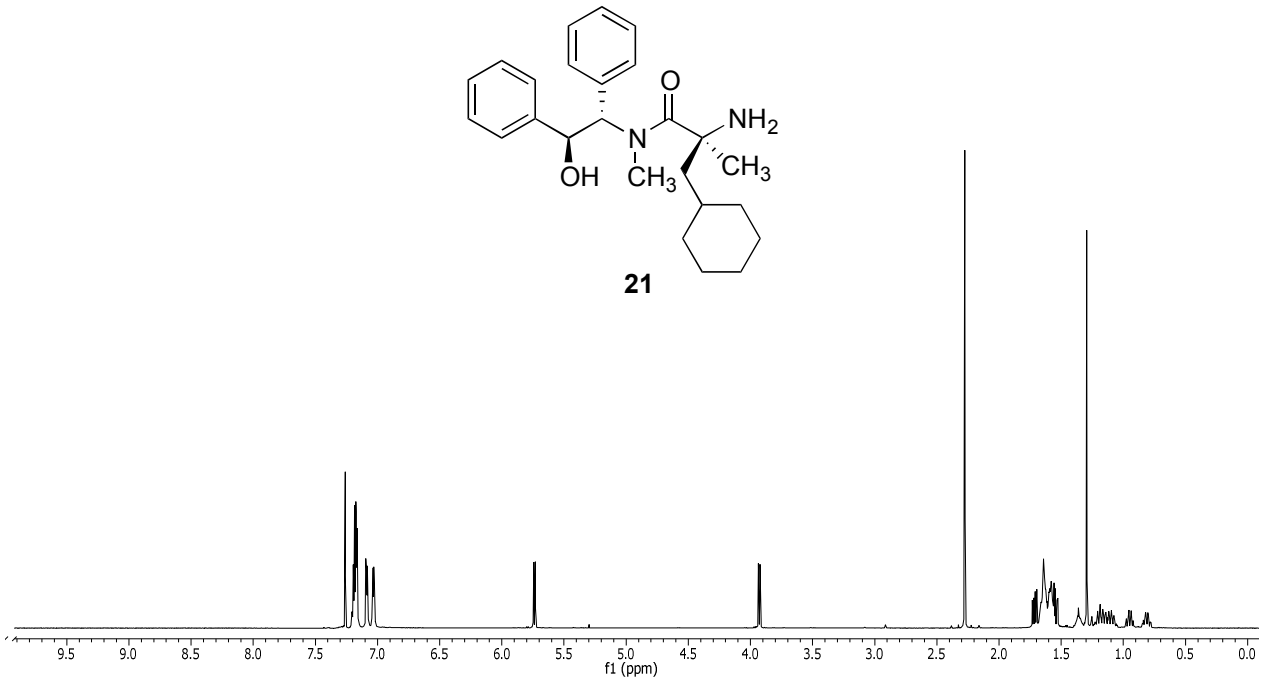
19


O
NH2
N
CH3
OH
CH3
CH3
H3C
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

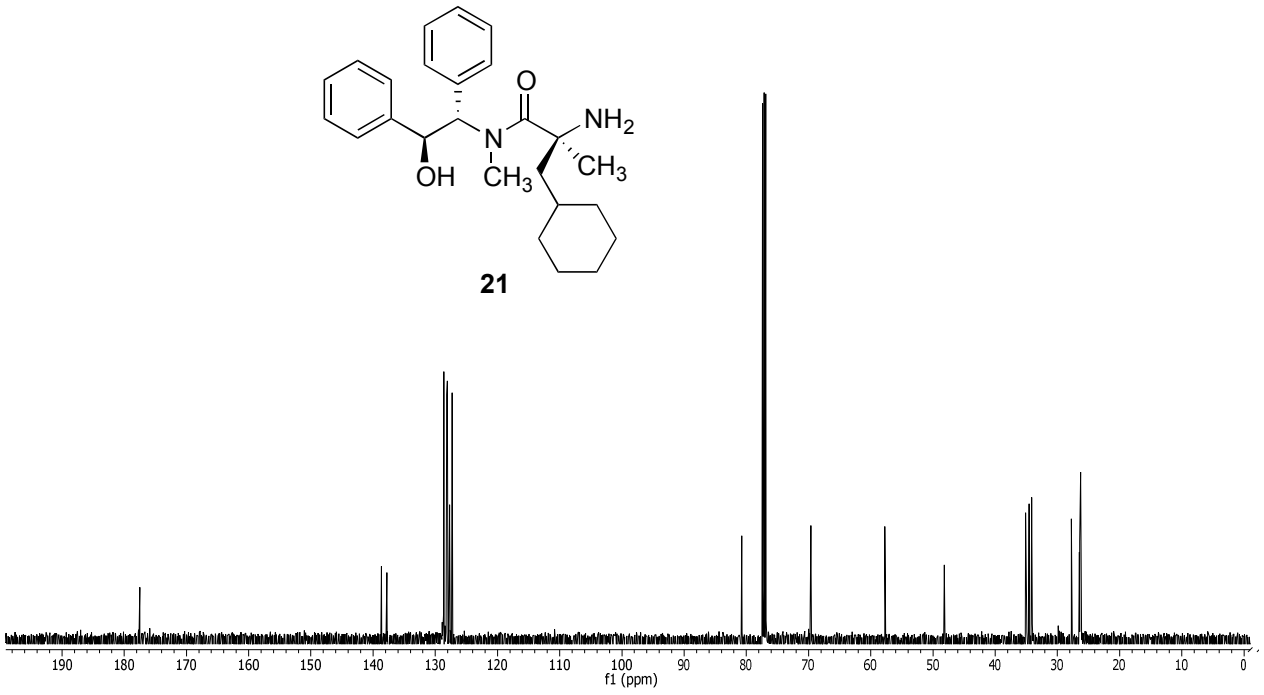
20


O
NH2
N
CH3
OH
CH3
CH3
H3C
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

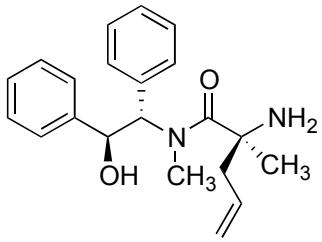
20


O
NH2
N
CH3
OH
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

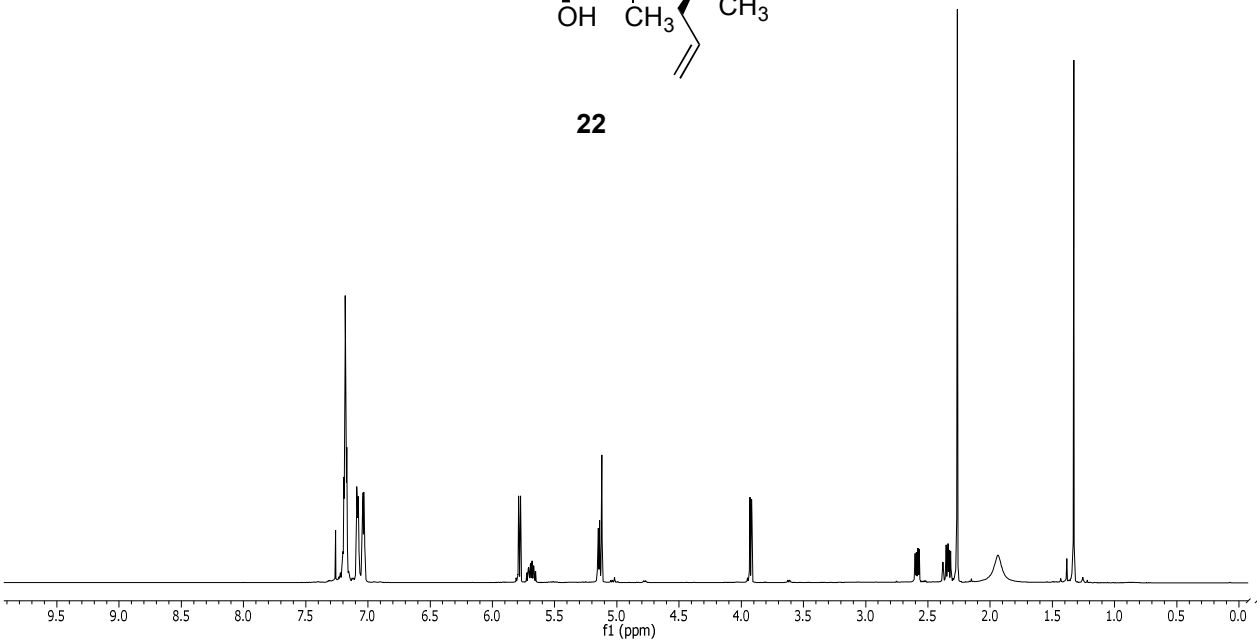
21

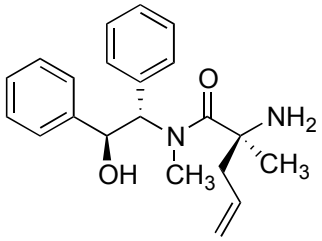

O
NH2
N
CH3
OH
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

21


O
NH2
N
OH
CH3
CH3

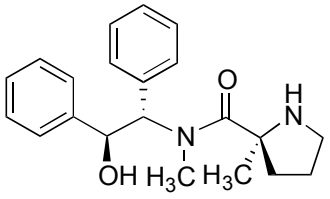
22


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

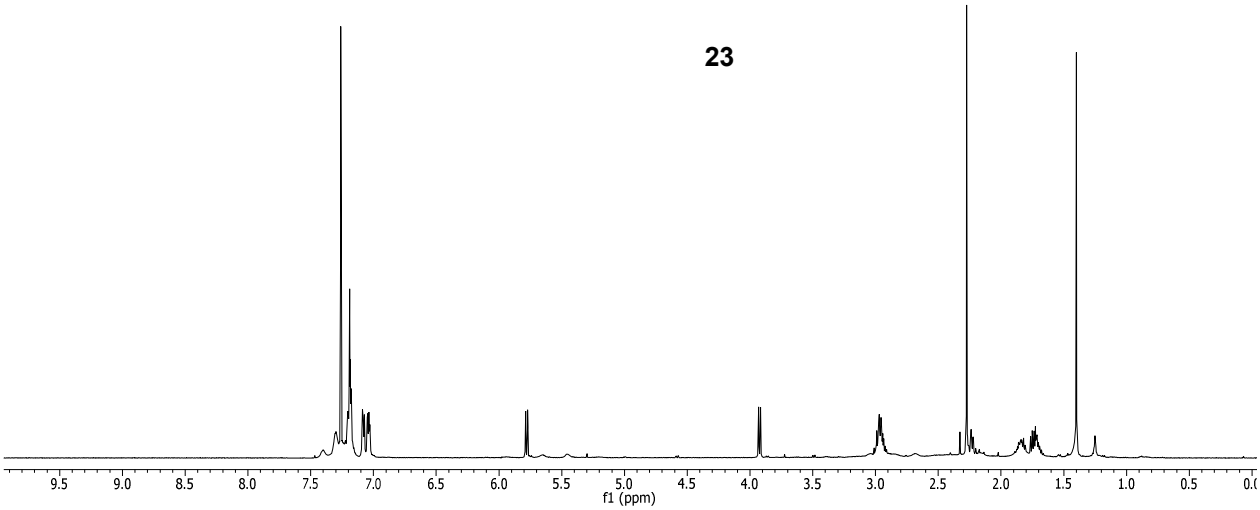

O
NH2
N
OH
CH3
CH3

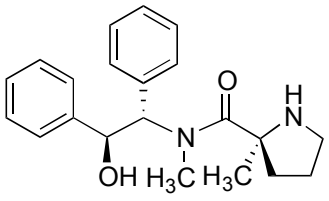
22

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
H
N
N
OH H3C H3C

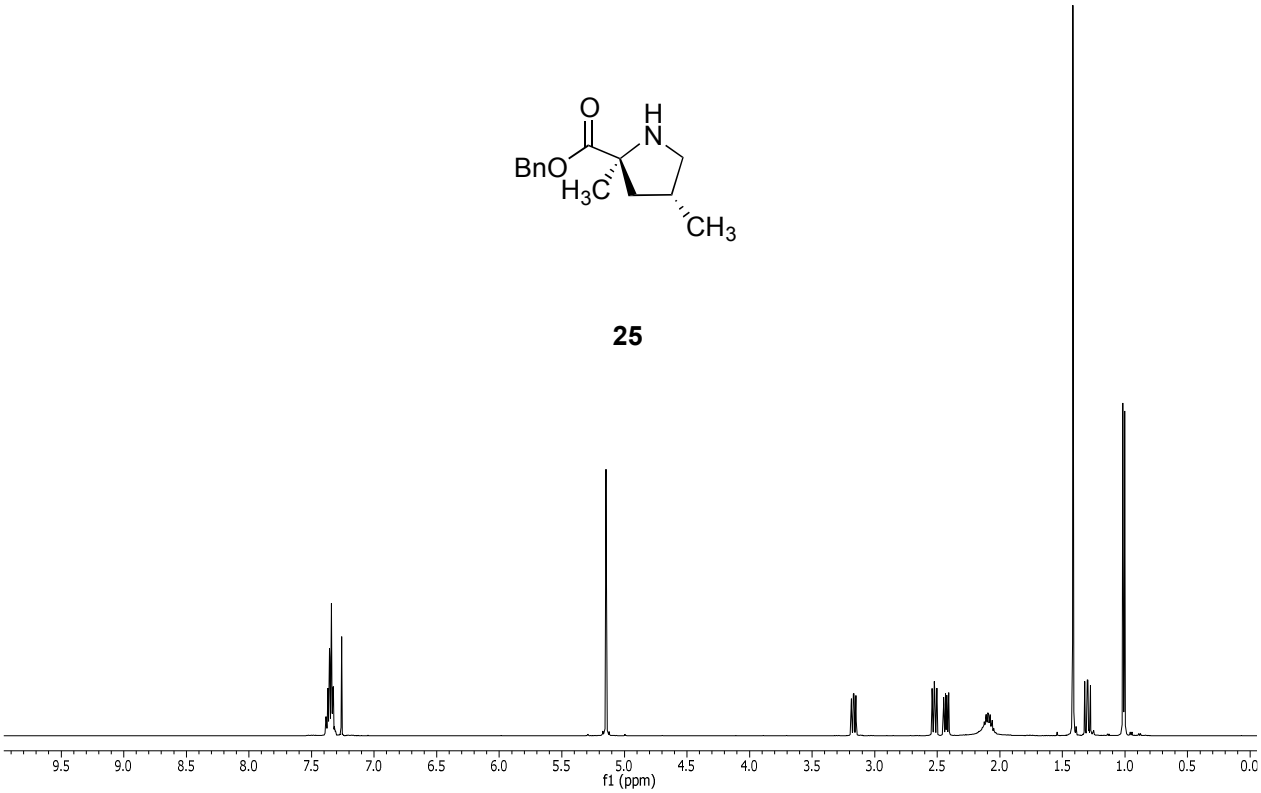
23


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

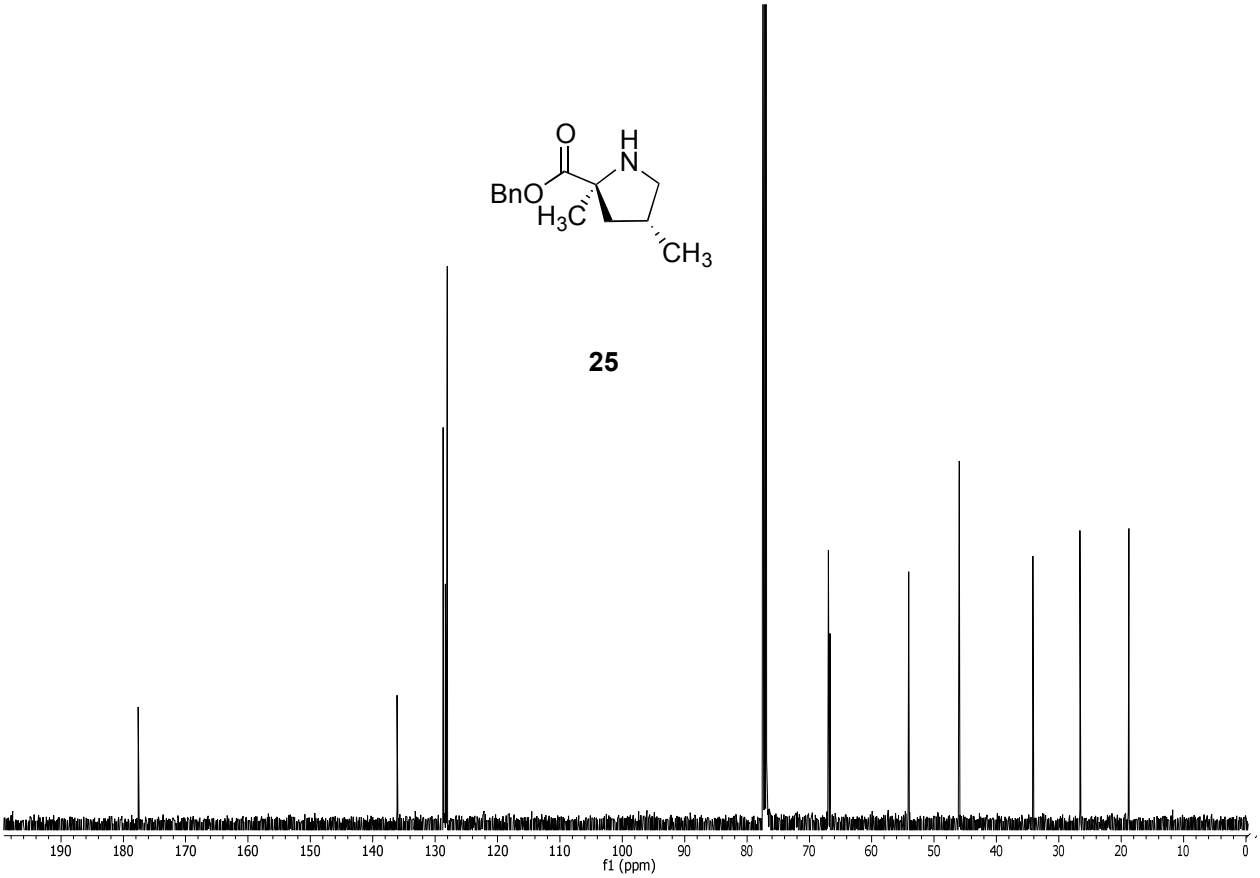

O
H
N
N
OH H3C H3C

23

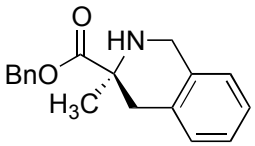
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
H
N
BnO
H3C
CH3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

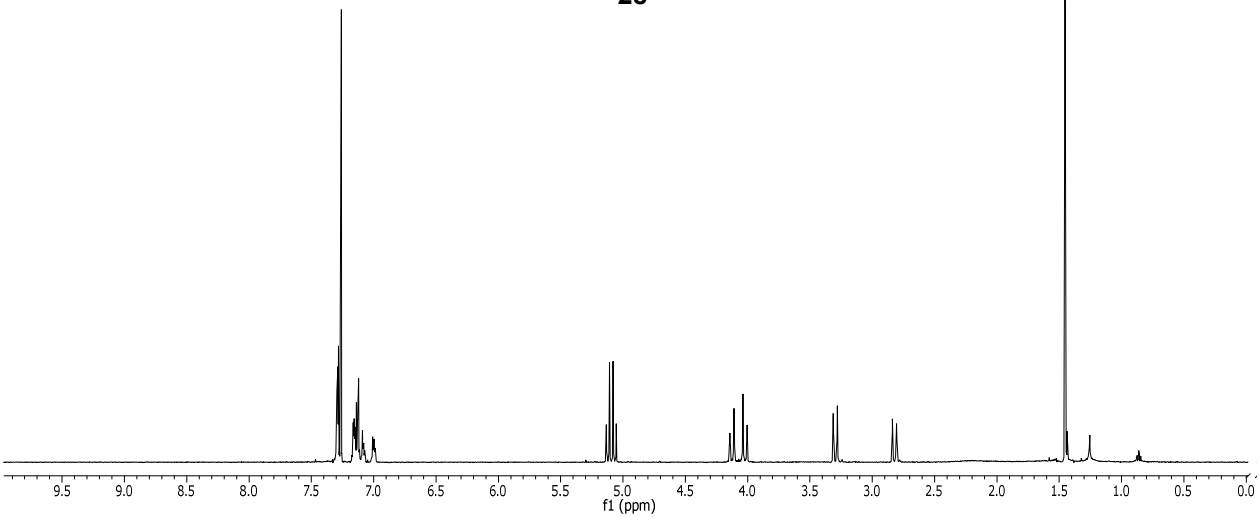
25

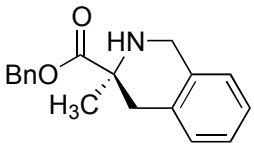

O
H
N
BnO
H3C
CH3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

25


O
HN
BnO
H3C

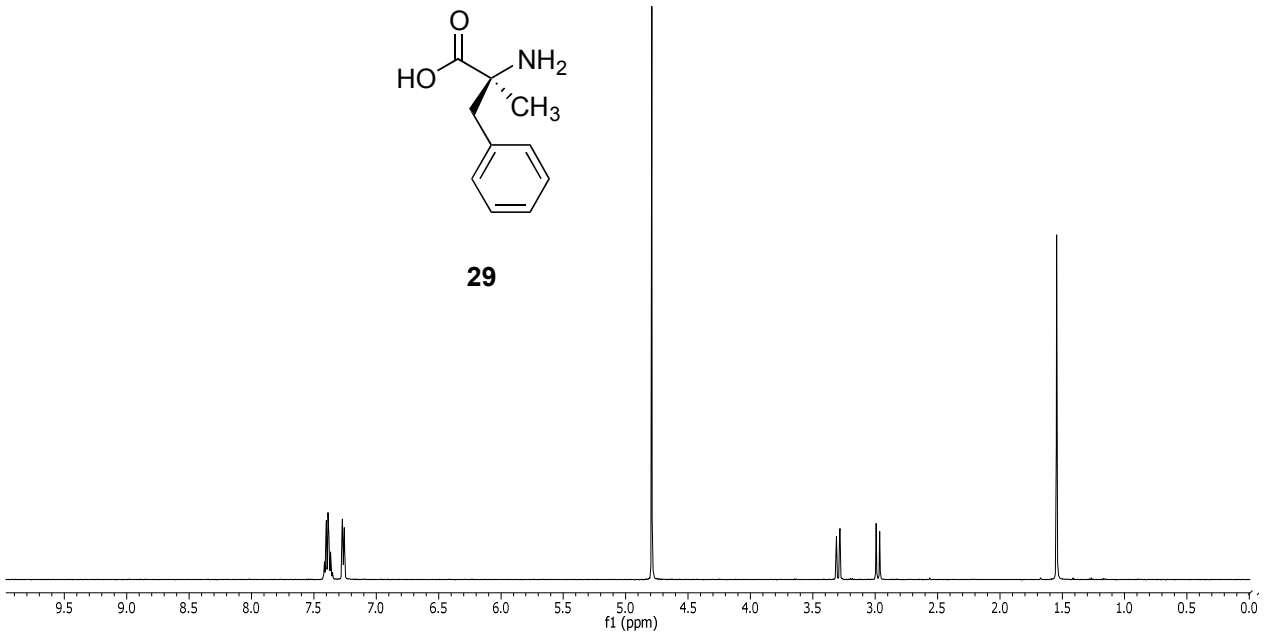
28


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

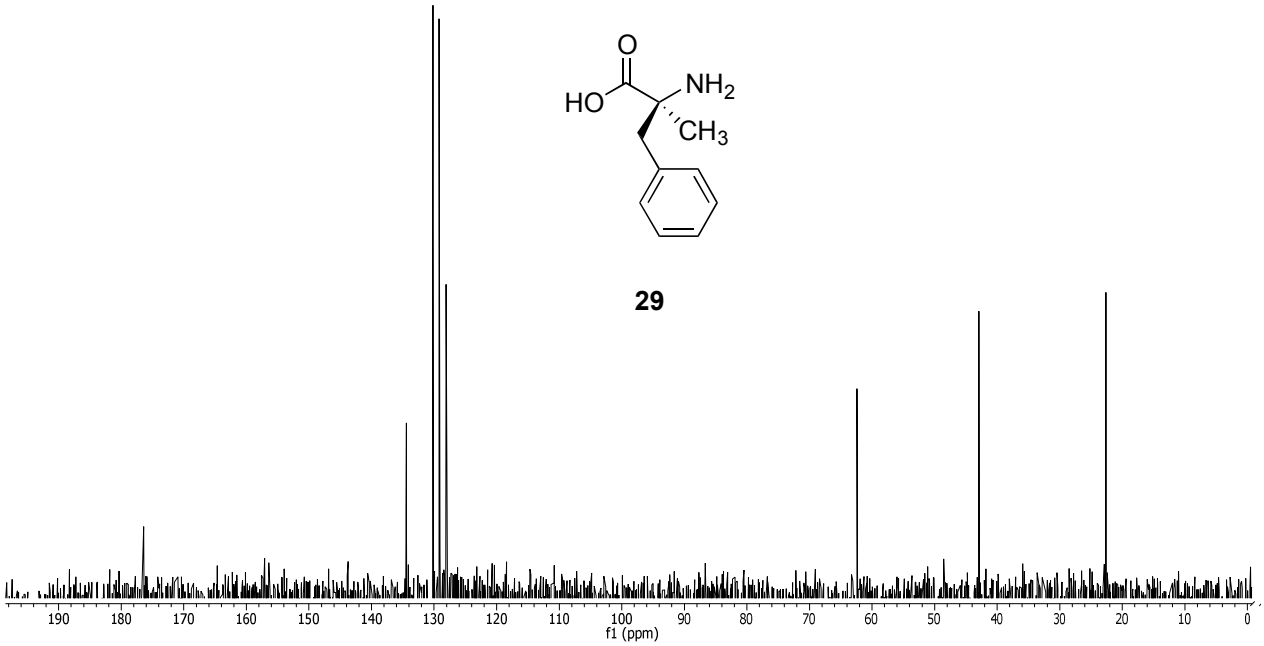

O
HN
BnO
H3C

28

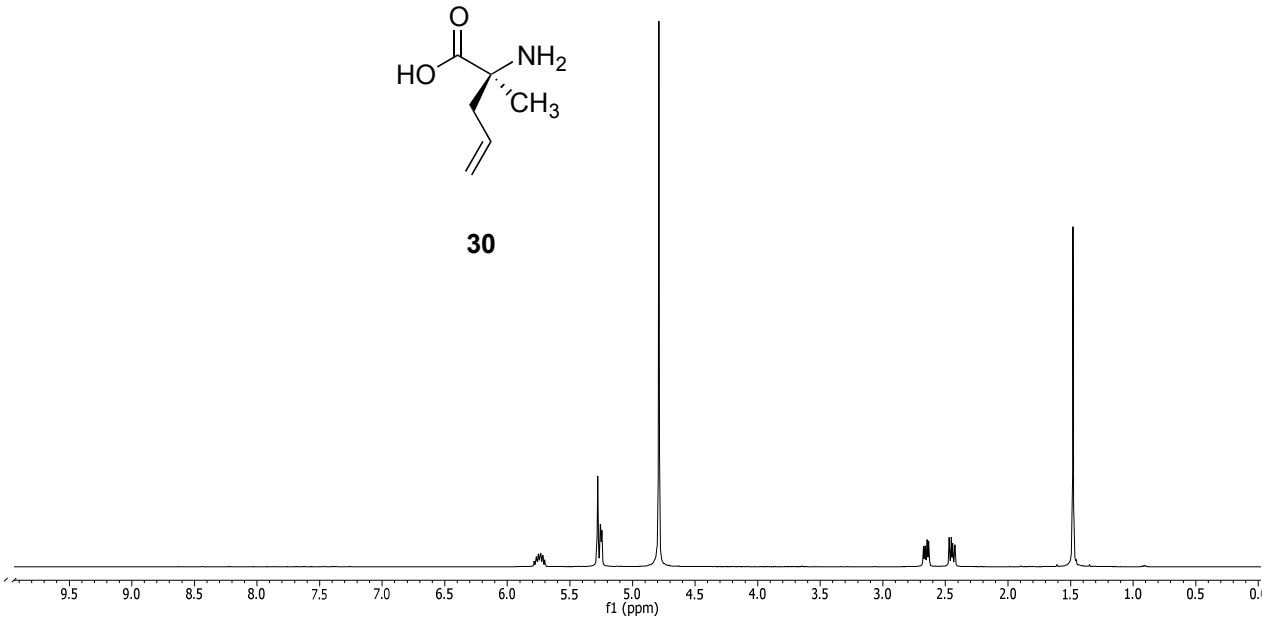
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO
NH2
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

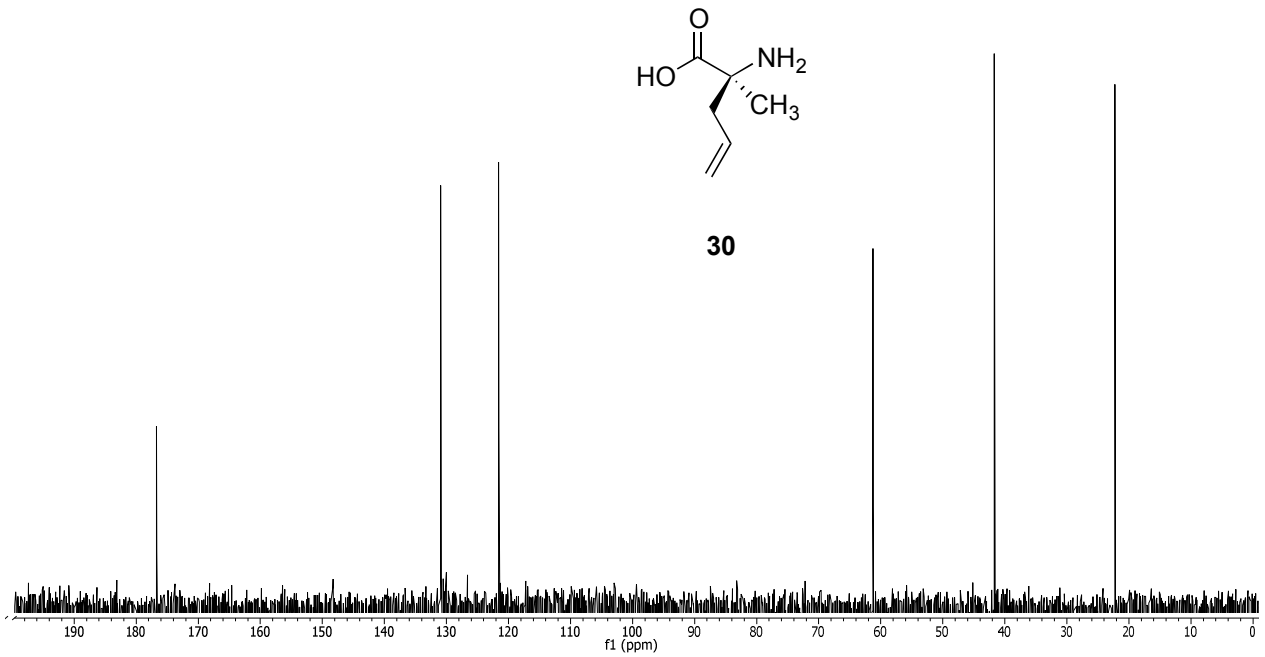
29


O
HO
NH2
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

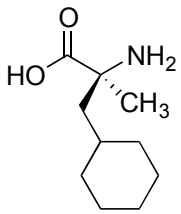
29


O
HO
NH2
CH3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

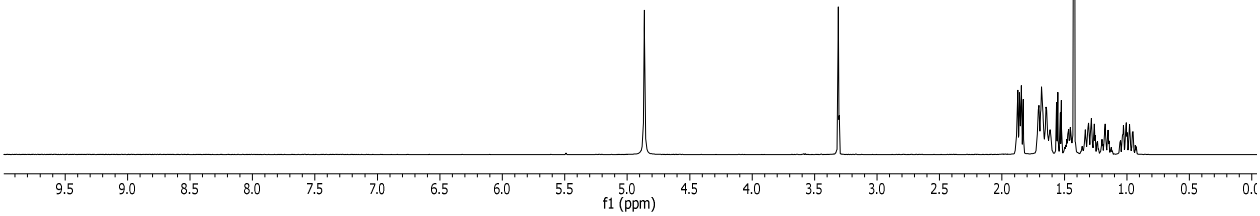
30

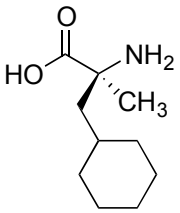

O
HO
NH2
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

30


O
HO
NH2
CH3

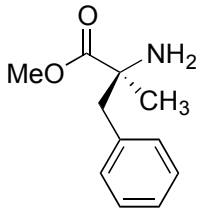
31


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

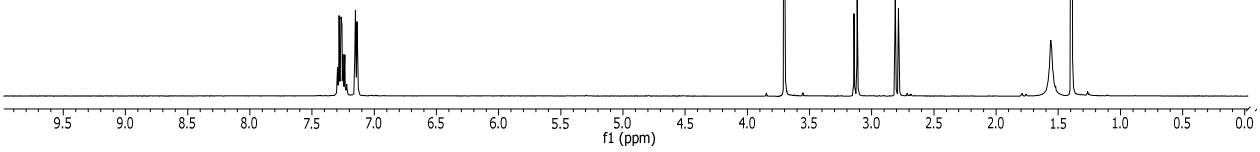

O
HO
NH2
CH3

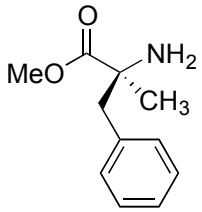
31

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

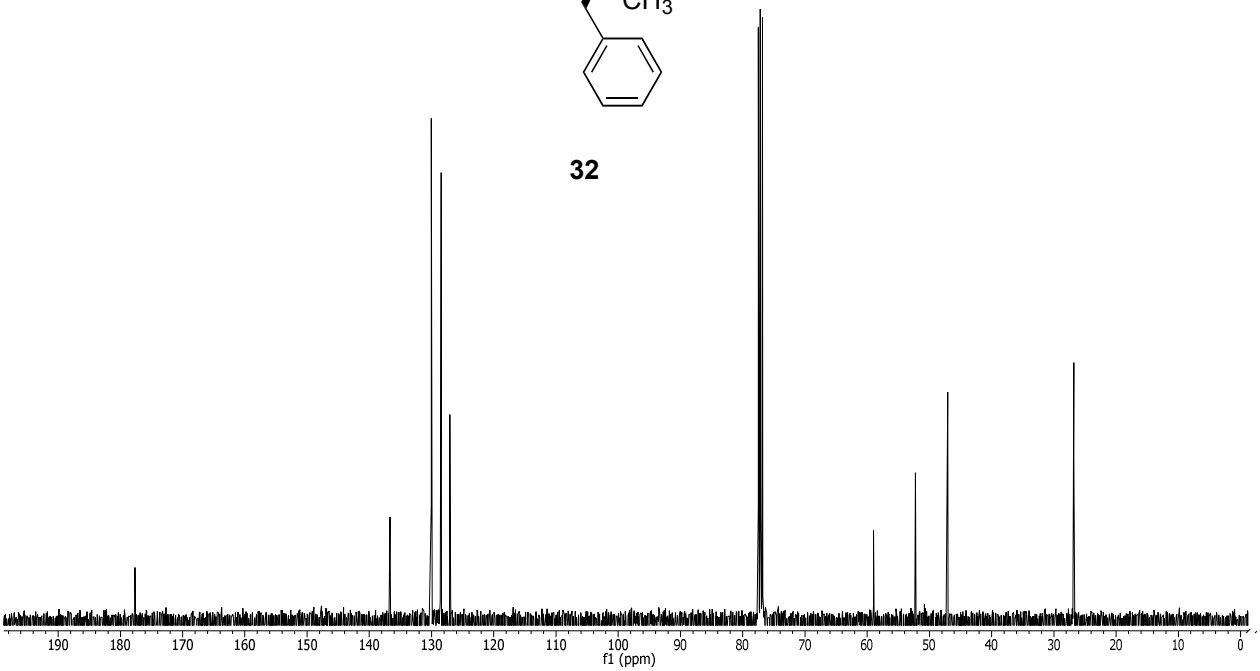

O
NH2
MeO
CH3

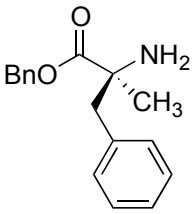
32


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

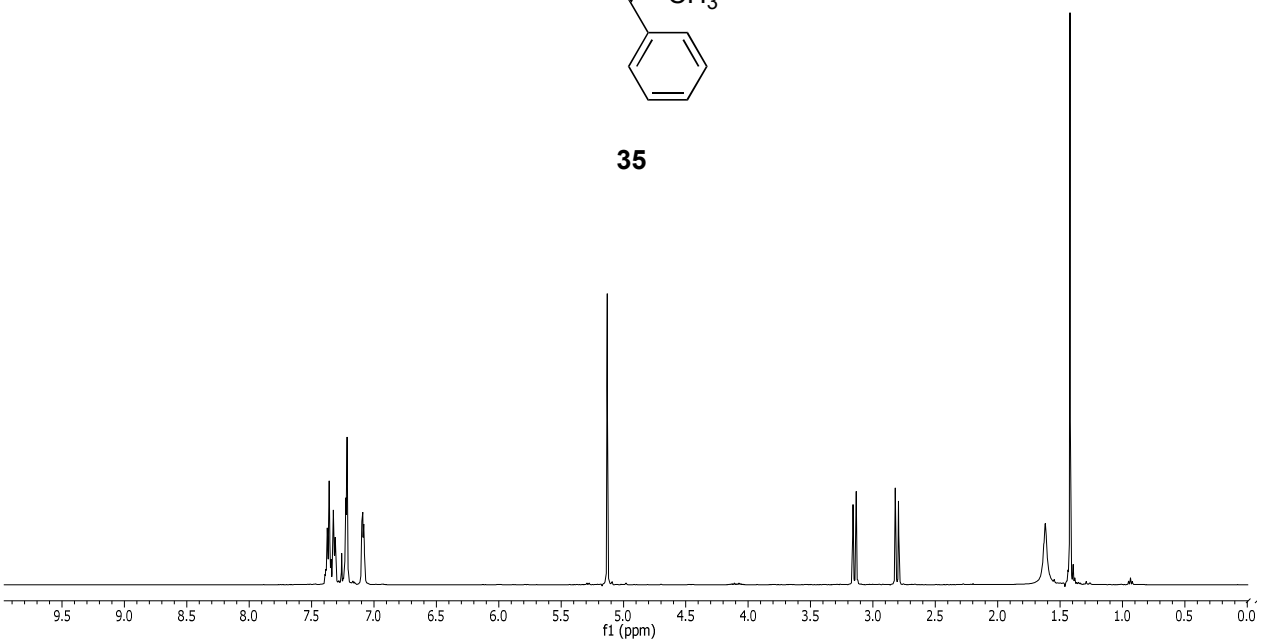

O
NH2
MeO
CH3

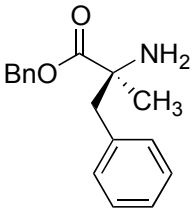
32


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
BnO
NH2
CH3

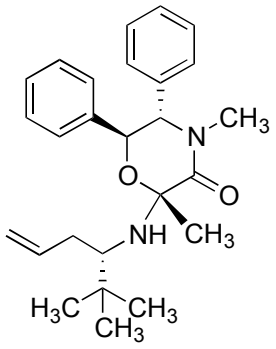
35


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


O
BnO
NH2
CH3

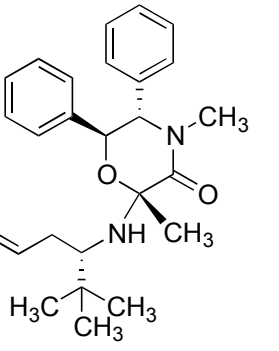
35

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


N
CH3
O
O
NH
CH3
H3C
CH3
CH3

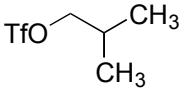
37

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


N
CH3
O
O
NH
CH3
H3C
CH3
CH3

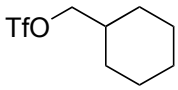
37

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

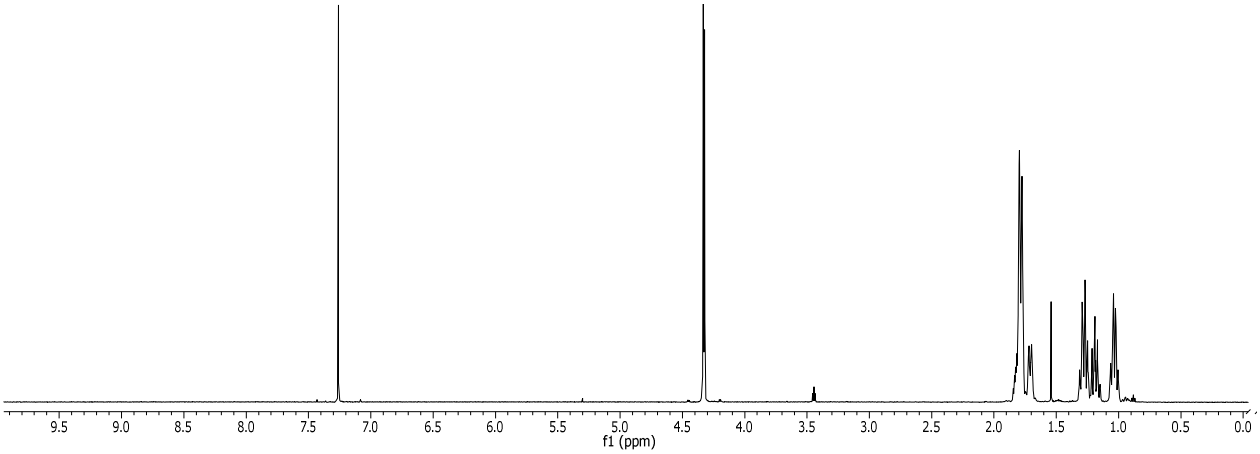

TfO
CH3
CH3

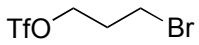
38

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

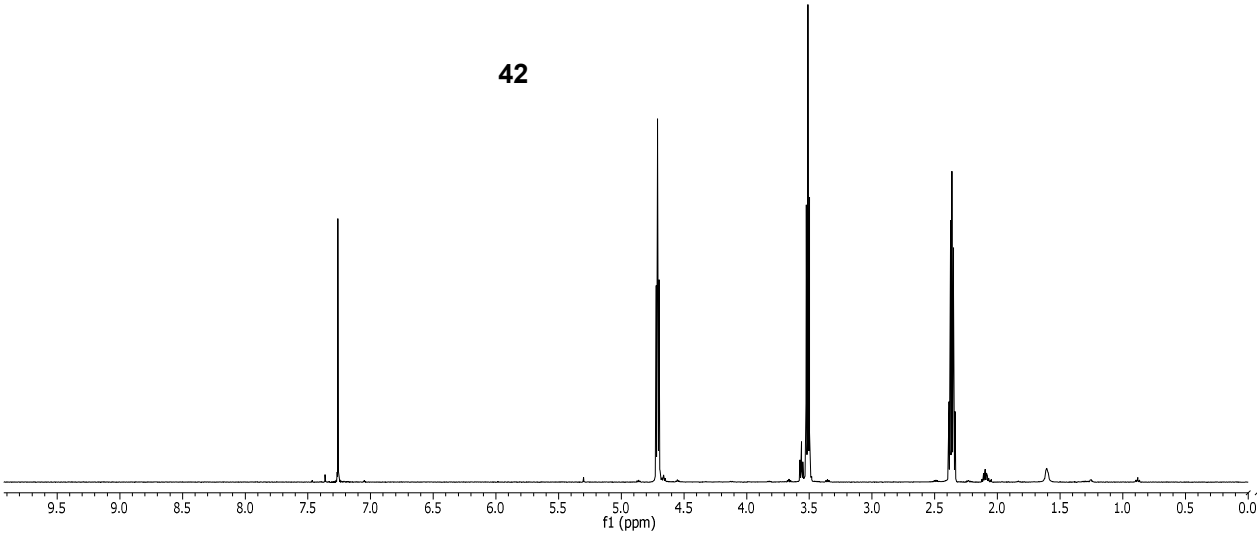

TfO

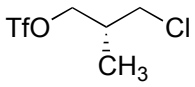
40


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

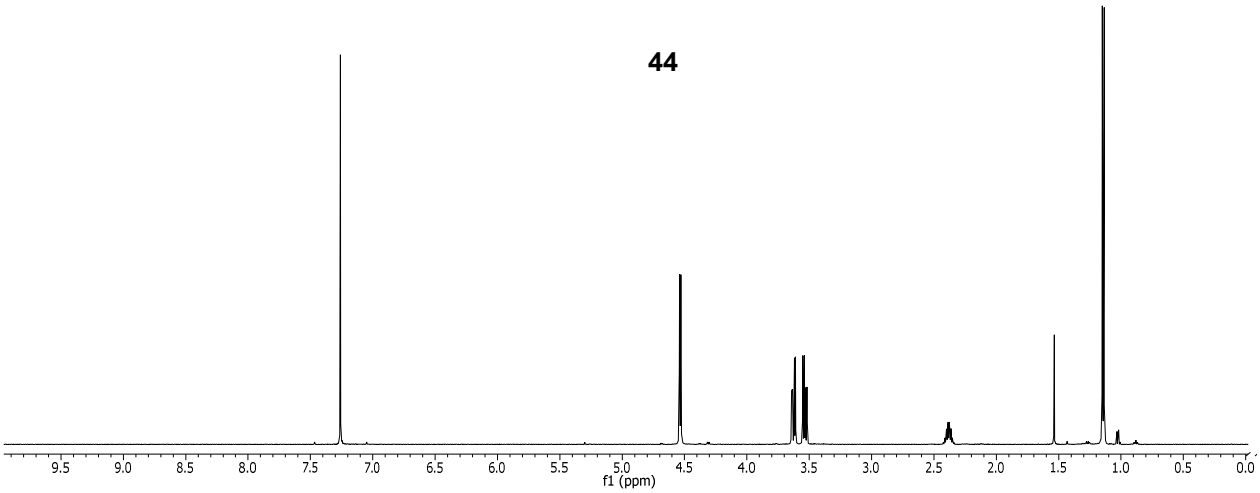

TfO
Br

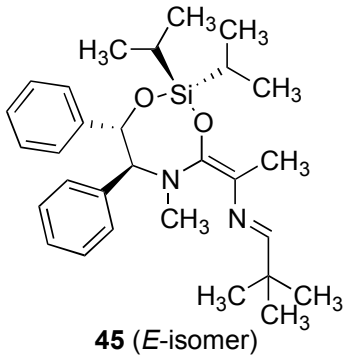
42


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

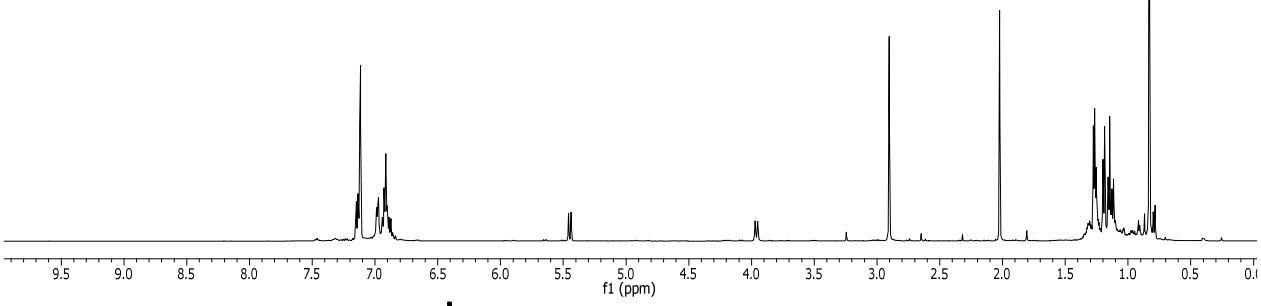

TfO
Cl
CH3

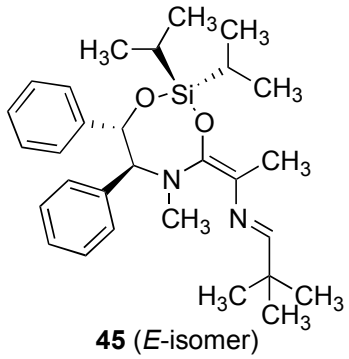
44


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



45 (*E*-isomer)





45 (*E*-isomer)