

Development of a Rapid, Room Temperature Dynamic Kinetic Resolution For Efficient Asymmetric Synthesis of α -Aryl Amino Acids

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Supporting Information

General Information. ^1H and ^{13}C NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for ^1H NMR are recorded as follows: chemical shift (δ , ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ , ppm). Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer and are reported in frequency of absorption. Low resolution mass spectra for all the new compounds done by either 20 eV, CH_4/CI or NH_3/CI were recorded on a Hewlett-Packard 5989A GC/MS, and exact mass spectra on a VG 7070 high resolution mass spectrometer. Specific rotations were measured on a Jasco Digital Polarimeter.

Analytical gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series instrument equipped with a split mode capillary injection system, a flame ionization detector, using a HP-5 GC column. High pressure liquid chromatography (HPLC) analysis was performed on a Hewlett-Packard 1100 Series instrument equipped with a quaternary pump, using a Daicel Chiralpak OJ, OD Column (250 x 4.6 mm) or Regis (*R,R*)Whelk-O1 Reversible Column (250 x 4.6 mm). UV detection was monitored at 220 nm or at 254 nm.

Modified cinchona alkaloids, 2-phenylglycine and DL- α -amino-2-thiopheneacetic acid were purchased from Aldrich (Milwaukee). 4-fluoro-DL- α -phenylglycine was purchased from Fluka, DL-2-(4-chlorophenyl)glycine was purchased from TCI (Tokyo), 4-(trifluoromethyl)phenylglycine was purchased from Indofine Chem. Company Inc., and DL- α -(3-thienyl)glycine was purchased from Sigma. These compounds were used without further purification. Racemic α -furylglycine and 5-methyl-2-furylglycine were prepared from furan and 2-methylfuran respectively (see page 2 for experimental details).¹ Racemic UNCAs (**1a-h**, **1j**) were prepared from the corresponding racemic amino acids following a literature procedure with slight modifications.² Racemic UNCA **1i** was prepared from racemic *N*-Benzyloxycarbonyl-1-tosyl-3-indoleglycine following a literature procedure (see page 2-5 for experimental details).^{3, 2b} All reactions were conducted in flame-dried glassware under N_2 atmosphere. 4Å molecular sieves was flame-dried under reduced pressure (0.2 mmHg) immediately prior to use. Diethyl ether,

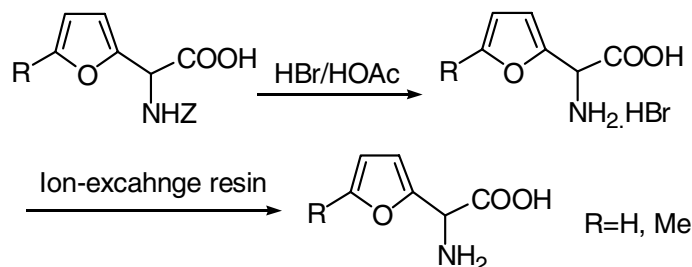
¹ (a) Zoller, U.; Ben-Ishai, D. *Tetrahedron*, **1975**, *31*, 863. (b) Ben-Ishai, D.; Sataty, I.; Bernstein, Z. *Tetrahedron*, **1976**, *32*, 1571. (c) Ben-Ishai, D.; Berger, A. *J. Org. Chem.* **1952**, *17*, 1564.

² (a) Fuller, W. D.; Cohen, M. P.; Shabankareh, M.; Blair, R. K. *J. Am. Chem. Soc.* **1990**, *112*, 7414. (b) Fuller, W. D.; Goodman, M.; Naider, F. R.; Zhu, Y. F. *Biopolymers (Peptide Science)* **1996**, *40*, 183. (c) Daly, W. H.; Poché, D. *Tetrahedron Lett.* **1988**, *29*, 5859.

³ Okada, S.; Takeno, H.; Kitaura, Y.; Hashimoto, M. *Chem. Pharm. Bull.* **1985**, *33*, 889.

tetrahydrofuran (THF) and *t*-butyl methylether (TBME) were distilled from sodium ketyl benzophenone immediately prior to use. Ethanol and methanol were freshly distilled from calcium hydride. Allyl alcohol was distilled from calcium sulfate.

Preparation of (±)- α -furylglycine and (±)-5-methyl-2-furylglycine:^{1c}



Carbamates (±)-*N*-benzyloxycarbonyl- α -furylglycine and (±)-*N*-benzyloxycarbonyl-5-methyl-2-furylglycine were prepared from furan and 2-methylfuran respectively following a literature procedure.^{1a, 1b}

Transformation of carbamates to the corresponding racemic amino acids was performed by following a literature procedure^{1c} with slight modifications:

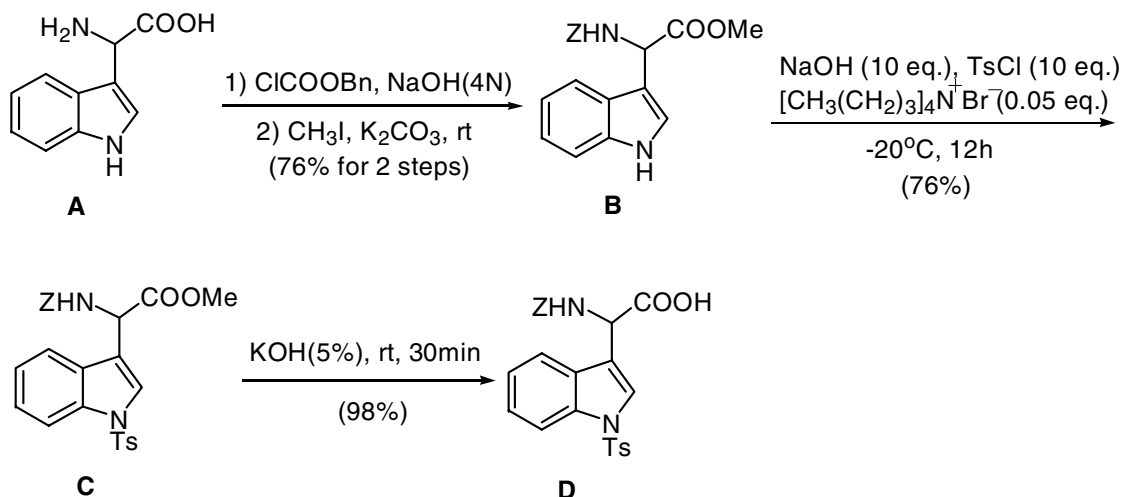
A saturated solution of dry hydrogen bromide in glacial acetic acid (36%, 50 g) was added to the carbamate (50 mmol) under N₂ atmosphere. The resulting mixture was stirred at room temperature for 1 hour, and dry ether (150 mL) was then added to precipitate the amine hydrobromide formed. The precipitate was filtered, washed with ether, dried in *vacuo* to give the HBr salt of (±)- α -furylglycine (R = H, 90% yield) and (±)-5-methyl-2-furylglycine (R = Me, 82% yield)

The amine hydrobromide (5.0 mmol) was dissolved in distilled water (10 mL) then ion exchange resin [Amberlite IR-120 (+), 4 g] was added and the resulting mixture was allowed to stand overnight. The resin was filtered and washed with distilled water until no precipitate was observed when a sample (0.1 mL) of the aqueous wash was added to 5% ethanolic AgNO₃ (5.0 mL). The resin was added to aqueous NH₄OH (6 M, 50 mL), stirred for 4 hours and filtered. The filtrate was evaporated in *vacuo* to give the (±)- α -furylglycine (R = H, 68% yield) and (±)-5-methyl-2-furylglycine (R = Me, 72% yield).

Preparation of (±)-*N*-Benzyloxycarbonyl-1-Tosyl-3-Indoleglycine

(±)-3-indoleglycine was prepared from indole following a literature procedure.⁴ (±)-*N*-Benzyloxycarbonyl-1-tosyl-3-indoleglycine was obtained from 3-indoleglycine as following:

⁴ (a) O'onnell, M. J.; Bennett, W. D. *Tetrahedron* **1988**, *44*, 5389. (b) O'onnell, M. J.; Bennett, W. D.; Polt, R. L. *Tetrahedron Lett.* **1985**, *26*, 695.



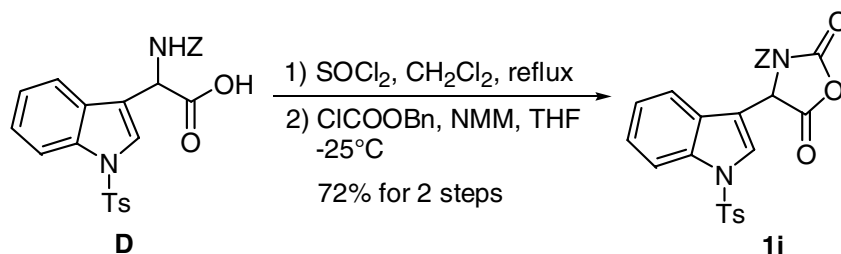
(±)-Methyl -N-benzyloxycarbonyl-3-indoleglycinate B: (±)-3-indoleglycine **A** (1.68 g, 8.9 mmol) was dissolved in aq. NaOH (4.0 N, 2.2 mL), the mixture was cooled with ice-water, then benzyl chloroformate (95%, 1.3 mL, 8.9 mmol) and aq. NaOH (4.0 N, 2.2 mL) were added at same time in 20 mins. The resulting mixture was stirred at r.t. for 30 mins, then water (20 mL) was added and the resulting mixture was washed with ether (2 x 20 mL). The aqueous layer was acidified to pH = 1-2 by adding conc. HCl, then extracted with ethyl acetate (2 x 40 mL), dried over Na₂SO₄, concentrated in *vacuo* to afford a solid. The solid was dissolved in DMF (70 mL). To this solution, K₂CO₃ (5.5 g, 44 mmol) and CH₃I (1.5 mL, 24 mmol) were added. The resulting mixture was stirred at r.t. for 4 hours and poured into water (170 mL), then extracted with ethyl acetate (2 x 100 mL). The organic layer was dried over Na₂SO₄, concentrated in *vacuo*. The residue was purified by flash chromatography (CH₂Cl₂) to give (±)-methyl-N-benzyloxycarbonyl-3-indoleglycinate **B** (2.3 g, 76% yield). ¹H NMR (400 MHz, CDCl₃) δ 3.72 (s, 3H), 5.08-5.14 (m, 2H), 5.66 (d, *J* = 6.8 Hz, 1H), 5.75 (d, *J* = 6.8 Hz, 1H), 7.12-7.33 (m, 9H), 7.68 (d, *J* = 8.0 Hz, 1H), 8.35 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 51.23, 52.66, 67.02, 110.95, 111.51, 118.98, 120.32, 122.71, 123.48, 125.18, 128.08, 128.14, 128.48, 136.11, 136.24, 155.62, 171.86; IR (CHCl₃) ν 3343, 1699, 1506, 1456, 1436 cm⁻¹; HRMS (EI) exact mass calcd for (C₁₉H₁₈N₂O₄⁺) requires m/z 338.1266, found m/z 338.1249.

(±)-Methyl-N-benzyloxycarbonyl-1-tosyl-3-indoleglycinate C: To a suspension of NaOH powder (1.37 g, 34.2 mmol) in dry CH₂Cl₂ (100 mL) at -20 °C under N₂ atmosphere, amino ester **B** (1.08 g, 3.2 mmol), tetrabutylammonium bromide (55 mg, 0.05 eq.) and TsCl (6.1 g, 32.0 mmol) were added sequentially. The resulting mixture was stirred under N₂ atmosphere at -20 °C overnight, then aq. HCl (2.0 N, 50 mL) was added to the reaction mixture. The organic layer was washed with brine (2 x 25 mL), dried over Na₂SO₄, concentrated. The residue was purified by flash chromatography (CH₂Cl₂) to afford (±)-methyl-N-benzyloxycarbonyl-1-tosyl-3-indoleglycinate **C** (1.2 g, 76%). ¹H NMR (400 MHz, CDCl₃) δ 2.30 (s, 3H), 3.72 (s, 3H), 5.09 (s, 2H), 5.65 (d, *J* = 7.2 Hz, 1H), 5.82 (d, *J* = 7.2 Hz, 1H), 7.18-7.96 (m, 14H); ¹³C NMR (100 MHz, CDCl₃) δ 21.47, 50.59, 52.87, 67.12, 113.58, 117.49, 119.86, 123.49, 124.77, 125.13, 126.84, 128.01, 128.14, 128.26, 128.43, 129.90, 134.81, 134.99, 135.91, 145.15, 155.39, 170.71;

IR (CHCl₃) ν 1717, 1506, 1448, 1174 cm⁻¹; HRMS (EI) exact mass calcd for (C₂₆H₂₄N₂O₅S⁺) requires m/z 492.1355, found m/z 492.1359.

(±)-*N*-benzyloxycarbonyl-1-tosyl-3-indoleglycine D: To a solution of (±)-methyl-*N*-benzyloxycarbonyl-1-tosyl-3-indoleglycinate **C** (1.11 g 2.25 mmol) in dioxane (80 mL) and water (40 mL) at 0 °C, 5% aq. KOH (6.3 mL, 5.6 mmol) was added. The resulting mixture was stirred at r.t. for 30 min, then acidified to pH = 2-3. The mixture was extracted with ethyl acetate (2 x 100mL). The organic layers were combined and dried over Na₂SO₄, concentrated, purified by flash chromatography (ethyl acetate/hexanes/acetic acid, 20/40/1) to give (±)-*N*-benzyloxycarbonyl-1-tosyl-3-indoleglycine **D** (1.06 g, 98%). m.p. 83-85 °C; ¹H NMR (acetone-d₆, 400 MHz) δ 2.32 (s, 3H), 5.10 (s, 2H), 5.66 (d, *J* = 7.9 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.24-7.42 (m, 8H), 7.72-7.78 (m, 1H), 7.82-7.90 (m, 3H), 7.99 (d, *J*=8.5Hz, 1H); ¹³C NMR (acetone-d₆, 100 MHz) δ 21.38, 51.37, 66.95, 114.27, 121.30, 124.22, 125.84, 126.02, 127.78, 128.64, 129.16, 129.90, 130.94, 135.81, 137.95, 146.50, 156.72, 171.68; IR (CHCl₃) ν 3028, 1716, 1506, 1447cm⁻¹; HRMS (EI) exact mass calcd for (C₂₆H₂₄N₂O₅S⁺) requires m/z 478.1199, found m/z 478.1189.

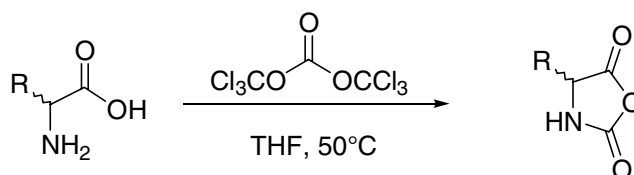
Procedure for Preparation of (±)-UNCA **1i**^{3, 2b}



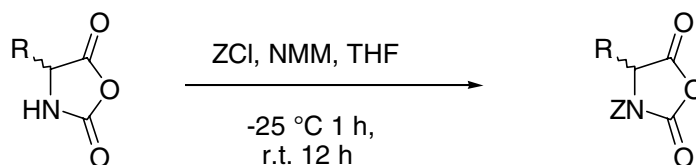
To a solution of the racemic *N*-Benzyloxycarbonyl amino-acid **D** (1.05 g, 2.2 mmol) in anhydrous CH₂Cl₂ (50 mL), SOCl₂ (1.2 eq) was added in one portion. The resulting mixture was refluxed under N₂ atmosphere for 3 hours until NMR analysis of the reaction mixture showing no starting materials, then the solvent was removed and the residue was dried *in vacuo* for 30 minutes. After which the residue was dissolved in anhydrous THF (50 mL), the resultant solution was cooled to -25 °C, benzyl chloroformate (1.3 eq.) was added, then *N*-methyl-morpholine (NMM) (1.5 eq. was introduced dropwise over a period of 15 min. The resulting mixture was stirred at -25 °C for 5 h, then acidified by HCl (4.0 M in Dioxane) until the pH of the mixture is approximately 3. The resulting mixture was allowed to warm to room temperature. The precipitate (NMM hydrochloride) was removed by filtration under N₂ atmosphere with the aid of dry Celite 521 (3.0 g) and washed with dry THF (2 x 20 mL). The filtrate was concentrated and the residue was subjected to recrystallization from Et₂O/THF/hexanes at -20 °C overnight. The solid was collected and dried under vacuum to give the desired UNCA **1i** in 72% yield. ¹H NMR (400 MHz, CDCl₃) δ 2.34(s, 3H), 5.14-5.22(m, 2H), 5.90(s, 1H), 7.16-7.39(m, 10H), 7.73-7.77(m, 3H), 7.97(d, *J* = 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.61, 56.91, 69.89, 111.97, 113.96, 118.72, 124.14, 125.73,

126.63, 127.00, 127.07, 128.17, 128.73, 128.95, 130.14, 133.54, 134.50, 134.92, 145.69, 145.77, 148.31, 163.27; IR (CHCl₃) ν 3032, 1875, 1817, 1747, 1447, 1175 cm⁻¹; HRMS (DCI) exact mass calcd for (C₂₆H₂₀O₇N₂S⁺) requires m/z 504.0991, found m/z 504.0967.

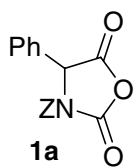
General Procedure for Preparations of (±)-UNCAs(1a-1h, 1j) from racemic amino acids



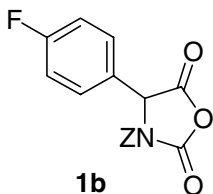
To a suspension of the racemic amino acid (3.0-25.0 mmol) in anhydrous THF (8-40 mL) at 50 °C was added triphosgene (1.0 eq.) in one portion. If a clear solution has not formed within one hour, 1-2 aliquots of triphosgene (0.1 eq/aliquot) were added to the reaction mixture at 45 min intervals. The reaction mixture was stirred at 50 °C for a total of 3 h, after which the insoluble material (if there is any) in the reaction mixture was removed by filtration. The filtrate was concentrated (to 2.0-10.0 mL) and poured into hexanes (20-120 mL), the resulting mixture was stored in a freezer (-20 °C) overnight. The white crystals formed during this time were collected and dried under vacuum to give the desired NCAs, which were used for the next step without further purification.



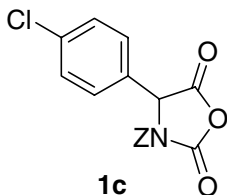
To a solution of the racemic NCA (1.0-10.0 mmol) in dry THF (5.0-25.0 mL) at -25 °C, benzyl or fluorenylmethyl chloroformate (1.2-1.3 eq.) was added. A solution of *N*-methyl-morpholine (NMM) (1.25-1.5 eq.) in THF (1.0-5.0 mL) was introduced dropwise to the reaction mixture over a period of 15 min. The resulting mixture was stirred at -25 °C for 1 h, then allowed to warm to room temperature overnight. The reaction mixture was cooled to -25 °C and acidified by HCl (4.0 M in Dioxane) until the pH of the mixture is approximately 3. The resulting mixture was allowed to warm to room temperature. The precipitate (NMM hydrochloride) was removed by filtration under N₂ atmosphere with the aid of dry Celite 521 (3.0 g) and washed with dry THF (2 x 20 mL). The filtrate was concentrated and the residue was subjected to recrystallization from TBME/THF/hexanes at -20 °C overnight. The solid was collected and dried under vacuum. The mother liquor was concentrated and subjected to recrystallization again from TBME/THF/hexanes, the solid was collected, dried and combined with the solid obtained from the first recrystallization to give the desired UNCAs in yields ranging from 70 to 81% from racemic amino acids.



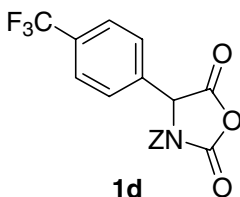
This product was obtained as a white solid in 74% yield from the corresponding racemic amino acid. m.p. 92-94 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.16 (d, *J* = 11.9 Hz, 1H), 5.25 (d, *J* = 11.9 Hz, 1H), 5.62 (s, 1H), 7.14-7.18 (m, 2H), 7.24-7.46 (m, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 63.38, 69.80, 126.55, 128.30, 128.64, 128.86, 129.52, 130.06, 131.48, 133.71, 146.10, 148.39, 163.73; IR (CHCl₃) ν 1874, 1812, 1746, 1498, 1456, 1354, 1242, 1008 cm⁻¹.



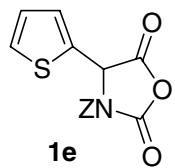
This product was obtained as a white solid in 80% yield from the corresponding racemic amino acid. m.p. 128-130 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.15 (d, *J* = 12.2 Hz, 1H), 5.26 (d, *J* = 12.2 Hz, 1H), 5.61 (s, 1H), 7.04-7.14 (m, 2H), 7.14-7.23 (m, 2H), 7.23-7.40 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 62.67, 69.86, 116.62(d, *J* = 22.0 Hz), 127.35(d, *J* = 3.1 Hz), 128.37, 128.64, 128.69(d, *J* = 6.8 Hz), 129.95, 133.63, 145.97, 148.36, 163.47 (d, *J* = 249.0 Hz), 163.71; IR (CHCl₃) ν 1870, 1810, 1749, 1512, 1457 cm⁻¹.



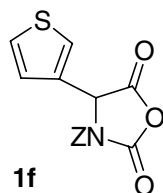
This product was obtained as a white solid in 73% yield from the corresponding racemic amino acid. m.p. 135-137 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.16 (d, *J* = 12.4 Hz, 1H), 5.29 (d, *J* = 12.4 Hz, 1H), 5.60 (s, 1H), 7.16-7.28 (m, 5H), 7.28-7.42 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 62.72, 69.99, 127.97, 128.44, 128.71, 129.03, 129.79, 129.92, 133.59, 136.33, 145.78, 148.32, 163.35; IR (CHCl₃) ν 1878, 1802, 1734, 1493, 1457 cm⁻¹.



This product was obtained as a white solid in 72% yield from the corresponding racemic amino acid. m.p. 147-149 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.15 (d, *J* = 12.2 Hz, 1H), 5.31 (d, *J* = 12.2 Hz, 1H), 5.69 (s, 1H), 7.14-7.26 (m, 2H), 7.26-7.38 (m, 3H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 62.82, 70.12, 123.44 (q, *J* = 270.2 Hz), 126.53, 127.01, 128.46, 128.70, 129.10, 132.28 (q, *J* = 32.6 Hz), 133.46, 135.16, 145.76, 148.24, 162.99; IR (CHCl₃) ν 1868, 1801, 1723, 1540, 1457 cm⁻¹.

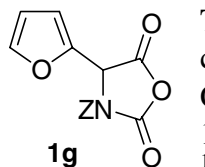


This product was obtained as a light brown solid in 70% yield from the corresponding racemic amino acid. m.p. 113-114 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.23 (d, *J* = 12.2 Hz, 1H), 5.30 (d, *J* = 12.2 Hz, 1H), 5.91 (s, 1H), 7.03 (dd, *J* = 4.9 and 3.7 Hz, 1H), 7.12-7.16 (m, 1H), 7.22-7.30 (m, 2H), 7.30-7.38 (m, 3H), 7.38-7.42 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 59.06, 69.93, 127.55, 127.66, 128.14, 128.39, 128.68, 128.94, 132.80, 133.68, 145.46, 148.35, 162.79.

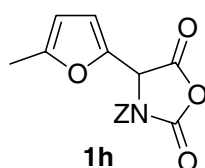


This product was obtained as a white solid in 74% yield from the corresponding racemic amino acid. m.p. 94-95 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.16 (d, *J* = 12.2 Hz, 1H), 5.26 (d, *J* = 12.2 Hz, 1H), 5.76 (s, 1H), 7.01 (dd, *J* = 4.9 and 1.2 Hz, 1H), 7.18-7.24 (m, 2H), 7.28-7.36 (m,

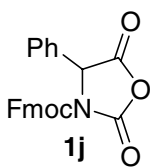
4H), 7.37 (dd, $J = 4.9$ and 3.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 59.16, 63.70, 124.89, 125.27, 127.90, 128.26, 128.64, 128.83, 131.26, 133.73, 145.99, 148.42, 163.41; IR (CHCl_3) ν 1876, 1802, 1748, 1496, 1456 cm^{-1} .



This product was obtained as a light yellow solid in 79% yield from the corresponding racemic amino acid. m.p. 107-108 °C ^1H NMR (400 MHz, CDCl_3) δ 5.21-5.32 (m, 2H), 5.73 (s, 1H), 6.40 (dd, $J = 3.2$ and 2.0 Hz, 1H), 6.54 (d, $J = 3.2$ Hz, 1H), 7.29-7.36 (m, 5H), 7.42 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100Hz, CDCl_3) δ 57.30, 69.80, 111.08, 112.67, 128.40, 128.66, 128.91, 133.76, 142.82, 144.34, 145.54, 148.31, 161.73; IR (CHCl_3) ν 1882, 1819, 1747, 1497, 1457, 1341 cm^{-1} .

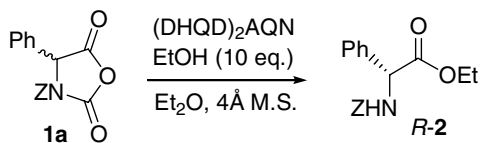


This product was obtained as a light yellow solid in 81% yield from the corresponding racemic amino acid. m.p. 121-122 °C ^1H NMR (400 MHz, CDCl_3) δ 2.24(s, 3H), 5.19-5.31(m, 2H), 5.65(s, 1H), 5.97(d, $J = 3.2$ Hz, 1H), 6.40(d, $J = 3.2$ Hz, 1H), 7.30-7.36(m, 5H); ^{13}C NMR (100Hz, CDCl_3) δ 13.82, 57.81, 70.04, 107.43, 114.18, 128.72, 128.98, 129.22, 134.14, 141.00, 145.96, 148.67, 154.99, 162.33; IR (CHCl_3) ν 1881, 1818, 1847, 1559, 1457, 1386, 1340 cm^{-1} .



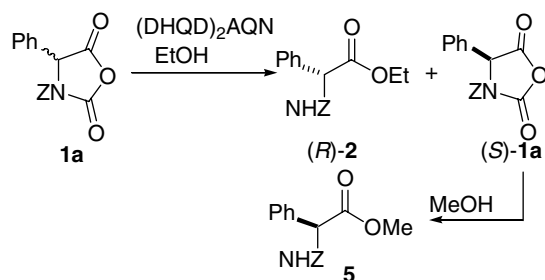
This product was obtained as a white solid in 75% yield from the corresponding racemic amino acid. m.p. 173-174 °C; ^1H NMR (400 MHz, actone- d_6) δ 4.24 (t, $J = 7.3$ Hz, 1H), 4.44 (dd, $J = 10.4$ and 7.3 Hz, 1H), 4.55 (dd, $J = 10.4$ and 7.3 Hz, 1H), 5.94 (s, 1H), 7.16-7.33 (m, 2H), 7.33-7.54 (m, 7H), 7.54-7.66 (m, 2H), 7.84 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR (100 MHz, actone- d_6) δ 47.20, 64.62, 70.28, 120.86, 120.91, 126.06, 126.17, 127.91, 128.06, 128.10, 128.75, 128.77, 130.14, 130.42, 133.72, 142.06, 144.06, 144.18, 147.62, 149.94, 166.00; IR (CHCl_3) ν 1868, 1810, 1733, 1506, 1456 cm^{-1} .

Cinchona Alkaloids-Catalyzed Kinetic Resolution of UNCA **1a** at Different Temperature (Table 1 in the text: Acceleration of Racemization Relative to Alcoholysis of UNCA **1a** by Increasing Reaction Temperature)



A mixture of UNCA **1a** (0.05 mmol) and 4Å molecular sieves (5 mg) in anhydrous diethyl ether (3.5 mL) was stirred at room temperature for 10 minutes, then cooled or heated to the temperature indicated in Table 1, after which $(\text{DHQD})_2\text{AQN}$ (0.01 mmol) was added to the mixture. The resulting mixture was stirred for another 5 minutes and then ethanol (0.50 mmol) was introduced in one portion (for entry 8, a 1.0% (v/v) solution of ethanol (0.06 mmol, 1.2 eq.) in ether was added in one hour). The resulting reaction mixture was stirred at the indicated temperature.

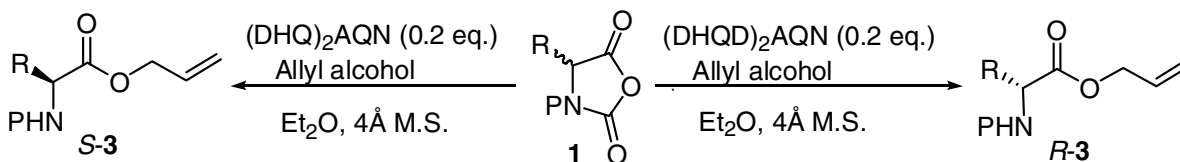
General Procedure for the Determination of the Conversion of Kinetic Resolution of UNCA 1a and the Enantiomeric Ratio of Ethyl Amino Ester 2



UNCAs (**1**) are found to be unstable toward conditions for GC and HPLC analysis. The conversion of the reaction was determined by converting the unreacted **1a** into ester **5** and subsequently GC analysis of the resulting mixture of ester **2** and **5** as following: A small aliquot (50 μL) of the reaction mixture was added to dry methanol (200 μL). The resulting mixture was stood at r.t. for 15min, then was allowed to pass through a plug of silica gel with ether as the eluent. The resulting solution of esters **2** and **5** was concentrated and then subjected to GC analysis (HP-5 column, 200 $^{\circ}\text{C}$, 4 min., 10 $^{\circ}\text{C}/\text{min}$ to 250 $^{\circ}\text{C}$, 250 $^{\circ}\text{C}$, 8 min).

The enantiomeric ratio of amino esters **2** was determined by HPLC analysis following conditions: Regis (*R,R*)-Whelk-O1, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm, $t(\text{major}) = 12.40$ min, $t(\text{minor}) = 19.47$ min.

General Procedure for Cinchona Alkaloids-Catalyzed Dynamic Kinetic Resolution of UNCAs 1 (Table 2 in the text)

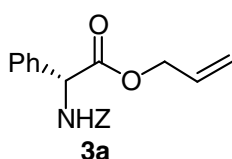


A mixture of UNCA **1** (0.20 mmol) and 4 \AA molecular sieves (20 mg) in anhydrous diethyl ether (14.0 mL) was stirred at room temperature for 10 minutes (cooled or warmed to the temperature indicated in Table 2 when necessary), after which the (DHQD)₂AQN or (DHQ)₂AQN (0.040 mmol) was added to the mixture. The resulting mixture was stirred for another 5 minutes and then a solution of allyl alcohol in ether (1.0%, v/v, 0.24 mmol) was introduced dropwise via a syringe over a period of 1 h (for entries 7, 8 and the alcoholysis of **2i** with (DHQ)₂AQN in entry 9, the addition time is 10 minutes). The resulting reaction mixture was stirred at the indicated temperature. The reaction went to completion in 0.5 - 2 h, the reaction mixture was washed with aq. HCl (2.0 N, 2 x 3.0 mL, these acidic aqueous phases were subjected to further treatment as described below for catalyst recovery) and brine (3.0 mL), dried (Na₂SO₄), and concentrated to provide desired crude product **3** in NMR-pure form (> 95% purity) and quantitative yield. The light yellow solid or oil **3** was further purified by flash

chromatography (Ethyl Acetate:Hexanes = 1:9) to give a white solid (**3a-f**, **3j**) or colorless oil (**3g-i**) in yields indicated in Table 2.

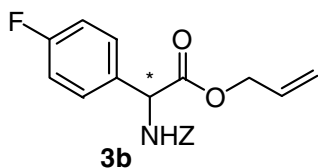
For catalyst recovery, the acidic aqueous phases were combined and washed with ether (2 x 2.0 mL) and basified with KOH to adjust the pH value to approximately 4, then with Na₂CO₃ to 11. The resulting mixture was extracted with ethyl acetate (2 x 5.0 mL). The combined extract was washed with brine (2.0 mL), dried (Na₂SO₄) and concentrated to give the recovered catalyst in NMR pure form and in quantitative yield.

The absolute configurations of amino esters **3a**, **3c**, **3e**, **3f** and **3j** were determined by comparing the optical rotation value of their corresponding acids **4a**, **4c**, **4e**, **4f** and **4j** with literature value. For experimental details of transformation of amino ester **3** to amino acid **4**, see page 12.



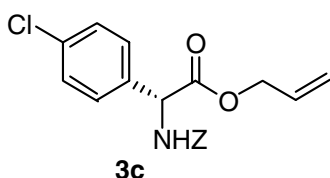
(R)-Allyl-(N-Benzyloxycarbonyl)phenylglycinate (3a):

This product was obtained as a white solid in 97% isolated yield and 91% ee as determined by HPLC analysis [Regis (*R,R*)Whelk-O1, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm, t(major) = 13.04 min, t(minor) = 21.68 min]. $[\alpha]_D = -74.2^\circ$ (c 1.42, CHCl₃); m.p. 85-86 °C; ¹H NMR (400 MHz, CDCl₃, 10:1 mixture of rotamers) δ 4.48-4.68 (m, 2H), 5.00-5.22 (m, 4H), 5.40 (d, *J* = 7.3 Hz, 1H), 5.72-5.90 (m, 2H), 7.20-7.44 (m, 10H); ¹H NMR (minor rotamer, partial) δ 5.22-5.32 (m, 1H), 5.64-5.72 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 58.00, 66.19, 67.12, 118.62, 127.13, 128.18, 128.52, 128.58, 128.93, 131.23, 136.13, 136.58, 155.35, 170.47; IR (CHCl₃) ν 3329, 1737, 1689, 1535, 1498, 1454 cm⁻¹; HRMS (EI) exact mass calcd for (C₁₉H₁₉NO₄+H⁺) requires m/z 326.1392, found m/z 326.1394.



(-)-Allyl-(N-Benzyloxycarbonyl)-*p*-fluorophenylglycinate (3b):

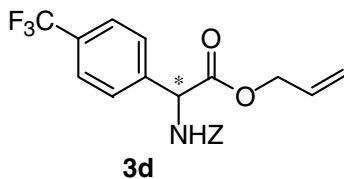
This product was obtained as a white solid in 96% isolated yield and 90% ee as determined by HPLC analysis [Regis (*R,R*)Whelk-O1, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm, t(major) = 8.87 min, t(minor) = 14.35 min]. $[\alpha]_D = -70.5^\circ$ (c 1.93, CHCl₃); m.p. 80-82 °C; ¹H NMR (400 MHz, CDCl₃) δ 4.52-4.66 (m, 2H), 5.06 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.14-5.24 (m, 2H), 5.34-5.42 (m, 1H), 5.72-5.86 (m, 1H), 5.88-5.98 (m, 1H), 6.98-7.08 (m, 2H), 7.24-7.40 (m, 7H); ¹³C NMR (100 MHz, CDCl₃) δ 57.22, 66.28, 67.12, 115.82 (d, *J* = 22.0 Hz), 118.78, 128.14, 128.21, 128.49, 128.88 (d, *J* = 8.4 Hz), 131.03, 132.52, 135.97, 155.21, 162.67 (d, *J* = 245.9 Hz), 170.23; IR (CHCl₃) ν 3336, 1736, 1686, 1531, 1453 cm⁻¹; HRMS (EI) exact mass calcd for (C₁₉H₁₈FNO₄+H⁺) requires m/z 344.1298, found m/z 344.1304.



(R)-Allyl-(N-Benzyloxycarbonyl)-*p*-chlorophenylglycinate (3c):

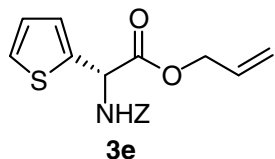
This product was obtained as a white solid in 97% isolated yield and 92% ee as determined by HPLC analysis [Regis (*R,R*)Whelk-O1, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm, t(major) = 9.48 min, t(minor) = 19.44 min]. $[\alpha]_D = -81.2^\circ$ (c

2.01, CHCl₃); m.p. 83-85 °C; ¹H NMR (400 MHz, CDCl₃) δ 4.02-4.18 (m, 2H), 5.05 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 5.14-5.24 (m, 2H), 5.32-5.40 (m, 1H), 5.72-5.86 (m, 1H), 5.92-6.00 (m, 1H), 7.22-7.40 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 57.27, 66.37, 67.15, 118.91, 128.14, 128.22, 128.46, 128.48, 129.03, 130.95, 134.43, 135.19, 135.92, 155.19, 169.99; IR (CHCl₃) ν 3329, 1736, 1687, 1531, 1492, 1454 cm⁻¹; HRMS (EI) exact mass calcd for (C₁₉H₁₈ClNO₄) requires m/z 359.0924, found m/z 359.0905.



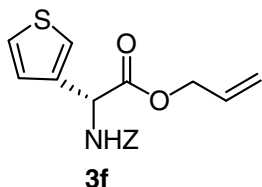
(-)-Allyl-(*N*-Benzyloxycarbonyl)-*p*-trifluoromethyl-phenylglycinate (3d):

This product was obtained as a white solid in 95% isolated yield and 90% ee as determined by chiral HPLC analysis [Regis (*R,R*)Whelk-O1, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm, t(major) = 8.99 min, t(minor) = 15.79 min]. [α]_D = -64.8° (c 1.10, CHCl₃); m.p. 104-105 °C; ¹H NMR (400 MHz, CDCl₃, 6.4:1 mixture of rotamers) δ 4.50-4.70 (m, 2H), 5.06 (d, *J* = 12.2 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 5.16-5.28 (m, 1H), 5.40-5.52 (m, 1H), 5.72-5.88 (m, 1H), 5.92-6.06 (m, 1H), 7.20-7.40 (m, 5H), 7.40-7.72 (m, 4H); ¹H NMR (minor rotamer, partial) δ 5.28-5.32 (m, 1H), 6.98-7.08 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 57.57, 66.63, 67.29, 119.18, 123.85 (q, *J* = 271.0 Hz), 125.87 (m), 127.49, 128.22, 128.33, 128.56, 130.73 (q, *J* = 32.7 Hz), 130.85, 135.88, 140.68, 155.20, 169.64; IR (CHCl₃) ν 3326, 1733, 1684, 1533, 1466 cm⁻¹; HRMS (EI) exact mass calcd for (C₂₀H₁₈F₃NO₄) requires m/z 393.1188, found m/z 393.1168.



(*R*)-Allyl-(*N*-Benzyloxycarbonyl)-2-thienylglycinate (3e):

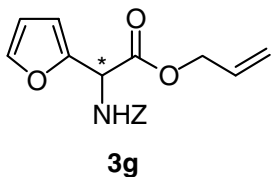
This product was obtained as a white solid in 93% isolated yield and 92% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm, t(major) = 25.94 min, t(minor) = 20.23 min]. [α]_D = -64.7° (c 2.00, CHCl₃); m.p. 54-55 °C; ¹H NMR (400 MHz, CDCl₃, 7:1 mixture of rotamers) δ 4.62-4.72 (m, 2H), 5.10 (d, *J* = 12.2 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 5.18-5.32 (m, 2H), 5.66-5.74 (m, 1H), 5.78-5.94 (m, 2H), 6.96 (dd, *J* = 4.9 and 3.5 Hz, 1H), 7.02-7.10 (m, 1H), 7.22-7.28 (m, 1H), 7.28-7.40 (m, 5H); ¹H NMR (minor rotamer, partial) δ 4.57-4.62 (m, 2H), 5.50-5.58 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 53.55, 66.50, 67.20, 118.96, 125.84, 126.13, 127.03, 128.11, 128.20, 128.48, 131.02, 135.92, 138.68, 155.22, 169.53; IR (CHCl₃) ν 3307, 1743, 1714, 1513, 1503, 1454 cm⁻¹; HRMS (EI) exact mass calcd for (C₁₆H₁₇NO₄S) requires m/z 331.0878, found m/z 331.0883.



(*R*)-Allyl-(*N*-Benzyloxycarbonyl)-3-thienylglycinate (3f):

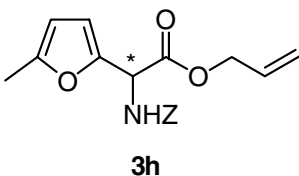
This product was obtained as a white solid in 95% isolated yield and 91% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm, t(major) = 33.96 min, t(minor) = 23.74 min]. [α]_D = -69.7° (c 1.91, CHCl₃); m.p. 70-71 °C; ¹H NMR (400 MHz, CDCl₃, 7:1 mixture of rotamers) δ 4.60-4.68 (m, 2H), 5.11 (s, 2H), 5.14-5.26 (m, 2H), 5.50-5.56 (m, 1H), 5.72-5.90 (m, 2H), 7.08 (d, *J* = 4.9 Hz, 1H), 7.20-7.40 (m, 7H); ¹H NMR (minor rotamer, partial) δ 4.54-4.60 (m, 2H), 5.38-5.44 (m, 1H), 5.56-5.64 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 53.79, 66.23, 67.11, 118.79,

123.12, 126.10, 126.69, 128.12, 128.18, 128.48, 131.16, 136.01, 136.60, 155.36, 170.15; IR (CHCl₃) ν 3308, 1740, 1686, 1536, 1500, 1453 cm⁻¹; HRMS (EI) exact mass calcd for (C₁₆H₁₇NO₄S+H⁺) requires m/z 332.0956, found m/z 332.0966.



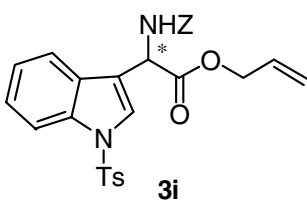
(-)-Allyl-(N-Benzylloxycarbonyl)-2-furylglycinate (3g):

This product was obtained as a colorless oil in 98% isolated yield and 91% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA, 80:20, 1.0 ml/min, λ 220 nm, t(minor) = 15.78 min, t(major) = 36.38 min]. $[\alpha]_D = -71.8^\circ$ (c 1.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 4.66 (d, J = 5.6 Hz, 1H), 5.08-5.14 (m, 2H), 5.19-5.25 (m, 2H), 5.55 (d, J = 8 Hz, 1H), 5.79 (d, J = 7.2 Hz, 1H), 5.81-5.88 (m, 1H), 6.33-6.36 (m, 2H), 7.28-7.36 (m, 5H); ¹³C NMR (100MHz, CDCl₃) δ 52.00, 66.42, 67.20, 108.62, 110.64, 118.67, 128.09, 128.18, 128.47, 131.11, 135.98, 142.84, 148.56, 155.40, 168.44; IR (CHCl₃) ν 1727, 1718, 1505, 1457, 1454 cm⁻¹; HRMS (EI) exact mass calcd for (C₁₇H₁₇NO₅+H⁺) requires m/z 316.1185, found m/z 316.1186.



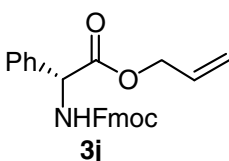
(-)-Allyl-(N-Benzylloxycarbonyl)-5-methyl-2-furylglycinate (3h):

This product was obtained as a colorless oil in 97% isolated yield and 93% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA 90:10, 1.0 ml/min, λ 220 nm, t (minor) = 17.54min, t (major) = 21.64 min]. $[\alpha]_D = -71.4^\circ$ (c 1.75, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 2.23 (s, 3H), 4.65 (d, J = 5.6 Hz, 2H), 5.10 (s, 2H), 5.24 (m, 2H), 5.48 (d, J = 8.0 Hz, 1H), 5.80 (d, 1H, J = 8 Hz), 5.83-5.90 (m, 1H), 5.94 (d, J = 2.4 Hz, 1H), 6.23 (d, J =2.4Hz, 1H), 7.27-7.34 (m, 5H); ¹³C NMR (100MHz, CDCl₃) δ 13.38, 52.07, 66.20, 67.04, 106.51, 109.41, 118.03, 128.02, 128.07, 128.39, 131.18, 135.99, 146.48, 152.63, 155.35, 168.63; IR (CHCl₃) ν 1723, 1506, 1455, 1317, 1454 cm⁻¹; HRMS (FAB) exact mass calcd for (C₁₈H₁₉NO₅⁺) requires m/z 329.1263, found m/z 329.1256.



(-)-Allyl-(N-benzylloxycarbonyl)-1-tosyl-3-indoleglycinate (3i):

This product was obtained as a colorless oil in 95% isolated yield and 90% ee as determined by HPLC analysis [Regis (R,R) Whelk-O1, Hexanes:IPA, 70:30, 0.8 mL/min, λ 254 nm, t (major) = 24.75 min, t (minor) = 36.14 min]. $[\alpha]_D = -44.1^\circ$ (c 1.06, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 2.34 (s, 3H), 4.65 (s, 2H), 5.08-5.15 (m, 2H), 5.17-5.22 (m, 2H), 5.67 (s, 2H), 5.76-5.86 (m, 1H), 7.21-7.35 (m, 9H), 7.59 (s, 1H), 7.62(d, J = 7.6 Hz, 1H), 7.74 (d, J = 8 Hz, 2H), 7.95 (d, J = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ ; IR (CHCl₃) ν 3031, 2954, 2359, 1725, 1448 cm⁻¹; HRMS (EI) exact mass calcd for (C₂₈H₂₆N₂O₆⁺) requires m/z 518.1512, found m/z 518.1499.

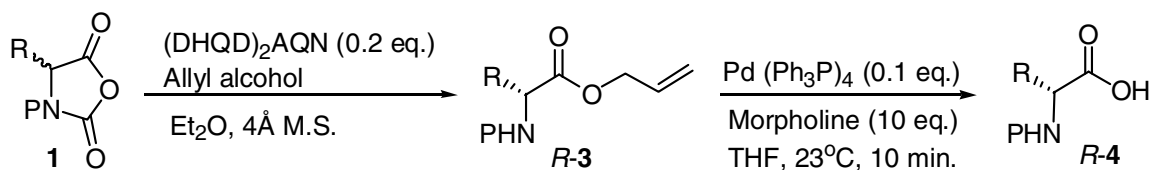


(R)-Allyl-(N-9-Fluorenylmethoxycarbonyl)phenylglycinate (3j):

This product was obtained as a white solid in 98% isolated yield and 90% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA, 80:20, 1.0 mL/min, λ 254 nm, t(major) = 28.99 min, t(minor) = 18.96 min]. $[\alpha]_D = -65.5^\circ$ (c 1.29, CHCl₃); m.p. 100-102

°C; ^1H NMR (400 MHz, CDCl_3 , 13:1 mixture of rotamers) δ 4.18-4.26 (m, 1H), 4.32-4.48 (m, 2H), 4.56-4.72 (m, 2H), 5.10-5.26 (m, 2H), 5.41 (d, $J = 7.8$ Hz, 1H), 5.72-5.84 (m, 1H), 5.84-5.94 (m, 1H), 7.24-7.46 (m, 9H), 7.58 (d, $J = 7.0$ Hz, 2H), 7.76 (d, $J = 7.0$ Hz, 2H); ^1H NMR (minor rotamer, partial) δ 4.08-4.18 (m, 2H), 7.16-7.24 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 47.12, 57.99, 66.24, 67.14, 118.67, 119.95, 125.05, 127.05, 127.15, 127.68, 128.61, 128.96, 131.20, 136.52, 141.27, 143.70, 155.35, 170.53; IR (CHCl_3) ν 3326, 1740, 1697, 1529, 1497, 1450 cm^{-1} ; HRMS (EI) exact mass calcd for ($\text{C}_{26}\text{H}_{23}\text{NO}_4 + \text{H}^+$) requires m/z 414.1705, found m/z 414.1706.

General Procedure of Transformation of Amino Ester **3** to Amino Acid **4**⁵



A mixture of UNCA **1** (0.20 mmol) and 4 Å molecular sieves (20 mg) in anhydrous diethyl ether (14.0 mL) was stirred at room temperature for 10 minutes, then cooled to the temperature indicated in Table 2, after which the $(\text{DHQD})_2\text{AQN}$ (0.040 mmol) was added to the mixture. The resulting mixture was stirred for another 5 minutes and then a solution of allyl alcohol in ether (1.0%, v/v, 0.24 mmol) was introduced dropwise via a syringe over a period of 1 h (for entry 7, 8, the addition time is 10 minutes). The resulting reaction mixture was stirred at the indicated temperature. When the reaction went to completion, the reaction mixture was washed with aq. HCl (2 N, 2 x 3.0 mL) and brine (3.0 mL), dried (Na_2SO_4), and concentrated to provide desired crude product **3** in NMR-pure form and quantitative yield. This crude product was dried *in vacuo* and used in the next step without further purification.

To a solution of crude amino ester **3** in dry THF at r.t., $\text{Pd}(\text{PPh}_3)_4$ (0.02 mmol, 0.1 eq.) was added. The resulting mixture was treated with morpholine (2.0 mmol, 10 eq., in transformation of **3j** to **4j**, 1.5 eq. of morpholine was used). After 10 minutes, the solvent was removed, the residue was taken up in CH_2Cl_2 (2.0 mL).

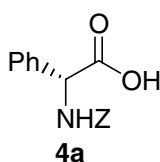
For substrates **3a-3h**, the resulting solution was washed with aq. HCl (2N, 2 x 2.0 mL) and water (2.0 mL), extracted with aq. Na_2CO_3 (1N, 2 x 3.0 mL). The basic aq. phases were combined, acidified with conc. HCl till $\text{pH} < 3$, extracted with ethyl acetate (2 x 5.0 mL). The organic phases were combined and washed with brine (2.0 mL), dried (Na_2SO_4), concentrated to give **4a-4h**.

For substrates **3i** and **3j**, the resulting solution was washed with aq. HCl (2N, 2 x 2.0 mL), dried (Na_2SO_4), concentrated. The resultant residue was purified by flash chromatography (Ethyl Ether:Hexanes:Acetic Acid = 1:1:0.01) to give **4i** and **4j** respectively.

⁵ Kunz, H.; Waldmann, H. *Angew. Chem. Int. Ed.* **1984**, 23, 71.

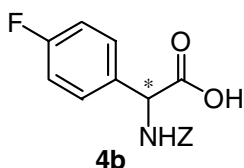
This procedure was used in a preparative scale transformation of (\pm)-UNCA **1h** (4.0 mmol) to amino acid **4h** in 94% overall yield and 91% ee.

The absolute configurations of amino acids **4a**, **4c**, **4e**, **4f** and **4j** were determined by comparing the optical rotation value with literature value.



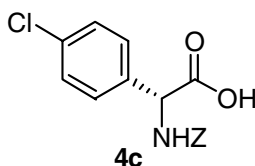
(R)-(N-Benzyloxycarbonyl)phenylglycine (4a):

This product was obtained as a white solid in 91% isolated yield and 90% ee as determined by HPLC analysis [Daicel chiralpak OJ, Hexanes:IPA:TFA, 75:25:0.1, 1.0 mL/min, λ 220 nm, t(major) = 9.12 min, t(minor) = 12.23 min]. $[\alpha]_D = -109.2^\circ$ (c = 1.06, 95% EtOH); (Literature,⁶ $[\alpha]_D = +116.4^\circ$ (c = 1, 95% EtOH), for *S*-enantiomer).



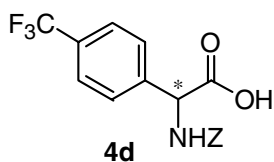
(-)-(N-Benzyloxycarbonyl)-p-fluorophenylglycine (4b):

This product was obtained as a white solid in 93% isolated yield and 90% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA:TFA, 90:10:0.1, 1.0 mL/min, λ 220 nm, t(major) = 23.00 min, t(minor) = 9.35 min]. $[\alpha]_D = -105.1^\circ$ (c = 1.14, EtOH).



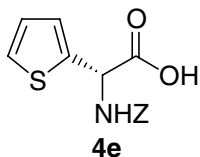
(R)-(N-Benzyloxycarbonyl)-p-chlorophenylglycine (4c):

This product was obtained as a white solid in 92% isolated yield and 92% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA:TFA, 90:10:0.1, 1.0 mL/min, λ 220 nm, t(major) = 20.45 min, t(minor) = 10.73 min]. $[\alpha]_D = -93.1^\circ$ (c = 1.18, EtOH); (Literature,⁷ $[\alpha]_D^{25} = +116.0^\circ$ (c = 1.0, EtOH), for *S*-enantiomer).



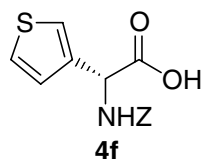
(-)-(N-Benzyloxycarbonyl)-p-trifluoromethyl-phenylglycine (4d):

This product was obtained as a white solid in 88% isolated yield and 90% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA:TFA, 85:15:0.1, 1.0 mL/min, λ 220 nm, t(major) = 7.36 min, t(minor) = 11.94 min]. $[\alpha]_D = -85.4^\circ$ (c = 1.25, EtOH).



(R)-(N-Benzyloxycarbonyl)-2-thienylglycine (4e):

This product was obtained as a light yellow solid in 93% isolated yield and 92% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA:TFA, 60:40:0.1, 0.7 mL/min, λ 220 nm, t(major) = 14.36 min, t(minor) = 8.54 min]. $[\alpha]_D = -75.9^\circ$ (c = 1.00, EtOH); (Literature,⁸ (-), for *R*-enantiomer).



(R)-(N-Benzyloxycarbonyl)-3-thienylglycinate (4f):

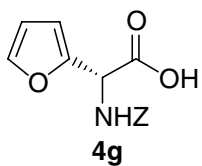
This product was obtained as a white solid in 94% isolated yield and 91% ee as determined by HPLC analysis [Daicel chiralpak OD,

⁶ Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207.

⁷ Schon, I.; Kisfaludy, L.; Nafradi, J.; Varga, L.; Vafro, V. *Hoppe-Seyler's Z. Physiol. Chem.* **1978**, 897.

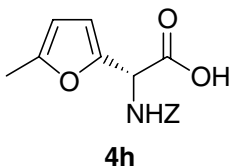
⁸ Crast, L. B. Jr.; Essery, J. M. U.S. Patent 3,352,858, (1967).

Hexanes:IPA:TFA, 75:25:0.1, 1.0 mL/min, λ 220 nm, $t(\text{major}) = 18.84$ min, $t(\text{minor}) = 8.31$ min]. $[\alpha]_D = -88.2^\circ$ ($c = 1.25$, EtOH); (Literature,⁹ (-), for *R*-enantiomer).



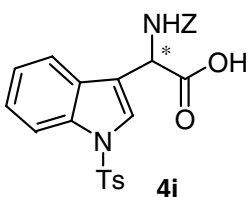
(-)-(N-Benzyloxycarbonyl)-2-furylglycine (4g):

This product was obtained as a light yellow solid in 86% isolated yield and 89% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA:TFA, 80:20:0.1, 0.75 mL/min, λ 220 nm, $t(\text{major}) = 23.61$ min, $t(\text{minor}) = 6.83$ min]. $[\alpha]_D = -64.1^\circ$ ($c = 0.80$, CHCl_3).



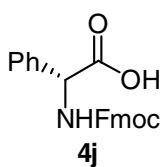
(-)-(N-Benzyloxycarbonyl)-5-methyl-2-furylglycine (4h):

This product was obtained as a light yellow solid in 92% isolated yield and 91% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA:TFA, 80:20:0.1, 1.00 mL/min, λ 220 nm, $t(\text{major}) = 13.30$ min, $t(\text{minor}) = 6.40$ min]. $[\alpha]_D = -30.8^\circ$ ($c = 0.70$, CHCl_3).



(-)-(N-Benzyloxycarbonyl)-1-tosyl-3-indoleglycine (4i):

This product was obtained as a light yellow solid in 95% isolated yield and 89% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA:TFA, 80:20:0.1, 1.00 mL/min, λ 254 nm, $t(\text{major}) = 14.43$ min, $t(\text{minor}) = 10.66$ min]. $[\alpha]_D = -28.8^\circ$ ($c = 1.60$, CHCl_3).



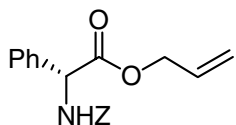
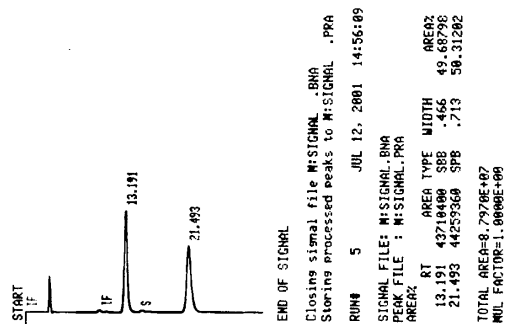
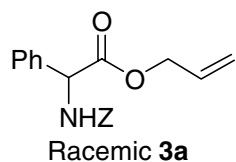
(*R*)-(N-9-Fluorenylmethoxycarbonyl)phenylglycine (4j):

This product was obtained as a light yellow solid in 92% isolated yield and 90% ee as determined by HPLC analysis [Daicel chiralpak OD, Hexanes:IPA:TFA, 75:25:0.1, 1.0 mL/min, λ 254 nm, $t(\text{major}) = 10.84$ min, $t(\text{minor}) = 8.42$ min]. $[\alpha]_D = -75.4^\circ$ ($c = 0.70$, MeOH); (Literature,¹⁰ $[\alpha]_D^{28} = -86.9^\circ$ ($c = 1.0$, MeOH), for *R*-enantiomer).

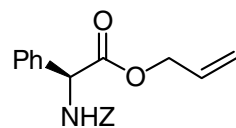
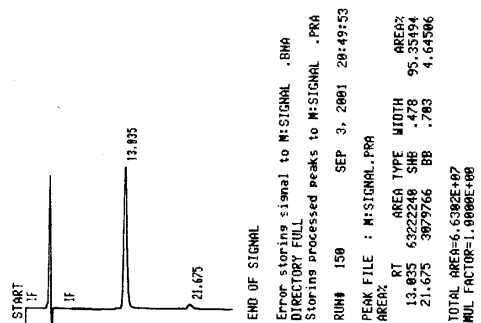
⁹ McGregor, D. N. U.S. Patent 3,579,514, (1971).

¹⁰ Ranu, B. C.; Sarkar, D. C. *J. Org. Chem.* **1988**, *53*, 878.

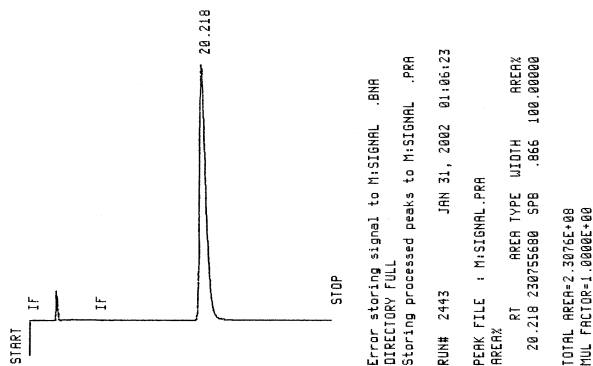
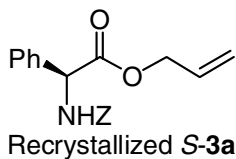
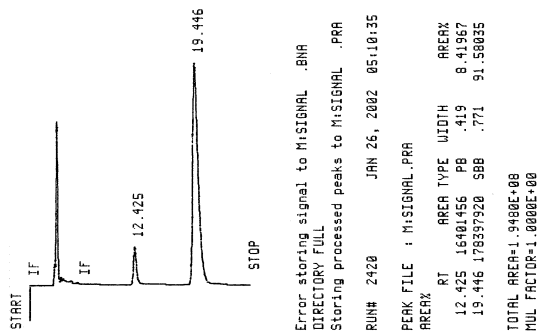
Regis (*R,R*)Whelk-O1, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm



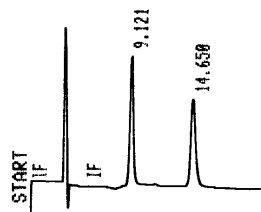
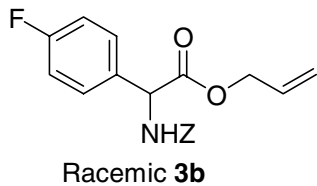
R-**3a** obtained from reaction with (DHQD)₂AQN



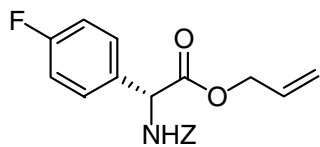
S-**3a** obtained from reaction with (DHQ)₂AQN



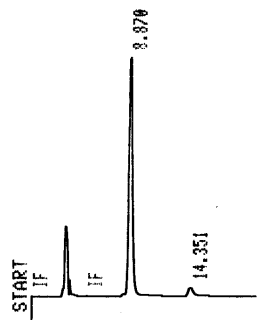
Regis (*R,R*)Whelk-O1, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm



STOP
Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 217 SEP 21, 2001 18:48:26
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA%
9.121 13683632 PB .336 49.51251
14.650 13953088 BB .502 50.48749
TOTAL AREA=2.7637E+07
MUL FACTOR=1.0000E+00

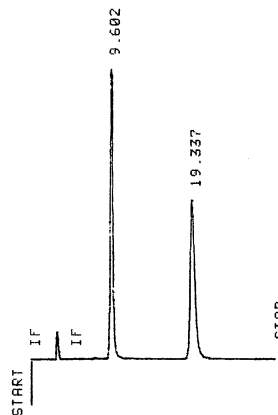
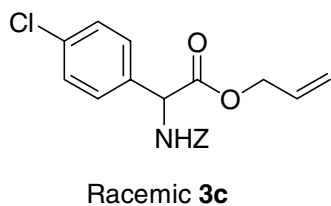


(-)-**3b** obtained from reaction
with (DHQD)₂AQN

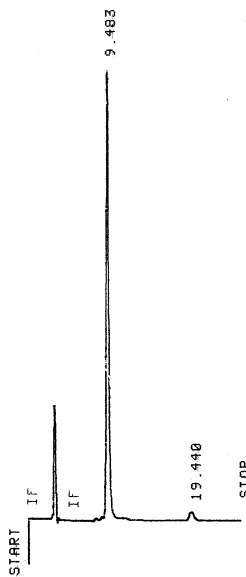
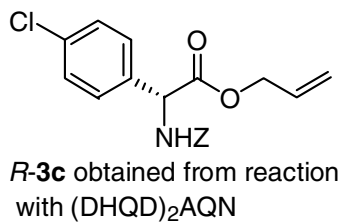


END OF SIGNAL
Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 222 SEP 22, 2001 19:05:18
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA%
8.870 105681800 SB .349 95.04886
14.351 5505024 BB .491 4.95115
TOTAL AREA=1.1119E+08
MUL FACTOR=1.0000E+00

Regis (*R,R*)Whelk-O1, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm

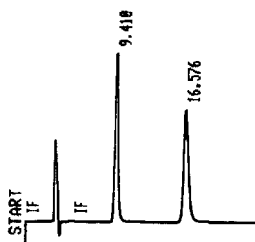
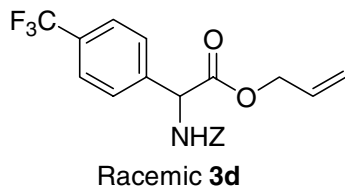


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 1472 AUG 20, 2001 05:49:19
PEAK FILE : M:SIGNAL.PRA
AREAX RT AREA TYPE WIDTH AREAX
9.602 84856192 SBB .358 49.80808
19.337 85518144 SBB .667 50.19192
TOTAL AREA=1.7037E+08
MUL FACTOR=1.0000E+00

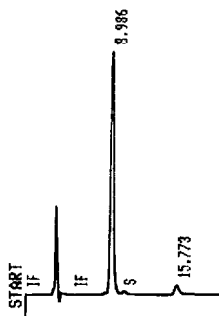
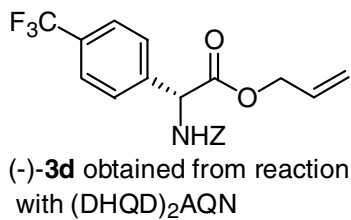


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 1665 SEP 16, 2001 23:33:20
PEAK FILE : M:SIGNAL.PRA
AREAX RT AREA TYPE WIDTH AREAX
9.483 62785920 SHB .348 95.96694
19.440 2638608 PB .660 4.03306
TOTAL AREA=6.5425E+07
MUL FACTOR=1.0000E+00

Regis (*R,R*)Whelk-O1, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm

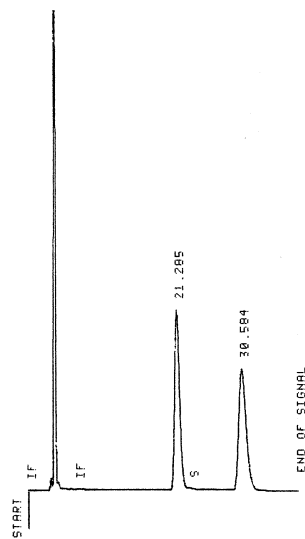
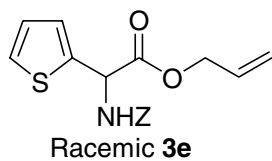


START
IF
IF
STOP
Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 162 SEP 6, 2001 14:47:46
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA%
9.418 4723206 SBB .383 49.67450
16.576 47851104 SBB .587 50.32550
TOTAL AREA=9.5983E+07
MUL FACTOR=1.0000E+00

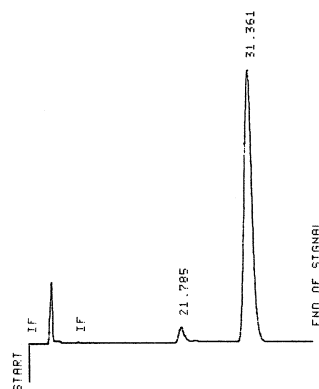
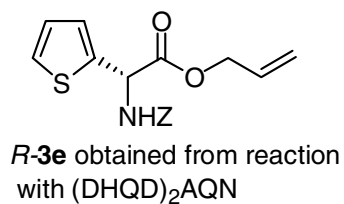


END OF SIGNAL
Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 170 SEP 8, 2001 22:00:04
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA%
8.986 139985600 SBB .394 94.86061
15.773 7584240 PB .549 5.13942
TOTAL AREA=1.4757E+08
MUL FACTOR=1.0000E+00

Daicel chiralpak OD, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm

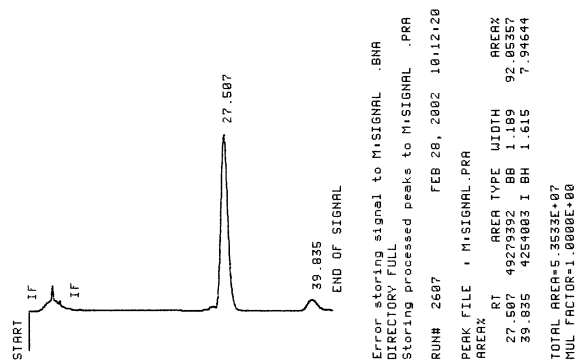
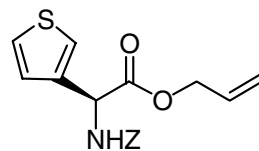
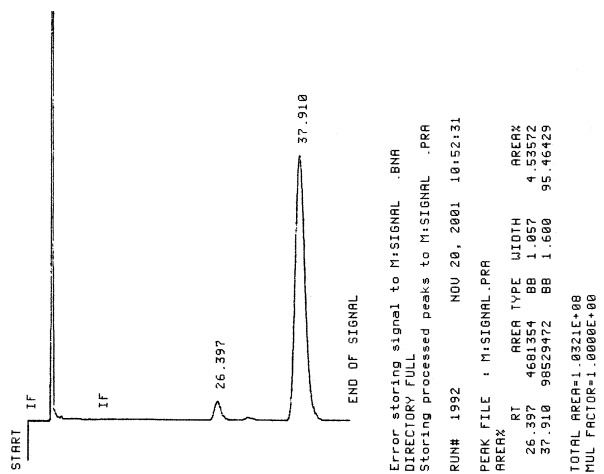
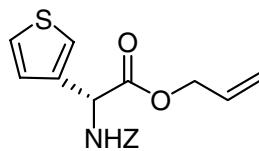
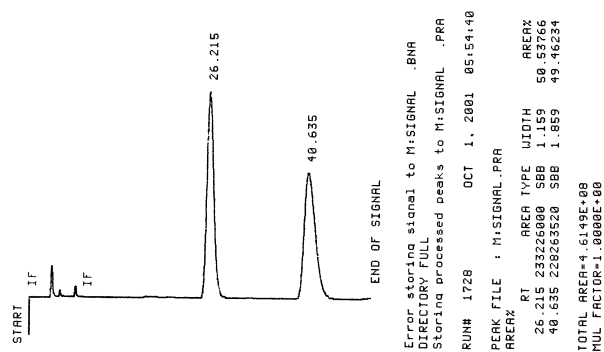
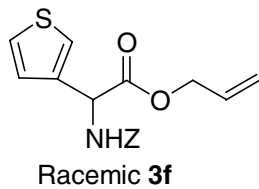


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 1910 NOV 8, 2001 04:13:24
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA
21.285 142791360 SPB 833 49.82397
30.584 143800320 SPB 1.240 50.17603
TOTAL AREA=2.8659E+08
MUL FACTOR=1.0000E+00

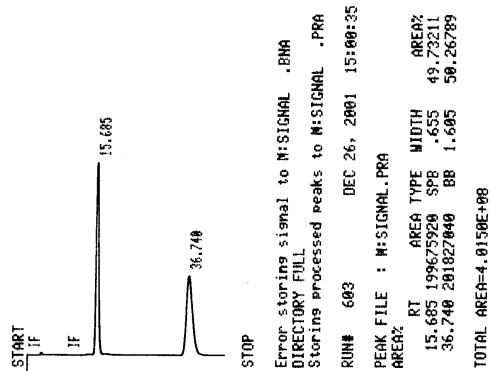
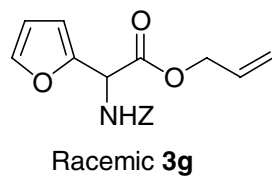


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 1909 NOV 7, 2001 23:55:57
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA
21.785 7030922 PB 971 4.00892
31.361 168350800 SB8 1.299 95.99110

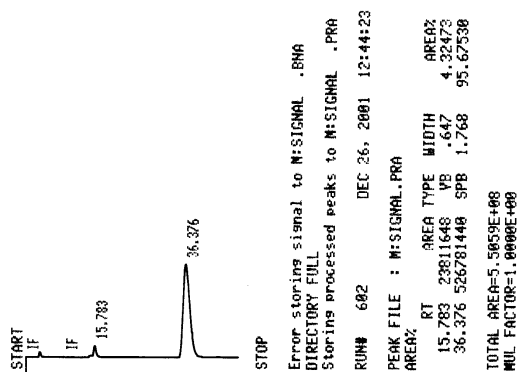
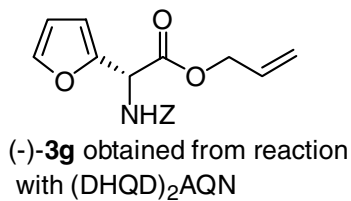
Daicel chiralpak OD, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm



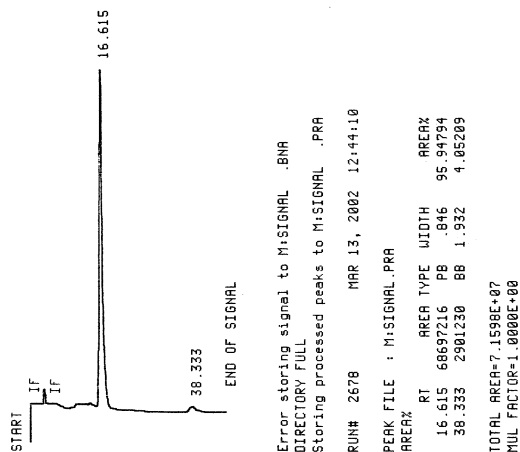
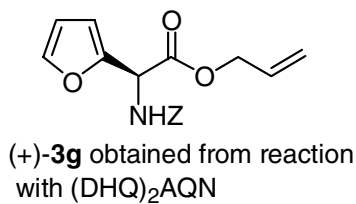
Daicel chiralpak OD, Hexanes:IPA, 80:20, 1.0 mL/min, λ 220 nm



Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 603 DEC 26, 2001 15:00:35
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH SPB BB
15.685 199675920 49.73211 1.655 1.605 50.26789
36.740 201827040 50.26789 1.605 1.605 50.26789
TOTAL AREA=4.0150E+08

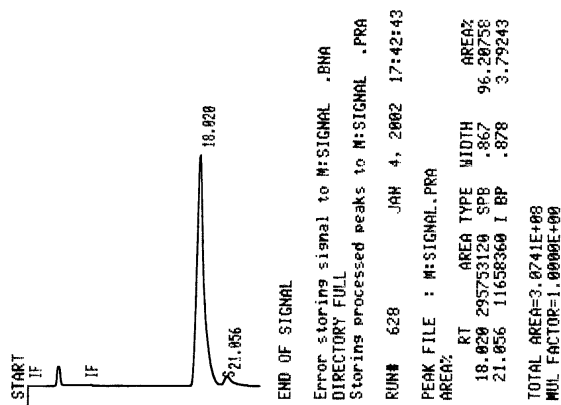
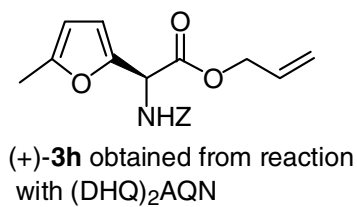
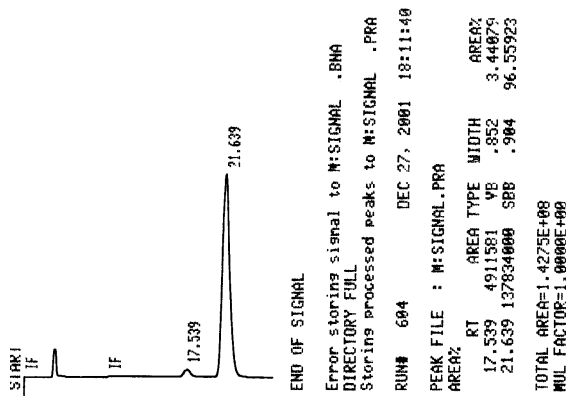
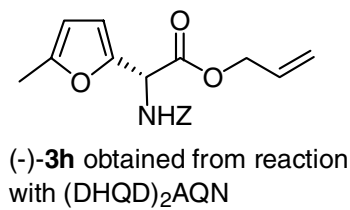
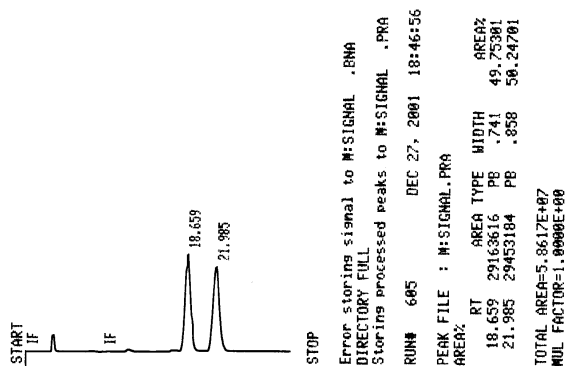
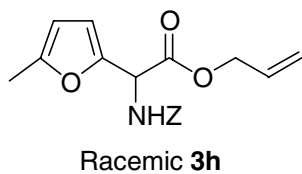


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 602 DEC 26, 2001 12:44:23
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH SPB BB
15.783 23811648 4.32473 1.647 1.768 95.67530
36.376 526781440 95.67530 1.768 1.768 95.67530
TOTAL AREA=5.5059E+08
MUL FACTOR=1.0000E+00

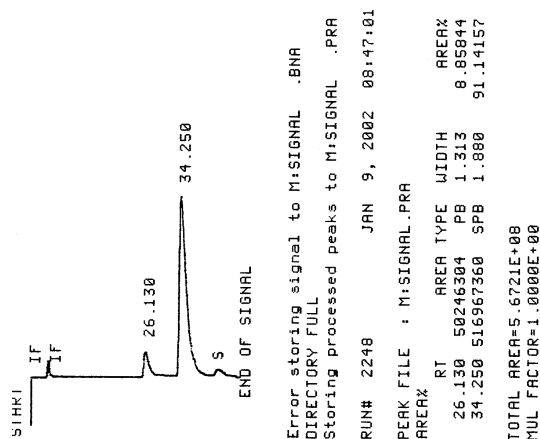
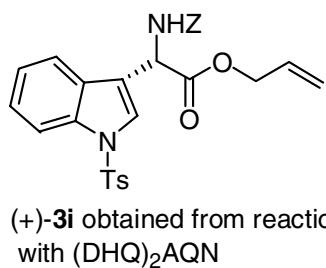
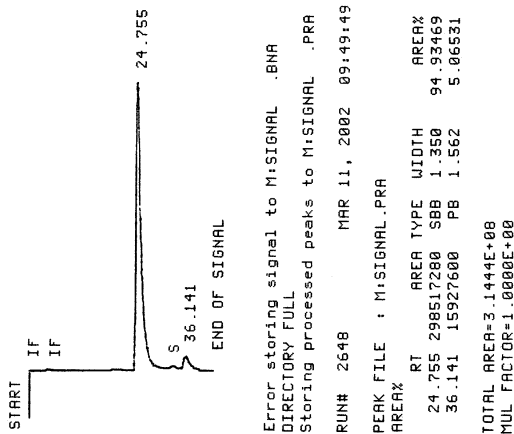
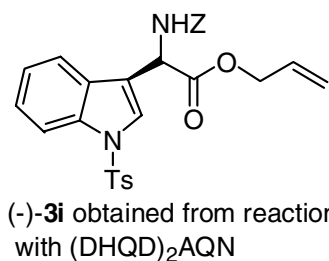
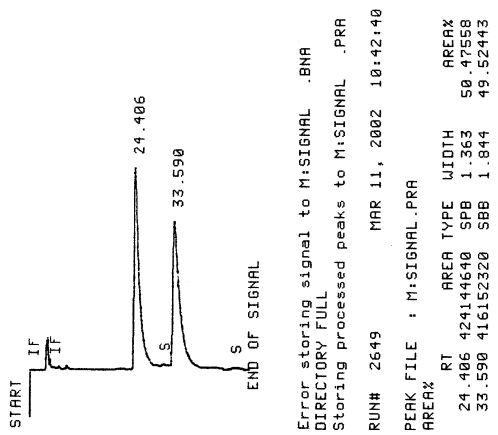
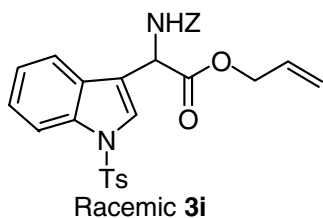


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 2678 MAR 13, 2002 12:44:10
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH SPB BB
16.615 66697216 95.94794 1.846 1.932 4.05209
38.333 2901230 4.05209 1.932 1.932 4.05209
TOTAL AREA=7.1598E+07
MUL FACTOR=1.0000E+00

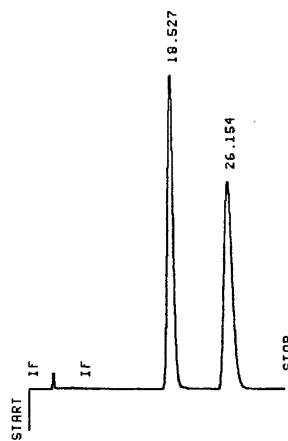
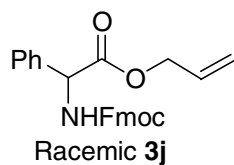
Daicel chiralpak OD, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm



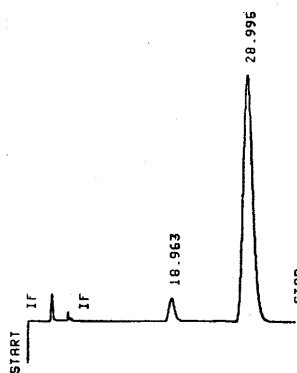
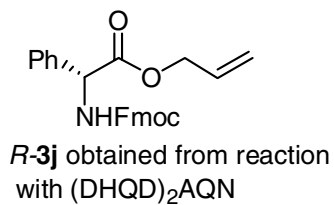
Regis (R,R)Whelk-O1, Hexanes:IPA, 70:30, 0.8 mL/min, λ 254 nm



Daicel chiralpak OD, Hexanes:IPA, 80:20, 1.0 mL/min, λ 254 nm

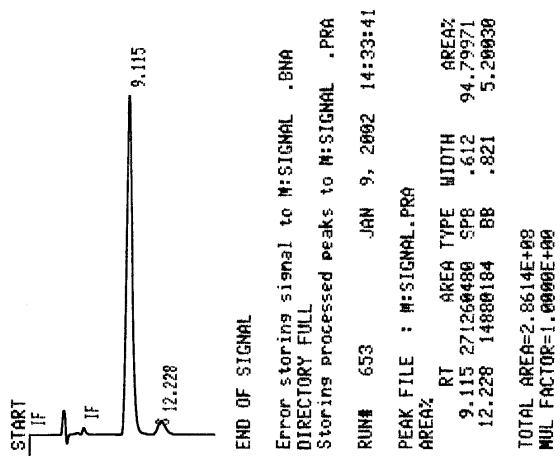
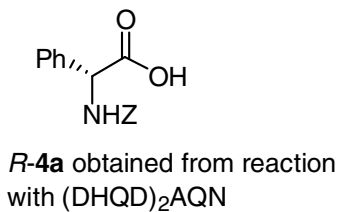
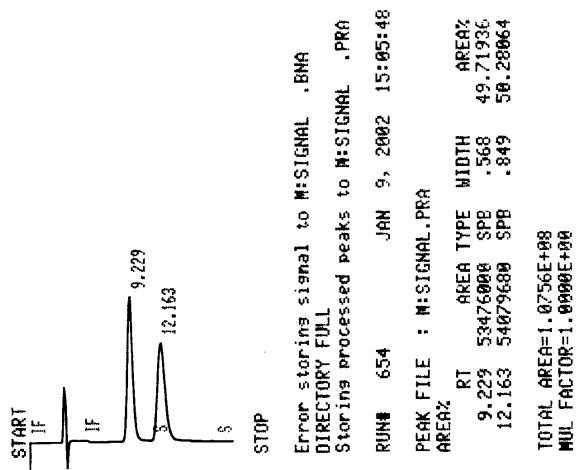
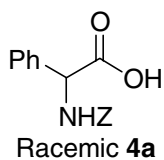


Closing signal file M:\SIGNAL .BNC
Storing processed peaks to M:\03032893.PRO
DIRECTORY FULL
RUN# 1603 SEP 6, 2001 21:45:54
SIGNAL FILE: M:\SIGNAL.BNC
PEAK FILE: M:\03032893.PRO
AREA# RT AREA TYPE WIDTH AREA#
18.527 119122040 BB .861 58.21759
26.154 118089800 BB 1.291 49.78213
TOTAL AREA=2.3721E+08
MUL FACTOR=1.0000E+00

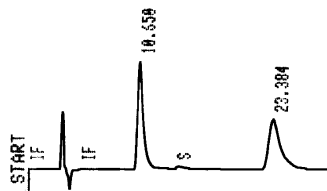
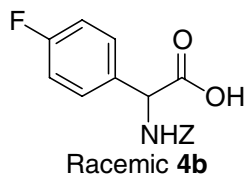


Closing signal file M:\SIGNAL .BNC
Storing processed peaks to M:\0303290C.PRO
DIRECTORY FULL
RUN# 1595 SEP 6, 2001 03:26:17
SIGNAL FILE: M:\SIGNAL.BNC
PEAK FILE: M:\0303290C.PRO
AREA# RT AREA TYPE WIDTH AREA#
18.963 8824269 BB .862 5.23477
20.995 159746000 ISPH 1.472 94.76522
TOTAL AREA=1.6857E+08
MUL FACTOR=1.0000E+00

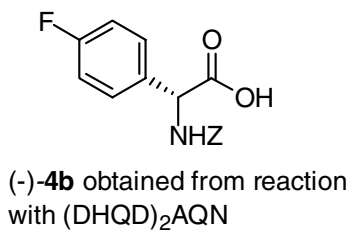
HPLC Conditions: Chiralpak OJ, Hexanes:IPA:TFA, 75:25:0.1, 1.0 mL/min, λ 220 nm



HPLC Conditions: Chiralpak OD, Hexanes:IPA:TFA, 90:10:0.1, 1.0 mL/min, λ 220 nm

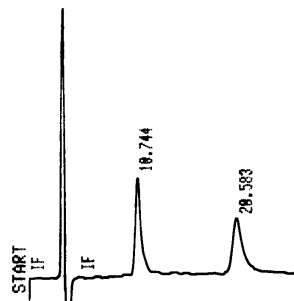
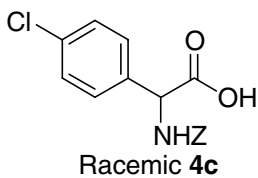


STOP
Closing signal file M:SIGNAL.BNC
Storing processed peaks to M:03E1FE8B.PRO
DIRECTORY FULL
RUN# 671 JAN 10, 2002 23:06:51
SIGNAL FILE: M:SIGNAL.BNC
AREA% RT AREA TYPE WIDTH AREA2
10.650 44122944 SBB .612 50.27197
23.384 43645536 BB 1.308 49.72893
TOTAL AREA=8.7769E+07
MUL FACTOR=1.0000E+00

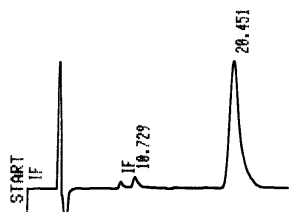
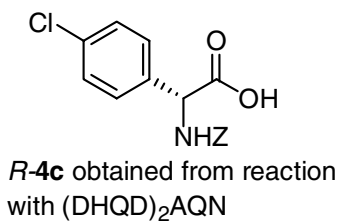


STOP
Closing signal file M:SIGNAL.BNC
Storing processed peaks to M:03E1F691.PRO
DIRECTORY FULL
RUN# 670 JAN 10, 2002 22:32:49
SIGNAL FILE: M:SIGNAL.BNC
AREA% RT AREA TYPE WIDTH AREA2
9.352 6746608 BV .475 3.61147
23.005 180064080 ISBH 1.457 96.38854
TOTAL AREA=1.8681E+08
MUL FACTOR=1.0000E+00

HPLC Conditions: Chiralpak OD, Hexanes:IPA:TFA, 90:10:0.1, 1.0 mL/min, λ 220 nm

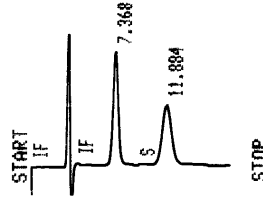
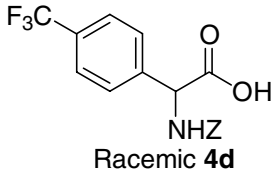


END OF SIGNAL
Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 668 JAN 10, 2002 18:46:45
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA%
18.744 10556336 BB .629 49.32317
20.303 10846256 BB 1.129 50.67685
TOTAL AREA=2.1403E+07
MUL FACTOR=1.0000E+00

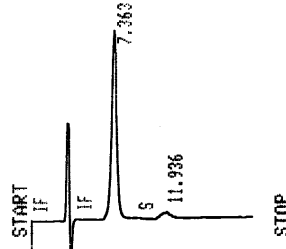
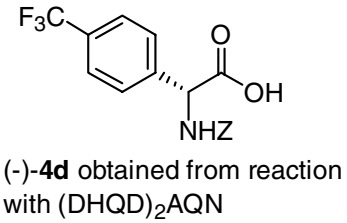


END OF SIGNAL
Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 667 JAN 10, 2002 18:11:35
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA%
10.729 2159710 BB .595 4.00205
20.451 51805376 BY 1.172 95.99795
TOTAL AREA=5.3965E+07
MUL FACTOR=1.0000E+00

HPLC Conditions: Chiralpak OD, Hexanes:IPA:TFA, 85:15:0.1, 1.0 mL/min, λ 220 nm

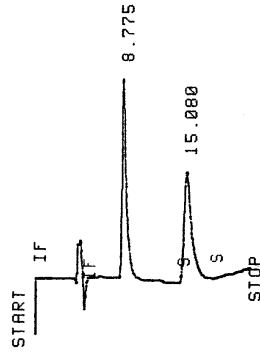
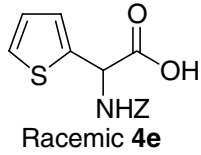


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 686 JAN 14, 2002 17:56:08
PEAK FILE : M:SIGNAL.PRA
AREA%
RT AREA TYPE WIDTH AREA%
7.368 36331264 SBB .515 49.39570
11.884 37220096 BB 1.003 50.60422
TOTAL AREA=7.3551E+07
MUL FACTOR=1.0000E+00

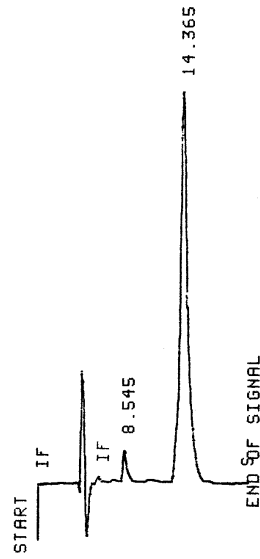
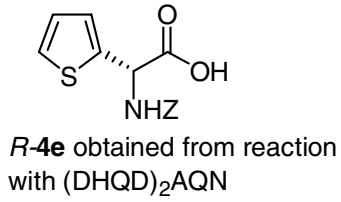


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 685 JAN 14, 2002 17:27:02
PEAK FILE : M:SIGNAL.PRA
AREA%
RT AREA TYPE WIDTH AREA%
7.363 61648672 SBB .520 94.79757
11.936 3383245 BB .921 5.20244
TOTAL AREA=6.5032E+07
MUL FACTOR=1.0000E+00

HPLC Conditions: Chiralpak OD, Hexanes:IPA:TFA, 60:40:0.1, 0.7 mL/min, λ 220 nm

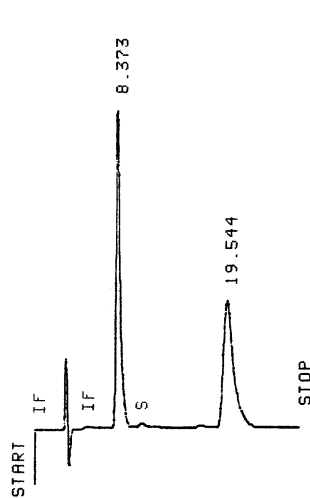
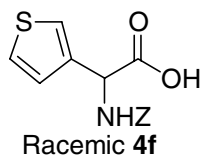


Error storing signal to M:SIGNAL .BNA
 DIRECTORY FULL
 Storing processed peaks to M:SIGNAL .PRA
 RUN# 2679 MAR 14, 2002 00:30:12
 PEAK FILE : M:SIGNAL.PRA
 AREA% RT AREA TYPE WIDTH AREA%
 8.775 63861728 SPB .481 50.13318
 15.080 63522464 SPB .866 49.86683
 TOTAL AREA=1.2738E+08
 MUL FACTOR=1.0000E+00

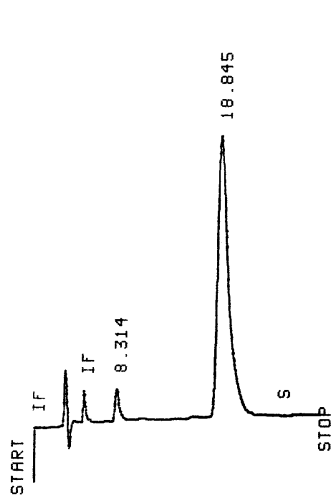
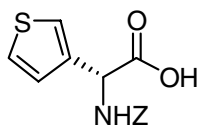


Error storing signal to M:SIGNAL .BNA
 DIRECTORY FULL
 Storing processed peaks to M:SIGNAL .PRA
 RUN# 2683 MAR 14, 2002 06:42:55
 PEAK FILE : M:SIGNAL.PRA
 AREA% RT AREA TYPE WIDTH AREA%
 8.545 5140563 UB .475 4.24627
 14.365 115920120 SBB .896 95.75373
 TOTAL AREA=1.2106E+08
 MUL FACTOR=1.0000E+00

HPLC Conditions: Chiralpak OD, Hexanes:IPA:TFA, 75:25:0.1, 1.0 mL/min, λ 220 nm

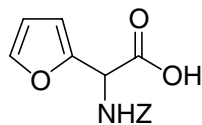


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 2673 MAR 13, 2002 02:31:45
PEAK FILE : M:SIGNAL.PRA
AREAX RT AREA TYPE WIDTH AREA%
8.373 101468520 SPB .472 49.73354
19.544 102555840 PB 1.196 50.26648
TOTAL AREA=2.0402E+08
MUL FACTOR=1.0000E+00

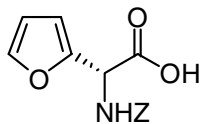
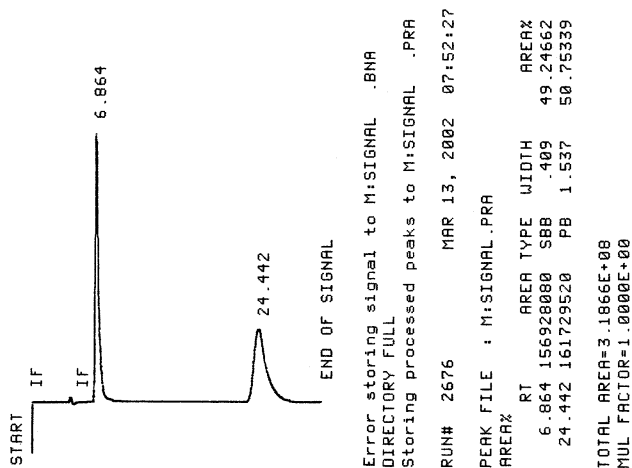


Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 2740 MAR 27, 2002 02:14:07
PEAK FILE : M:SIGNAL.PRA
AREAX RT AREA TYPE WIDTH AREA%
8.314 10977128 PB .504 4.31782
18.845 243251040 SBB 1.289 95.68218
TOTAL AREA=2.5423E+08
MUL FACTOR=1.0000E+00

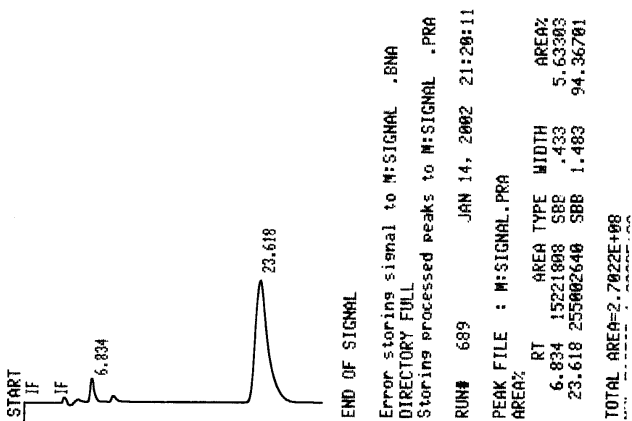
Daicel chiralpak OD, Hexanes:IPA:TFA, 80:20:0.1, 0.75 mL/min, λ 220 nm



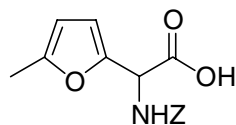
Racemic **4g**



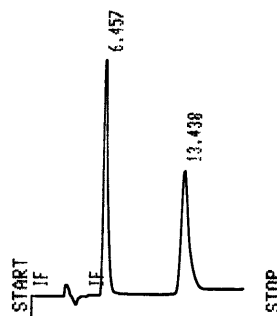
(-)-**4g** obtained from reaction with (DHQD)₂AQN



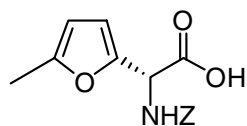
Daicel chiralpak OD, Hexanes:IPA:TFA, 80:20:0.1, 1.00 mL/min, λ 220 nm



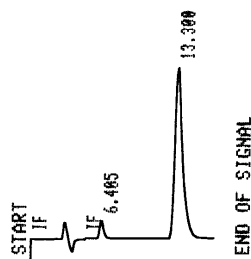
Racemic **4h**



Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 672 JAN 11, 2002 16:18:04
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA%
6.457 119941248 SBB .412 49.68554
13.438 121459520 SBB .808 50.31448
TOTAL AREA=2.4140E+08
MUL FACTOR=1.0000E+00

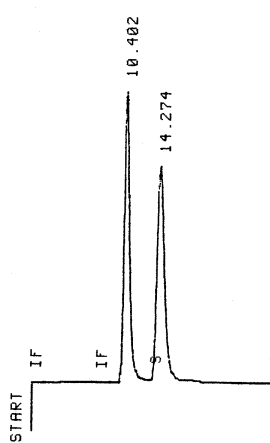
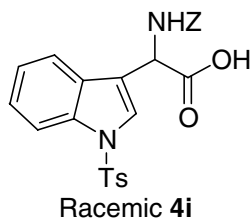


(-)-**4h** obtained from reaction
with (DHQD)₂AQN



END OF SIGNAL
Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA
RUN# 674 JAN 11, 2002 17:13:47
PEAK FILE : M:SIGNAL.PRA
AREA% RT AREA TYPE WIDTH AREA%
6.405 8069768 SB .357 4.40483
13.300 175132640 ISPH .803 95.59520
TOTAL AREA=1.8320E+08
MUL FACTOR=1.0000E+00

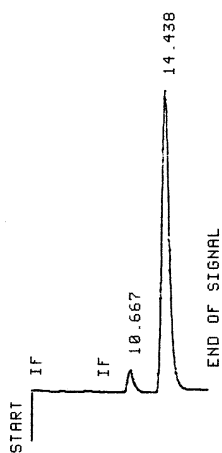
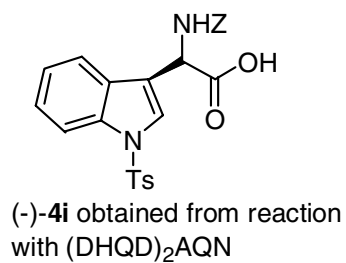
Daicel chiralpak OD, Hexanes:IPA:TFA, 80:20:0.1, 1 mL/min, λ 220 nm



END OF SIGNAL
 Error storing signal to M:SIGNAL .BNA
 DIRECTORY FULL
 Storing processed peaks to M:SIGNAL .PRA
 RUN# 2657 MAR 12, 2002 05:00:46
 PEAK FILE : M:SIGNAL.PRA
 AREAX

| RT | AREA | TYPE | WIDTH | AREAX |
|--------|-----------|------|-------|----------|
| 10.402 | 314863040 | SBB | .722 | 50.07766 |
| 14.274 | 313886400 | SPB | .975 | 49.92234 |

 TOTAL AREA=6.2875E+08
 MUL FACTOR=1.0000E+00



END OF SIGNAL
 Error storing signal to M:SIGNAL .BNA
 DIRECTORY FULL
 Storing processed peaks to M:SIGNAL .PRA
 RUN# 2658 MAR 12, 2002 05:41:31
 PEAK FILE : M:SIGNAL.PRA
 AREAX

| RT | AREA | TYPE | WIDTH | AREAX |
|--------|-----------|------|-------|----------|
| 10.667 | 12879000 | PB | .791 | 5.51740 |
| 14.438 | 220546000 | ISPH | 1.009 | 94.48259 |

 TOTAL AREA=2.3343E+08
 MUL FACTOR=1.0000E+00

HPLC Conditions: Chiralpak OD, Hexanes:IPA:TFA, 75:25:0.1, 1.0 mL/min, λ 254 nm

