Asymetric Transfer Hydrogenation Coupled with Dynamic Kinetic Resolution in Water: Synthesis of *anti*-β-Hydroxy-α-Amino Acid Derivatives

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Supporting Information

General Experimental Procedure.

^{1}H and ^{13}C NMR spectra were recorded at 500 MHz (125 MHz) or 400 MHz in $CDCl_3$ using the residual peak of $CHCl_3$ (^{1}H NMR δ = 7.26 ppm) and $CDCl_3$ (^{13}C NMR δ = 77.16 ppm) as an internal standard on Bruker Varian Avance instruments. Chemical shifts are reported in the δ-scale with multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constant (Hz) and integration. Dichloromethane (CH_2Cl_2), ether (Et_2O), hexanes, toluene (PhMe), dimethylformamide (DMF) and tetrahydrofuran (THF) were dried by passing through a solvent column composed of activated alumina. Deionized water was degassed by the freeze-pump-thaw method, by freezing and refilling with N_2. Air- and moisture sensitive reactions were carried out in flame-dried, septum-capped flasks under an atmospheric pressure of nitrogen. All liquid reagents were transferred via oven-dried syringes. Commercially available compounds were used without further purification unless otherwise indicated. TLC analyses were run on TLC alumina sheets (Merck Silica gel 60 F_{254}) and were visualized using UV and a solution of phosphomolybdic acid in ethanol (5 wt%), $KMNO_4$ stain or *p*-anisaldehyde stain. Flash chromatography was performed using silica gel 60 (35-63 μm). Melting points were recorded with a Stuart Scientific melting point apparatus (SMP3) and are not corrected. IR was recorded with an ATI Mattson Infinity 60 Mi Plus.
SDS = Sodium dodecyl sulfate (Sodium lauryl sulfate)
CTAB = hexadecyl-trimethyl-ammonium bromide (Cetrimonium bromide)
Tween 20 = Polyoxyethylene (20) sorbitan monolaurate (Polysorbate 20)

Substrate Preparation

All the substrates have been prepared previously. For detailed substrate preparation, as well as ^{1}H, ^{13}C and IR data please see: (a) Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274-5277; (b) Seashore-Ludlow, B.; Villo, P.; Somfai, P. *Chem. – Eur. J.* **2012**, 7219-7223.

ATH via DKR Reaction Procedures

Method A: $[RuCl_2(arene)]_2$ (3 mol %), ligand (10 mol %) and 0.5 mL water were stirred in a vial at 40 °C for 1 h under N_2. The septa was removed and the substrate (0.17 mmol, 1 equiv), the surfactant (0.5 equiv for SDS) and the reducing agent (5-15 equiv) were added. The reaction was stirred at the temperature indicated in Table 1 for the indicated time under N_2. Then the reaction mixture was transferred to a separatory funnel containing 1 mL sat. NaCl solution and the aqueous phase was extracted 4 times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude oil was subjected to column chromatography (usually 210:40 mL hexanes: EtOAc).

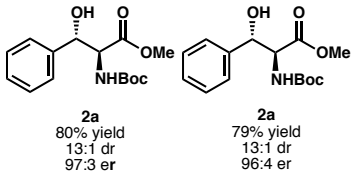
Method B: $[RuCl_2(arene)]_2$ (3 mol %), ligand (10 mol %) and 0.8 mL CH_2Cl_2 were stirred in a vial at 40 °C for 1 h under N_2. The solvent was removed by vacuum and then the septa was removed and the substrate (0.17 mmol, 1 equiv), the surfactant (0.5 equiv for SDS and CTAB) and the reducing agent (5 equiv) were added. Then 0.5 mL water was added and the reaction was stirred under N_2 at the indicated

temperature and time (see Table 1). When Tween 20 was used the Tween 20 (0.2 equiv) was not added with the substrate, but added directly after the water and then the reaction was set to stir for the indicated time under N_2 and at the indicated temperature under N_2. Then the reaction mixture was transferred to a separatory funnel containing 1 mL sat. NaCl solution and the aqueous phase was extracted 4 times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude oil was subjected to column chromatography (usually 210:40 mL hexanes: EtOAc).

Method C: (Scheme 1): $[RuCl_2(arene)]_2$ (3 mol %), ligand (10 mol %), Tween 20 (20 mol %) and 0.5 mL water were stirred in a vial at 40 °C for 1 h under N_2. Then the septa was removed and the the substrate (0.17 mmol, 1 equiv), and the reducing agent (5 equiv) were added. The reaction was stirred under N_2 at the indicated temperature and time (see Scheme 1). Finally the reaction mixture was transferred to a separatory funnel containing 1 mL sat. NaCl solution and the aqueous phase was extracted 4 times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude oil was subjected to column chromatography (usually 210:40 mL hexanes: EtOAc).

Characterization of products 2a-2j.

All products have been prepared previously and full characterization, including ^{1}H, ^{13}C and IR are reported in: (a) Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. *Org. Lett.* **2010**, *12*, 5274-5277; (b) Seashore-Ludlow, B.; Villo, P.; Somfai, P. *Chem. – Eur. J.* **2012**, 7219-7223. The data for these substrates is identical to those previously reported.

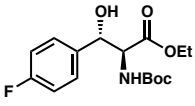


(2*S*,3*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxy-3-phenylpropanoate (2a)

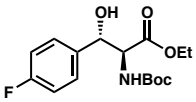
Method B: Prepared from **1a** (54.1 mg, 0.18 mmol) to give the product **2a** (43.4 mg, 0.15 mmol, 80%) as an oil. 13:1 dr from ^{1}H NMR; 97:3 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R,R* isomer 20.4 min, *S,S* isomer 21.3 min)

Method C: Prepared from **1a** (51.5 mg, 0.17 mmol) to give product **2a** (41.3 mg, 0.14 mmol, 92%). 13:1 dr from ^{1}H NMR; 96:4 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R,R* isomer 20.4 min, *S,S* isomer 21.3 min)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.22 (m, 5H), 5.27 (m, 1H), 5.19 (m, 1H), 4.72 (m, 1H), 3.87 (m, 1H), 3.70 (bs, 3H), 1.43 (bs, 9H).



2b
83% yield
20:1 dr
97:3 er



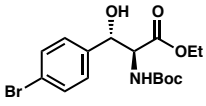
2b
84% yield
18:1 dr
96:4

(2*S*,3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(4-fluorophenyl)-3-hydroxypropanoate (2b)

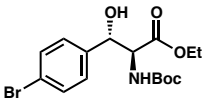
Method B: Prepared from amide **1b** (50.0 mg, 0.15 mmol) to give amino alcohol **2b** (41.6 mg, 0.13 mmol, 83% yield); 20:1 dr determed by ^{1}H NMR; 97:3 er determined by HPLC analysis (Chiralcel OD-H, 3% 2-propanol in hexanes, 0.5 mL/min, λ =254 nm, *R,R* isomer 14.4 min, *S,S* isomer 15.5 min).

Method C: Prepared from **1b** (53.5 mg, 0.17 mmol) to give amino alcohol **2b** (45.7 mg, 0.14 mmol, 84% yield); 18:1 dr determed by ^{1}H NMR; 96:4 er determined by HPLC analysis (Chiralcel OD-H, 3% 2-propanol in hexanes, 0.5 mL/min, λ = 254 nm, *R,R* isomer 15.1 min, *S,S* isomer 15.8 min).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (m, 2H), 7.01 (m, 2H), 5.31 (m, 1H), 5.17 (m, 1H), 4.65 (m, 1H), 4.20-4.10 (m, 3H), 1.43 (bs, 9H), 1.21 (t, J = 7.1 Hz, 3H).



2c
82% yield
13:1 dr
95:5 er



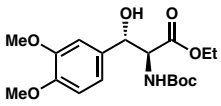
2c
81% yield
15:1
96:4

(2*S*,3*S*)-ethyl 3-(4-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (2c)

Method B: Amino alcohol **2c** (48.8 mg, 0.13 mmol, 82%) was obtained as a beige oil from **1c** (59.4 mg, 0.15 mmol). 13:1 dr determed by ^{1}H NMR; 95:5 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ = 254 nm, *R,R* isomer 16.1 min, *S,S* isomer 16.9 min).

Method C: Amino alcohol **2c** (47.8 mg, 0.12 mmol, 81%) was obtained as a beige oil from **1c** (58.9 mg, 0.15 mmol). 15:1 dr determed by ^{1}H NMR; 96:4 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ = 254 nm, *R,R* isomer 16.1 min, *S,S* isomer 16.9 min).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.14 (m, 2H), 5.31 (m, 1H), 5.16 (m, 1H), 4.65 (m, 1H), 4.16 (m, 2H), 1.43 (bs, 9H), 1.21 (t, J = 7.1 Hz, 3H).

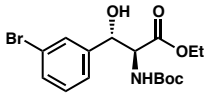


2d
79% yield
14:1 dr
98:2 er

(2*S*,3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(3,4-dimethoxyphenyl)-3-hydroxypropanoate (2d)

Method B: Amino alcohol **2d** (43.9 mg, 0.12 mmol, 79%) was prepared from **1d** (55.4 mg, 0.15 mmol) and obtained as a beige oil. 14:1 dr determed by ^{1}H NMR; 98:2 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ = 254 nm, *R,R* isomer 43.5 min, *S,S* isomer 45.6 min).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 – 6.74 (m, 3H), 5.26 (bs, 1H), 5.14 (bs, 1H), 4.65 (s, 1H), 4.21 – 4.10 (m, 2H), 3.86 (bs, 3H), 3.86 (bs, 3H), 1.42 (bs, 9H), 1.22 (t, J = 7.1 Hz, 3H).

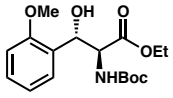


2e
84% yield
15:1 dr
89:11 er

(2*S*, 3*S*)-ethyl 3-(3-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (2e)

Method B: Amino alcohol **2e** (51.7 mg, 0.13 mmol, 94%) was prepared from **1d** (61.1 mg, 0.16 mmol). 15:1 dr determed by ^{1}H NMR; 89:11 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ = 254 nm, *R,R* isomer 14.0 min, *S,S* isomer 15.5 min).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.40 (m, 2H), 7.22-7.15 (m, 2H), 5.34 (m, 1H), 5.18 (m, 1H,), 4.65 (m, 1H), 4.30 (m, 1H), 4.23-4.11 (m, 2H), 1.45 (bs, 9H), 1.22 (t, J = 7.1 Hz, 3H).

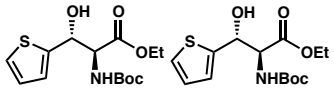


2f
78% yield
14:1 dr
98:2 er

(2*S*,3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-hydroxy-3-(2-methoxyphenyl)propanoate (2f)

Method B: Prepared from **1f** (49.2 mg, 0.15 mmol) to give amino alcohol **2f** (38.8 mg, 0.11 mmol, 78%); 14:1 dr determed by ^{1}H NMR; 98:2 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ =254 nm, *R,R* isomer 26.8 min, *S,S* isomer 31.0 min)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (m, 1H), 7.26 (m, 1H), 6.95 (m, 1H), 6.84 (m, 1H), 5.36 (m, 1H), 5.27 (m, 1H), 4.67 (m, 1H), 4.18-4.03 (m, 2H), 3.81 (bs, 3H), 1.40 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H).



2g
85% yield
7:1 dr
94:6 er

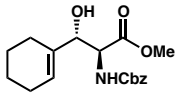
2g
96% yield
7:1 dr
95:5

(2*S*, 3*S*)-Ethyl 2-(*tert*-butoxycarbonylamino)-3-hydroxy-3-(thiophen-2-yl)propanoate (2g)

Method B: β-ketoester **1g** (49.5 mg, 0.16 mmol) was subjected to ATH via DKR conditions to yield **2g** (42.6 mg, 0.14 mmol, 73%), 7:1 dr as determined by ^{1}H NMR; 94:6 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ =254 nm, *R,R* isomer 16.9 min, *S,S* isomer 18.3 min)

Methdod C: β-ketoester **1g** (50.5 mg, 0.16 mmol) yielding alcohol **2g** (46.0 mg, 0.15 mmol, 96%) amino; 7:1 dr as determined by ^{1}H NMR; 95:5 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ =254 nm, *R,R* isomer 18.6 min, *S,S* isomer 20.0 min).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 - 7.24 (m, 1H), 6.98 - 6.95 (m, 1H), 6.90 - 6.86 (m, 1H), 5.52 - 5.46 (m, 1H), 5.42 - 5.36 (m, 1H), 4.85 - 4.69 (m, 1H), 4.46 (d, J = 5.4 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.46 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H).

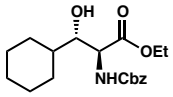


2h
80% yield
23:1 dr
96:4 er

(2*S*, 3*S*)-Methyl 2-(benzyloxycarbonylamino)-3-cyclohexenyl-3-hydroxypropanoate (2h)

Method B: Prepared from **1h** (52.8 mg, 0.16 mmol) to give the product **2h** (42.2 mg, 0.13 mmol, 80%) as a beige oil. 23:1 dr determined by ^{1}H NMR; 96:4 er determined by HPLC analysis (Chiralcel OD-H, 2% 2-propanol in hexanes, 0.5 mL/min, λ =254 nm, *R,R* isomer 158 min (minor), *S,S* isomer 159 min (major).

^{1}H NMR (500 MHz, $CDCl_3$): 7.40 - 7.29 (m, 5H), 5.70 (s, 1H), 5.54 (d, *J* = 7.8 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 1H), 4.52 (dd, *J* = 7.7, 5.7 Hz, 1H), 4.26 (s, 1H), 3.73 (s, 3H), 2.70 (s, 1H), 2.08 - 1.97 (m, 3H), 1.94 - 1.80 (m, 1H), 1.64 - 1.58 (m, 2H), 1.57 - 1.52 (m, 2H).

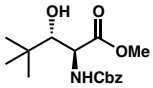


2i
72% yield
9:1 dr
97:3 er

(2*S*,3*S*)-Ethyl 2-(benzyloxycarbonylamino)-3-cyclohexyl-3-hydroxypropanoate (2i)

Method B: (using (*S*,*S*)-TsDPEN as the ligand and ($RuCl_2$(*p*-cymene))$_2$): Prepared from **1i** (54.0 mg, 0.16 mmol) to give the product **2i** (39.1 mg, 0.12 mol, 72%) as a beige oil; 9:1 dr as determined by ^{1}H NMR; 97:3 er determined by HPLC analysis (Chiralcel OD-H, 3% 2-propanol in hexanes, 0.5 mL/min, λ =254 nm, *R* isomer 65.9 min (minor), *S* isomer 68.1 min (major)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 - 7.30 (m, 5H), 5.79 (d, *J* = 7.7 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 4.52 (dd, *J* = 7.9, 3.2 Hz, 1H), 4.30 - 4.16 (m, 2H), 3.64 - 3.44 (m, 1H), 2.44 (d, *J* = 7.5 Hz, 1H), 1.99 (d, *J* = 12.6 Hz, 1H), 1.83 - 1.71 (m, 3H), 1.66 (d, *J* = 10.3 Hz, 1H), 1.50 -1.36 (m, 1H), 1.34 - 1.09 (m, 6H), 1.07 - 0.93 (m, 2H).

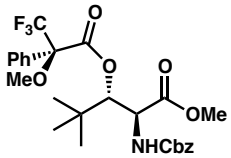


2j
68% yield
20:1 dr
89:11 er

(2*S*, 3*S*)-Methyl 2-(benzyloxycarbonylamino)-3-hydroxy-4,4-dimethylpentanoate (2j)

Emulsion (-5 °C): Prepared from **1j** (51.2 mg, 0.17 mmol) to give the product **2j** (35.2 mg, 0.11 mmol, 68%) as a beige oil; 20:1 dr determined by ^{1}H NMR; 89:11 er was determined by preparation of Mosher's ester (see below)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 - 7.28 (m, 5H), 5.83 (d, *J* = 8.1 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 1H), 4.53 (dd, *J* = 8.4, 3.3 Hz, 1H), 3.74 (s, 3H), 3.48 (d, *J* = 4.9 Hz, 1H), 2.92 (d, *J* = 8.6 Hz, 1H), 0.94 (s, 9H).



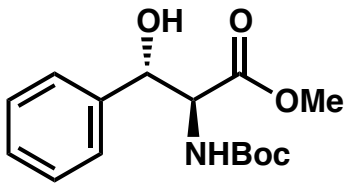
(2*S*,3*S*)-Methyl 2-(benzyloxycarbonylamino)-4,4-dimethyl-3-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)pentanoate (S14)

To a stirred mixture of **2j** (28.6 mg, 92 μmol) and *R(+)*-α-methoxy-α-triflouromethyl phenyl acetic acid (67.1 mg, 0.28 mmol) in $CDCl_3$ (0.5 mL) was added *N,N'*-dicyclohexylcarbodiimide (DCC, 59.1 mg, 0.28 mmol) and 4-dimethyl aminopyridine

(DMAP, 35.0 mg, 0.28mmol).[1] The reaction was stirred for 25 h at r.t. under nitrogen atmosphere until full conversion. Crude ^{1}H NMR spectrum was taken from the mixture revealing consumption of starting material and 99:1 er. Then the mixture was concentrated *in vacuo* and subjected to flash chromatography (10% EtOAc/hexanes). A colourless solid was isolated to confirm peaks. Peaks were compared to a racemic sample of the same Mosher ester product. Further more ^{19}F peaks were also used to corroborate the values.

^{1}H NMR for 2a-2j:

[1] Hoye, T.R.; Jeffrey, C.S.; Shao, F., *Nature Protocols,* **2007**, 2(10), 2451-2458



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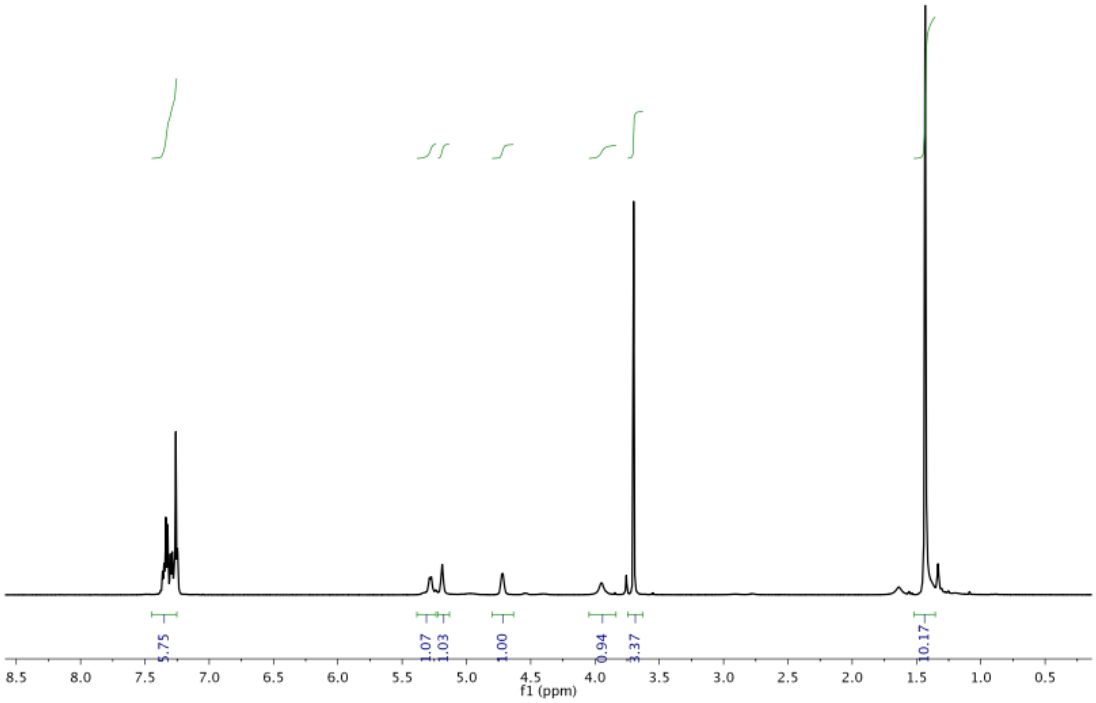
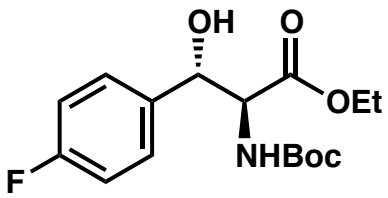
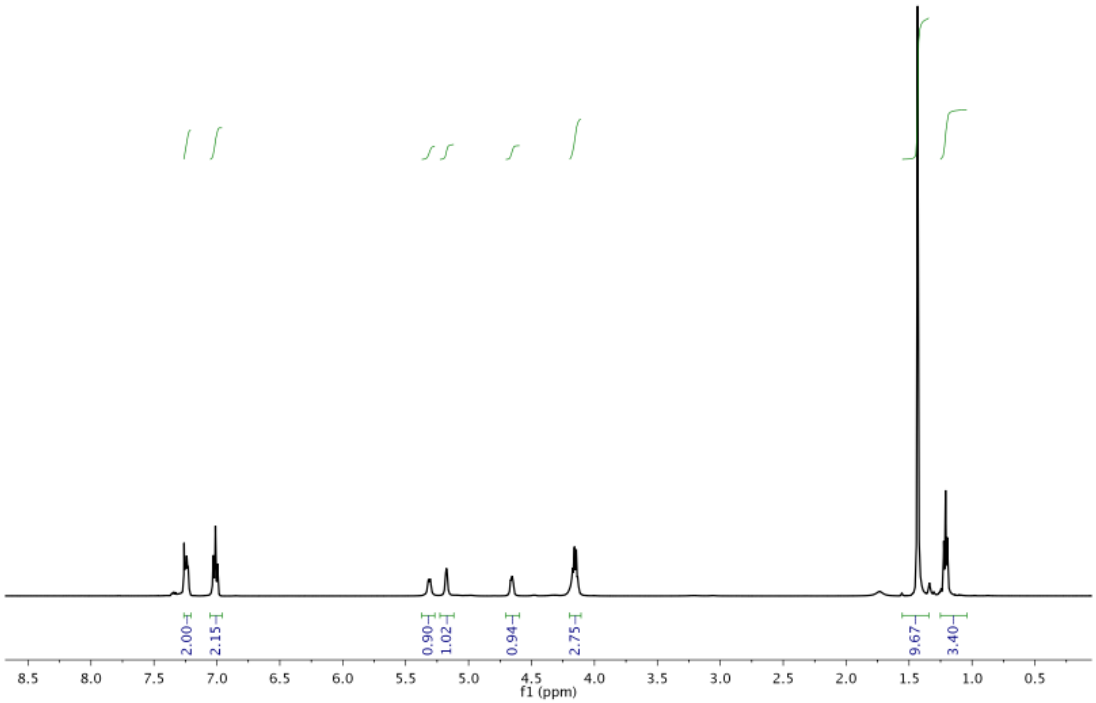
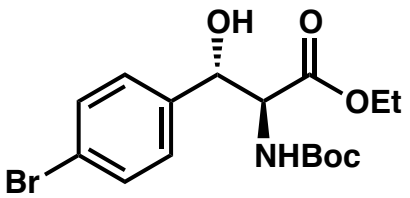


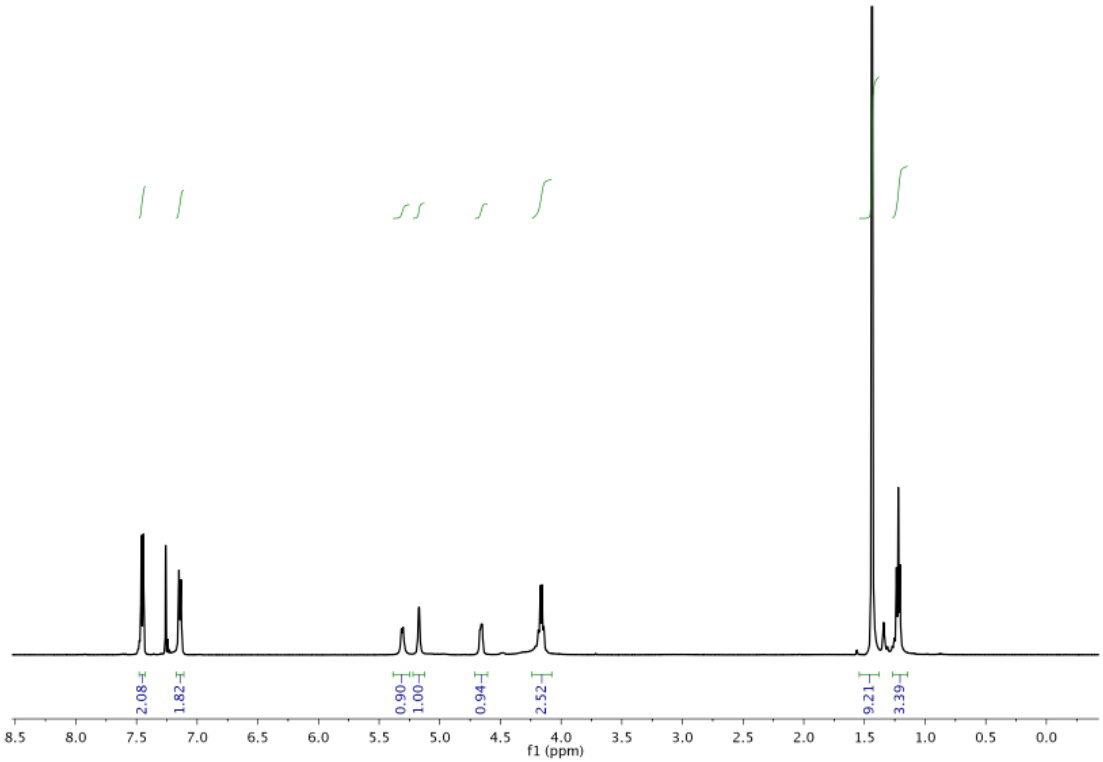


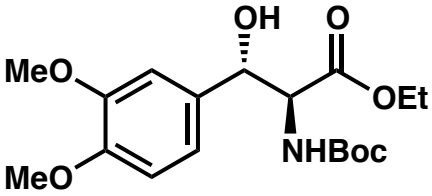
(2*S*,3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(4-fluorophenyl)-3-hydroxypropanoate (2b)



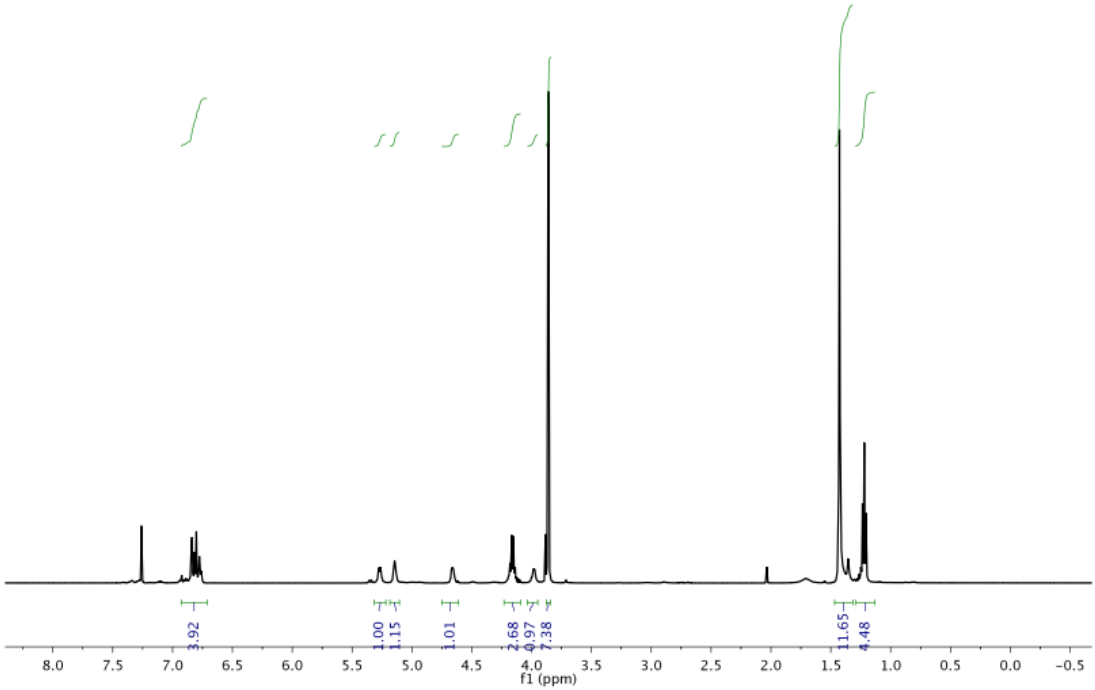


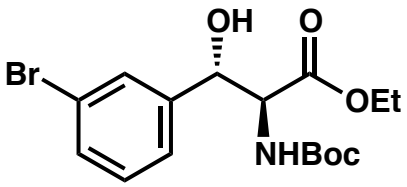
(2*S*,3*S*)-ethyl 3-(4-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (2c)



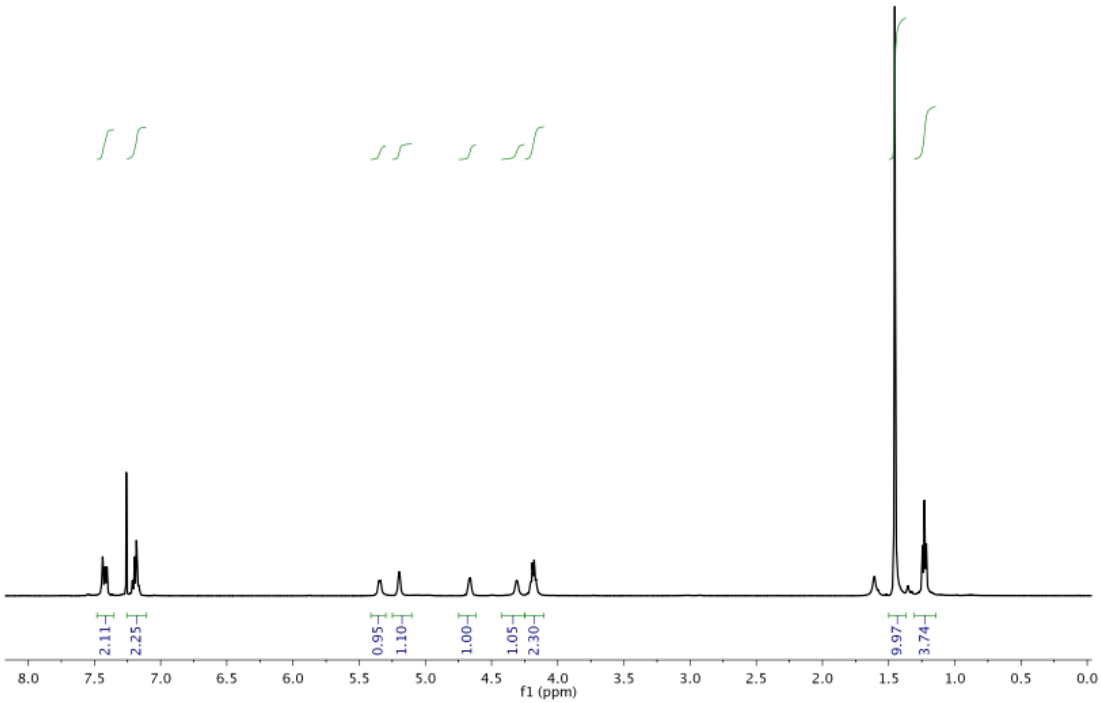


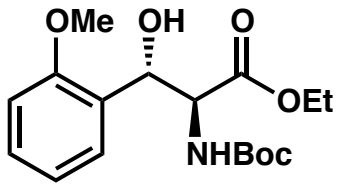
(2*S*,3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(3,4-dimethoxyphenyl)-3-hydroxypropanoate (2d)



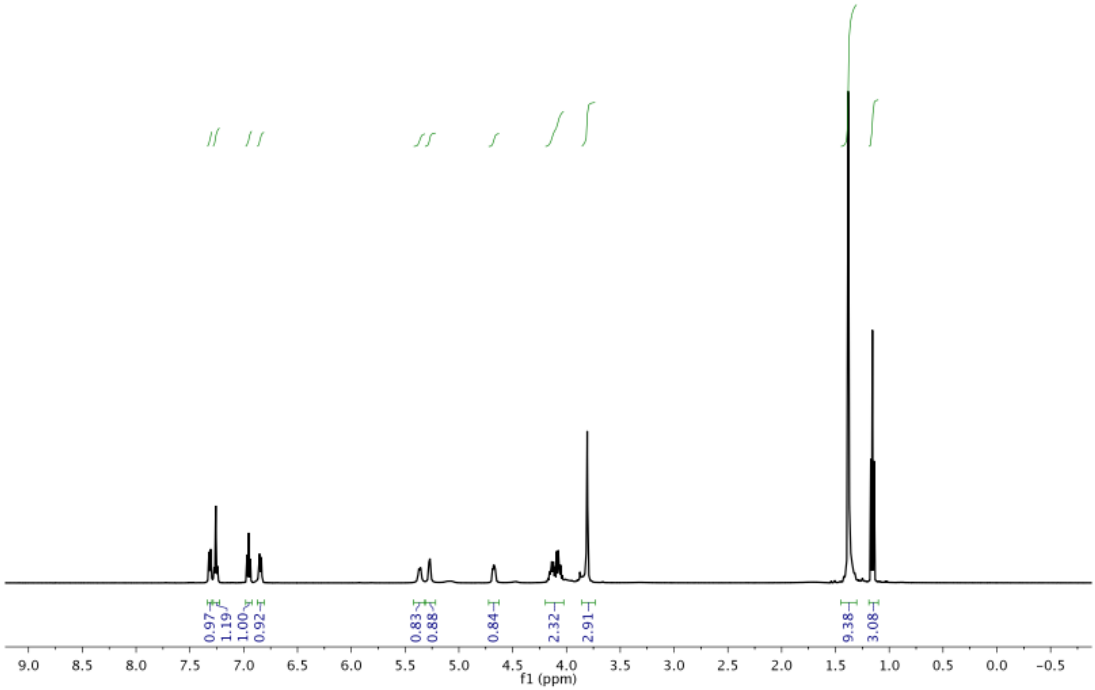


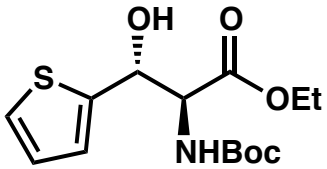
(2*S*, 3*S*)-ethyl 3-(3-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (2e)



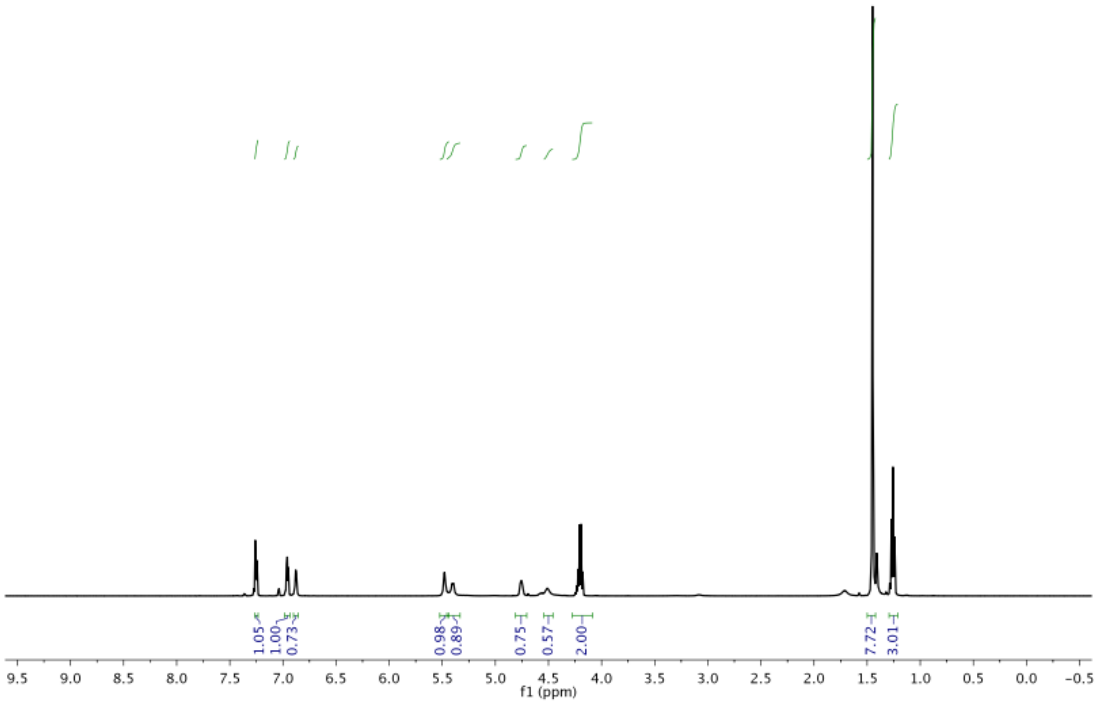


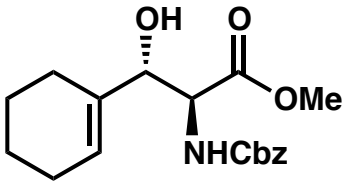
(2*S*,3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-hydroxy-3-(2-methoxyphenyl)propanoate (2f)



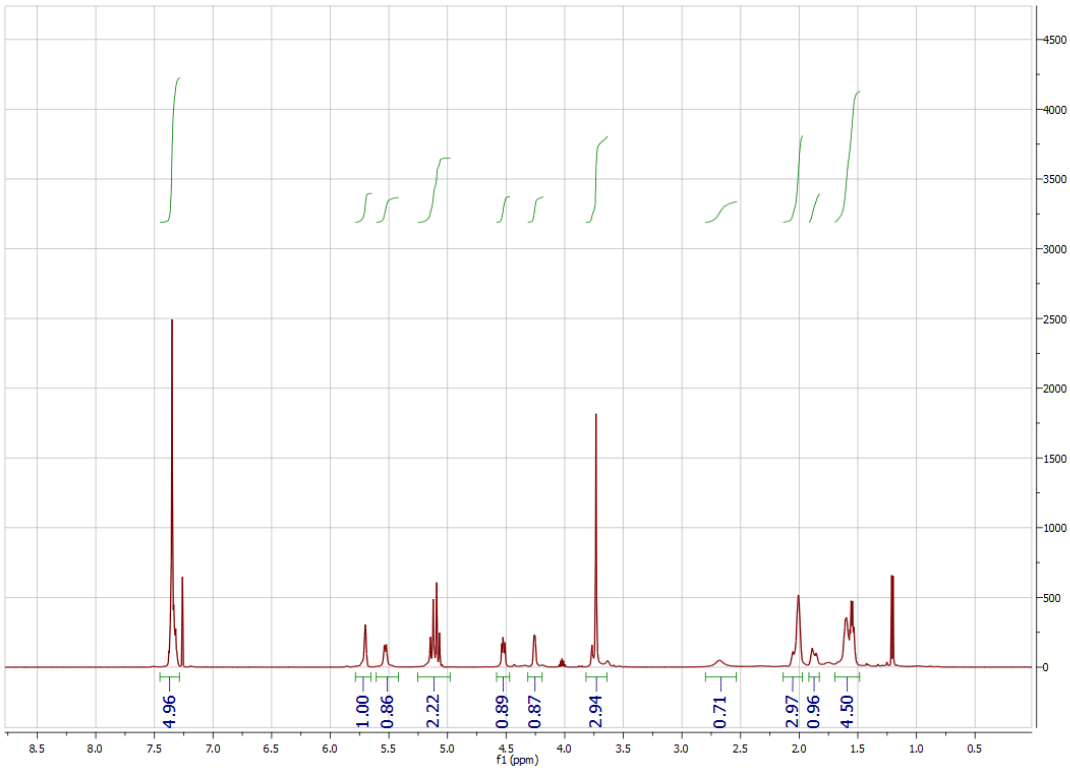


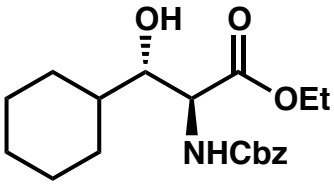
(2*S*, 3*S*)-Ethyl 2-(*tert*-butoxycarbonylamino)-3-hydroxy-3-(thiophen-2-yl)propanoate (2g)



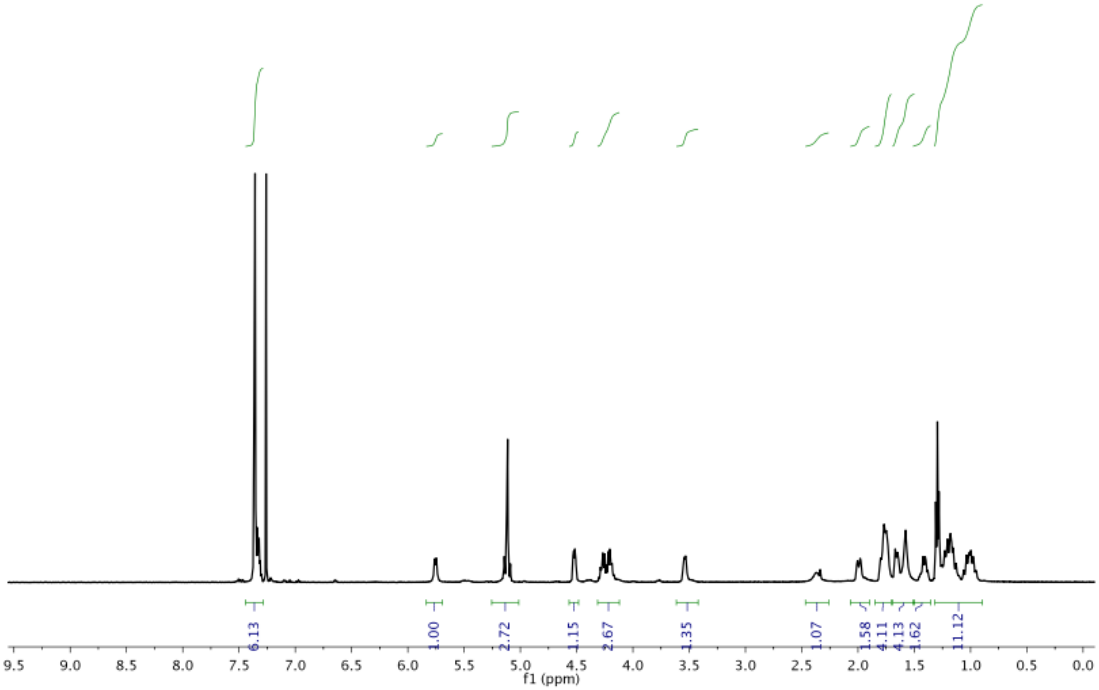


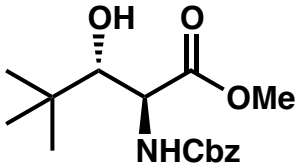
(2*S*, 3*S*)-Methyl 2-(benzyloxycarbonylamino)-3-cyclohexenyl-3-hydroxypropanoate (2h)





(2*S*,3*S*)-Ethyl 2-(benzyloxycarbonylamino)-3-cyclohexyl-3-hydroxypropanoate (2i)





(2*S*, 3*S*)-Methyl 2-(benzyloxycarbonylamino)-3-hydroxy-4,4-dimethylpentanoate (2j)