**Catalytic Enantioselective Synthesis of Quaternary All-Carbon Stereogenic Centers.
Preparation of α,α' -Dialkyl- β,γ -Unsaturated Esters through Cu-Catalyzed Asymmetric
Allylic Alkylations**

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A. General

Infrared (IR) spectra are recorded on a Perkin Elmer 781 spectrophotometer, $\nu_{\max}$ in cm^{-1} . Bands are characterized as broad (br), strong (s), medium (m) or weak (w). ^1H NMR spectra are recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal standard (CDCl_3 : 7.26). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants and assignment. ^{13}C NMR spectra are recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl_3 : 77.16). Enantiomer ratios are determined by chiral GLC analysis (Alltech Associates Chiraldex GTA column, 30 m x 0.25 mm or Supelco Betadex 120 column, 30 m x 0.25 mm) or by high pressure liquid chromatography (HPLC) (Chiralcel OJ column, 4.6 x 250 mm) in comparison to authentic racemic materials. S_N2' : S_N2 ratios are determined by achiral GLC analysis (J&W Scientific HP-5, 30 m x 0.25 mm) or by 400 MHz ^1H NMR. Elemental analyses are performed by Robertson Microlit Laboratories (Madison, New Jersey). High resolution mass spectrometry is performed by the University of Illinois Mass Spectrometry Laboratories (Urbana, Illinois) and at the Mass Spectrometry Facility, Boston College (on a Micromass LCT ESI-MS (positive mode)). Optical Rotation values are recorded on a Rudolph Research Analytical Autopol IV Polarimeter. Unless otherwise stated, all reactions are conducted in oven (135 °C) and flame-dried glassware under an inert atmosphere of nitrogen.

B. Preparation and purification of reagents

Solvents:

Acetonitrile: Distilled from calcium hydride.

Chloroform: Purchased from Aldrich Chemical Company and used as received.

Dichloroethane: Distilled from calcium hydride.

Dichloromethane: Purified under a positive pressure of dry argon through two alumina columns.

Dimethylformamide: Purchased from Fisher (sequencing grade) and used without further purification.

Methanol: Distilled from Mg(0).

Tetrahydrofuran: Purified under a positive pressure of dry argon through two alumina columns.

Substrates:

***Tert*-Butyl-4-(diethoxyphosphoryloxy)-2-methylbut-2-enoate (1b):** Synthesized according to a modified published procedure¹ followed by phosphate formation to deliver the desired substrates.²

***Tert*-Butyl-4-(diethoxyphosphoryloxy)-2-phenylbut-2-enoate (12b):** Prepared according to the same procedure as **12a**, except phenyl acetic acid *tert*-butyl ester is employed in the aldol reaction.

Methyl-4-(diethoxyphosphoryloxy)-2-methylbut-2-enoate (1a): Synthesized according to published procedure¹ followed by phosphate formation to deliver the desired substrates.²

Methyl-4-(diethoxyphosphoryloxy)-2-phenylbut-2-enoate (12a): Aldol reaction between phenyl acetic acid and *tert*-butyldimethylsilyloxy)-acetaldehyde (LDA, -78 °C to -30 °C, 12 h) affords a secondary alcohol. The resultant secondary alcohol is mesylated with mesyl chloride, Et₃N, DCM. The mesylate is eliminated to the α,β -unsaturated ester by treatment with K₂CO₃ in MeOH for 1 h. Subsequent removal of the silyl ether with HF•pyridine in THF (24 h) delivers the desired allylic alcohol that is phosphorylated according to published procedure.²

Commercially available aldehydes for ligand synthesis: Purchased from commercial sources and used without further purification.

Commercially available amines for ligand synthesis: Purchased from commercial sources and used without further purification.

Acetic anhydride: Distilled from P₂O₅ prior to use.

Aminomethyl polystyrene resin 100-200 mesh (0.6 mmol/g): Purchased from Advanced Chemtech.

Benzyl amine: Purchased from Acros chemical company and is distilled from sodium hydroxide prior to use.

Boc-L-amino acids: Purchased from Advanced Chemtech and used without further purification.

9-Borabicyclo[3.3.1]nonane (9-BBN): Freshly prepared according to the procedure of H. C. Brown.³

¹ Wolff, M.; Seemann, M.; Grosdemange-Billiard, C.; Tritsch, D.; Campos, N.; Rodríguez-Concepción, M.; Boronat, A.; Rohmer, M. *Tetrahedron Lett.* **2002**, *43*, 2555-2559.

² Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456-1460.

Butylamine: Purchased from Acros chemical company and used without further purification.

***Tert*-butyldimethylsilyl chloride:** Purchased from Acros Chemical Company and used as received.

***Tert*-Butyldimethylsilyloxy)-acetaldehyde:** Prepared by treatment of 1,4-bis-(*tert*-butyldimethylsilyloxy)-but-2-ene in DCM with ozone at $-78\text{ }^{\circ}\text{C}$, followed by treatment with triphenylphosphine. 1,4-Bis-(*tert*-butyldimethylsilyloxy)-but-2-ene is prepared by treatment of *cis*-2-butene-1,4-diol, which is purchased from Aldrich Chemical Company and used without purification, with TBSCl and imidazole in DMF.

Calcium hydride: Purchased from Strem Chemical Company and used as received.

Copper (I) triflate (benzene complex, 2:1): Prepared using known methods.⁴

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU): Purchased from Aldrich chemical company and is distilled from itself before use.

Di-butylacetatezinc: Prepared by hydroboration of 3-butenylacetate followed by boron-zinc exchange according to Knochel's procedure.⁵ 3-Butenylacetate was prepared by acetylation of 3-buten-1-ol in the presence of acetic anhydride, Et_3N and catalytic DMAP.

Diethylchlorophosphate: Purchased from Aldrich Chemical Company and used without further purification.

Diethylzinc: Purchased from Strem and used without purification.

Diisopropylcarbodiimide (DIC): Purchased from Advanced Chem Tech and used without further purification.

Di-*iso*-propylzinc (30): Purchased from Aldrich Chemical Company and used as received.

1-(3-*N,N*-Dimethylaminopropyl)-3-ethylcarbodiimide (EDC•HCl): Purchased from Advanced Chemtech and used without further purification.

***N,N*-Dimethylaminopyridine (DMAP):** Purchased from Advanced Chemtech and used without further purification.

Dimethylzinc: Purchased from Strem and used without purification.

Di-4-methylpentylzinc: Prepared by hydroboration of 4-methyl-1-pentene followed by boron-zinc exchange according to Knochel's procedure.⁵

HF•pyridine complex: Purchased from Aldrich Chemical Company and used as received.

***N*-Hydroxybenzotriazole (HOBT•H₂O):** Purchased from Advanced Chem Tech and used without further purification.

Fmoc-amino acids: Purchased from Advanced Chem Tech and used without further purification.

Glacial acetic acid: Purchased from Fisher Scientific and used without further purification.

³ Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765-7770.

⁴ a) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889-1897. b) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300-3310.

⁵ Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229-8243.

Lithium aluminumhydride (LiAlH_4): Purchased from Strem chemicals and used without further purification.

Lithium chloride: Recrystallized from MeOH and then dried at 130 °C under reduced pressure before use.

Lithium hydroxide: Purchased from Fisher Scientific and used without further purification.

Methanesulfonyl chloride: Distilled from P_2O_5 prior to use.

5-Methoxysalicyl aldehyde: Purchased from Aldrich Chemical Company and used as received.

Methyl sulfide (DMS): Purchased from Aldrich chemical company and used without further purification.

Oxalyl chloride: Purchased from Aldrich chemical company and used without further purification.

Peroxide (H_2O_2 30% wt. in H_2O): Purchased from Acros chemical company and used without further purification.

Piperidine: Purchased from Advanced Chem Tech and used without further purification.

Phenyl acetic acid: Distilled from calcium chloride prior to use.

Potassium carbonate: Purchased from Fisher Scientific and used as received.

Pyridine: Distilled from sodium hydroxide prior to use.

Salicyl aldehyde: Purchased from Aldrich Chemical Company and used as received.

Sodium bicarbonate: Purchased from Fisher Scientific and used without further purification.

Sodium triacetoxyborohydride: Purchased from Aldrich chemical company and used without further purification.

Triethylamine: Purchased from Acros chemical company and is distilled from CaH_2 prior to use.

Triethylphosphonoacetate: Purchased from Acros chemical company and is distilled from itself before use.

Trifluoroacetic acid: Purchased from Aldrich Chemical Company and used without further purification.

Triphenylphosphine: Purchased from Aldrich Chemical Company and recrystallized from hot methanol prior to use.

2-Hydroxy-1-naphthaldehyde-L-Thr(*Ot*-Bu)-L-Trp(Boc)-NHBn (11b). Fmoc-L-Trp(Boc) (2.00 g, 3.80 mmol) is dissolved in 10 mL CH_2Cl_2 and $\text{HOBt}\cdot\text{H}_2\text{O}$ (0.582 g, 3.80 mmol) and EDC $\cdot\text{HCl}$ (0.729 g, 3.80 mmol) are added successively. The solution is cooled to 0 °C with an ice bath and benzylamine (0.415 mL, 11.4 mmol) is added. The mixture is allowed to warm to room temperature and stir for 2 h, over which time white solids precipitate out of the solution. Reaction is quenched by addition of 20 mL 10 wt. % aqueous citric acid, and the solution is diluted by addition of 20 mL CH_2Cl_2 . The organic layer is washed with 20 mL of a saturated aqueous solution of NaHCO_3 and 20 mL of a saturated aqueous solution of NaCl , dried over MgSO_4 , filtered and concentrated to give Fmoc-L-Trp(Boc)-NHBn as a white solid. The solid is dissolved in 10 mL of CH_2Cl_2 and cooled to 0 °C in an ice bath. Piperidine is added (1.88 mL, 19.0 mmol) and the reaction is allowed to warm to room temperature and stir for 2 h at which time TLC analysis indicates complete consumption of starting material (10:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$; R_f starting material = 0.8, R_f product = 0.2). The reaction is concentrated and purified by silica gel column chromatography (4:1 hexanes/EtOAc to 8:1 EtOAc/MeOH) to yield a yellow oil (0.990 g, 2.52 mmol, 66%).

To a solution of H_2N -L-Trp(Boc)-NHBn (0.990 g, 2.52 mmol) and Fmoc-L-Thr(*Ot*-Bu)-OH (1.00 g, 2.52 mmol) in 7 mL of CH_2Cl_2 , $\text{HOBt}\cdot\text{H}_2\text{O}$ (0.386 g, 2.52 mmol) and EDC $\cdot\text{HCl}$ (0.483 g, 2.52 mmol) are added and the reaction is cooled to 0 °C with an ice bath. Et_3N (0.349 mL, 2.52 mmol) is added and the solution is allowed to warm to room temperature and stir for 6 h. The reaction is quenched by addition of 20 mL 10 wt. % aqueous citric acid, and the solution is diluted by addition of 20 mL CH_2Cl_2 . The organic layer is washed with 20 mL of a saturated aqueous solution of NaHCO_3 and 20 mL of a saturated aqueous solution of NaCl , dried over MgSO_4 , filtered and concentrated to give a white solid. The solids are suspended in 10 mL of CH_2Cl_2 and the flask is cooled to 0 °C. Piperidine (1.25 mL, 12.6 mmol) is added and the solids slowly dissolve. The mixture is allowed to warm to room temperature and stir for 2 h at which time the resulting solution is concentrated. Solids are purified by silica gel chromatography (4:1 hexanes/EtOAc to 8:1 EtOAc/MeOH) to yield a white solid (1.16 g, 2.11 mmol, 86%).

To a solution of H_2N -L-Thr(*Ot*-Bu)-L-Trp(Boc)-NHBn (1.16 g, 2.11 mmol) in 5 mL CH_2Cl_2 , 2-hydroxy-1-naphthaldehyde (0.363 g, 2.11 mmol) is added followed by addition of MgSO_4 (0.506 g, 4.22 mmol). The mixture is allowed to stir for 12 h. After this time, solvent is evaporated and the brownish solid is purified by silica gel chromatography (1:1 hexanes/EtOAc

to 100% EtOAc, R_f product (1:1 Hexane/EtOAc) = 0.15) to yield a bright yellow solid (1.12 g, 1.58 mmol, 75%). mp 112-120 °C. IR (neat): 3288 (s), 3065 (m), 3035 (m), 2974 (s), 2932 (m), 1738 (s), 1659 (s), 1629 (s), 1551 (m), 1527 (w), 1454 (m), 1370 (s), 1261 (m), 1237 (w), 1195 (w), 1165 (m), 1086 (m), 917 (w), 863 (w) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 8.89 (1H, d, J = 4.8 Hz, $\text{CH}=\text{N}$), 8.15 (1H, d, J = 7.6 Hz, NHCH_2Ph), 7.95 (1H, d, J = 8.4 Hz, ArH), 7.62 (1H, d, J = 9.2 Hz, ArH), 7.68 (2H, dd, J = 7.2, 7.2 Hz, ArH), 7.48 (2H, m, ArH), 7.30 (3H, m, ArH), 7.20 (3H, m, ArH), 7.05 (1H, d, J = 9.2 Hz, ArH), 6.99 (2H, m, ArH), 6.90 (1H, d, J = 8.4 Hz, ArH), 6.33 (1H, br m, NH), 4.87 (1H, m, $\text{NCHC}(\text{O})$), 4.38 (1H, dd, J = 5.6, 14.8 Hz, NHCHHPh), 4.24 (1H, dd, J = 5.6, 14.8 Hz, NHCHHPh), 3.88 (2H, m, $\text{NCHC}(\text{O})$ and $\text{MeCHO}t\text{-Bu}$), 3.41 (1H, dd, J = 5.6, 14.8 Hz, CHHAr), 3.19 (1H, dd, J = 7.2, 14.4 Hz, CHHAr), 1.66 (9H, s, $(\text{CH}_3)_3\text{CO}$), 1.07 (3H, d, J = 6.0 Hz, $(\text{CH}_3)\text{CH}(\text{CO}t\text{-Bu})$), 0.93 (9H, s, $(\text{CH}_3)_3\text{CO}$). ^{13}C NMR (100 MHz, CDCl_3): δ 170.8, 170.6, 169.0, 149.6, 137.5, 136.6, 135.7, 133.4, 130.4, 129.3, 128.7, 128.0, 127.9, 127.6, 127.1, 124.9, 124.5, 123.3, 123.0, 122.8, 119.3, 118.8, 115.5, 108.1, 83.9, 75.3, 73.5, 69.1, 53.5, 43.8, 28.3, 28.1, 27.2, 18.9. HRMS Calcd for $\text{C}_{42}\text{H}_{48}\text{N}_4\text{O}_6$ $[\text{M}+1]$: 705.3574. Found: 705.3647. $[\alpha]_{\text{D}}^{20}$ -4.34° (c = 0.507, CHCl_3).

2-Hydroxybenzaldehyde-L-Gln(Trt)-L-Tyr(OBn)-NHBu (4a). mp 156-160 °C. IR (neat): 3415 (m), 3307 (s), 3091 (w), 3069 (w), 3035 (w), 2961 (w), 2876 (w), 1660 (s), 1587 (w), 1513 (s), 1490 (m), 1450 (w), 1388 (w), 1286 (m), 1246 (m), 1183 (w), 1155 (w), 1115 (w), 1087 (w), 1036 (w) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 12.28 (1H, s, ArOH), 8.14 (1H, s, $\text{CH}=\text{N}$), 7.36-7.17 (23H, m, ArH), 7.09 (2H, d, J = 8.8 Hz, ArH), 6.97 (1H, d, J = 8.8 Hz, $\text{NHC}(\text{O})$), 6.90 (1H, dt, J = 1.2, 7.6 Hz, ArH), 6.86 (2H, m, ArH), 6.51 (1H, d, J = 8.0 Hz, $\text{NHC}(\text{O})$), 5.78 (1H, t, J = 5.6 Hz, NHCH_2), 4.95 (2H, s, OCH_2Ph), 4.49 (1H, dt, J = 7.6, 7.6 Hz, $\text{NHCHC}(\text{O})$), 3.73 (1H, dd, J = 6.8, 6.8 Hz, $\text{NCHC}(\text{O})$), 3.11 (2H, m, $\text{NHC}(\text{O})\text{CH}_2$), 2.96 (2H, d, J = 7.6 Hz, CHCH_2Ar), 2.26 (2H, m, NHCH_2CH_2), 2.15 (1H, m, $\text{CHCHHCH}_2\text{C}(\text{O})$), 1.99 (1H, m, $\text{CHCHHCH}_2\text{C}(\text{O})$), 1.31 (2H, m, aliphatic CH), 1.18 (2H, m, aliphatic CH), 0.84 (3H, t, J = 7.2 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 171.1, 171.0, 170.3, 168.3, 160.9, 158.0, 144.8, 137.0, 133.4, 132.4, 130.5, 128.9, 128.8, 128.7, 128.1, 127.6, 127.2, 119.3, 118.5, 117.3, 115.3, 71.3, 70.7, 70.1, 54.7, 39.4, 37.4, 33.1, 31.5, 30.8, 20.1, 18.8, 13.8. HRMS Calcd for $\text{C}_{51}\text{H}_{52}\text{N}_4\text{O}_5$ $[\text{M}+1]$: 801.3938. Found: 801.4028. $[\alpha]_{\text{D}}^{20}$ -33.8° (c = 0.507, CHCl_3).

2-Hydroxy-5-methoxybenzaldehyde-L-Gln(Trt)-L-Tyr(Obn)-NH-Bu (4b). mp = 186-192 °C. IR (neat): 3416 (m), 3310 (s), 3093 (w), 3069 (m), 3034 (m), 2963 (m), 2934 (m), 2875 (m), 1975 (w), 1892 (w), 1810 (w), 1651 (s), 1598 (m), 1522 (s), 1445 (s), 1386 (m), 1345 (m), 1286 (s), 1245 (s), 1186 (s), 1168 (m), 1086 (w), 1051 (m), 907 (m) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 11.80 (1H, s, ArOH), 8.11 (1H, s, CH=N), 7.37-7.20 (20H, m, ArH), 7.10 (2H, d, J = 8.8 Hz, ArH), 6.95 (2H, m, ArH), 6.85 (3H, t, J = 8.8 Hz, ArH), 6.70 (1H, d, J = 2.8 Hz, NHC(O)), 6.46 (1H, d, J = 7.6 Hz, NHC(O)), 5.74 (1H, t, J = 5.6 Hz, NHCH₂), 4.95 (2H, s, OCH₂Ph), 4.49 (1H, dt, J = 7.2, 7.2 Hz, NHCHC(O)), 3.75 (3H, s, CH₃O), 3.73 (1H, dd, J = 6.4, 6.4 Hz, NCHC(O)), 3.12 (2H, m, C(O)CH₂), 2.97 (2H, d, J = 7.2 Hz, CHCH₂Ar), 2.22 (3H, m, aliphatic CH), 1.98 (1H, m, aliphatic CH), 1.29 (2H, m, aliphatic CH), 1.18 (2H, m, aliphatic CH), 0.84 (3H, t, J = 7.2 Hz, CH₂CH₃). ^{13}C NMR (100 MHz, CDCl_3): δ 171.1, 171.0, 170.3, 168.1, 158.0, 155.1, 152.4, 144.7, 137.0, 130.5, 128.9, 128.8, 128.7, 128.1, 127.6, 127.2, 120.8, 118.1, 115.4, 115.3, 77.4, 71.3, 70.7, 70.1, 56.0, 54.7, 39.4, 37.7, 33.1, 31.5, 30.8, 20.1, 13.8. HRMS Calcd for $\text{C}_{52}\text{H}_{54}\text{N}_4\text{O}_6$ [M+1]: 831.4043. Found: 831.4126. $[\alpha]_{\text{D}}^{20}$ -29.7° (c = 0.467, CHCl_3).

Methyl-2-ethyl-2-methylbut-3-enoate (2). In a glovebox, a flask is charged with $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$ (2.0 mg, 4.0 μmol) and 2-hydroxybenzaldehyde-L-Gln(Trt)-L-Tyr(Bzl)-NHBU (4a) (7.7 mg, 9.6 μmol), sealed with a septum and then removed from the glovebox. To the Cu-salt and ligand, 0.5 mL of THF is added and the mixture is immediately cooled to -30°C in a dry ice/acetone bath, after which time diethylzinc (50 μL , 0.48 mmol) is added. Finally, a solution of methyl-4-(diethoxyphosphoryloxy)-2-methylbut-2-enoate (1a) (43 mg, 0.16 mmol) in 0.5 mL of THF is transferred by a cannula into the mixture. The resulting solution is allowed to stir at -30°C for 24 h, when TLC analysis indicates complete consumption of starting material (1:1 hexanes/EtOAc; R_f starting material = 0.12, R_f product = 0.90). The reaction is quenched at -30°C by dropwise addition of 2 mL of a saturated aqueous NH_4Cl solution. The suspension is allowed to warm to room temperature and is then diluted with 1 mL of H_2O to dissolve salts. The solution is washed three times with 1 mL of Et_2O . The organic layers are dried over MgSO_4 , and the Et_2O is removed in vacuo to yield a yellow oil. The oil is purified by silica gel chromatography (100% pentane to 50:1 pentane/ Et_2O , R_f of the product in 50:1 pentane/ Et_2O = 0.47) to yield the desired product (5) as a colorless oil (12 mg, 0.083 mmol, 52%). IR (neat): 2969 (s), 2926 (s), 2883 (w), 2852 (m), 1735 (s), 1642 (w), 1456 (w), 1245 (m), 1207 (w), 1152 (m), 1015 (w), 928 (w) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 6.01 (1H, dd, J = 10.8, 17.6 Hz, $\text{CH}=\text{CH}_2$), 5.09 (2H, m, $\text{CH}=\text{CH}_2$), 3.68 (3H, s, $\text{CH}_3\text{O}_2\text{C}$), 1.77 (1H, dq, J = 7.6, 14 Hz, CHHCH_3), 1.61 (1H, dq, J = 7.6, 14 Hz, CHHCH_3), 1.26 (3H, s, $\text{C}(\text{CH}_3)(\text{CO}_2\text{CH}_3)$), 0.84 (3H, dd, J = 7.6, 7.6 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 176.5, 141.7, 113.7, 52.0, 49.2, 32.0, 20.1, 9.1. HRMS Calcd for $\text{C}_8\text{H}_{14}\text{O}_2$: 142.0094. Found: 142.0991. $[\alpha]_D^{20}$ -31.4° (c = 0.233, CHCl_3) for an optically enriched sample of 90% ee.

The optical purity of the sample is determined by hydrolysis to the corresponding carboxylic acid. Treatment of the desired product in 0.5 mL THF with 0.5 mL 1 M LiOH at reflux for 2 h, acid/base work-up followed by silica gel chromatography (3:1 pentane/ Et_2O) delivers the desired carboxylic acid.

2-Ethyl-2-methylbut-3-enoic acid. IR (neat): 3098 (m), 2985 (s), 2925 (s), 2889 (m), 2657 (w), 1703 (s), 1643 (w), 1458 (m), 1416 (m), 1387 (w), 1261 (s), 1178 (w), 1094 (m), 1028 (m), 927 (m) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 9.12 (1H, br s, HO_2C), 6.02 (1H, dd, J = 10.8, 17.6 Hz, $\text{CH}=\text{CH}_2$), 5.15 (2H, m, $\text{CH}=\text{CH}_2$), 1.80 (1H, dq, J = 7.6, 14 Hz, CHHCH_3), 1.65 (1H, dq, J = 7.6, 13.4 Hz, CHHCH_3), 1.28 (3H, s, $\text{C}(\text{CH}_3)(\text{CO}_2\text{H})$), 0.89 (3H, dd, J = 7.6, 7.6 Hz, CH_2CH_3).

^{13}C NMR (100 MHz, CDCl_3): δ 181.8, 141.0, 114.4, 48.9, 31.9, 19.8, 9.0. HRMS Calcd for $\text{C}_7\text{H}_{12}\text{O}_2$: 128.0837. Found: 128.0841.

The carboxylic acid is subjected to chiral GLC analysis (β -dex, 85 $^\circ\text{C}$, 15 psi); chromatograms are illustrated below:

Peak	Ret time (min)	Area (%)	Ret time (min)	Area (%)
1	152.82	50.125	154.22	4.803
2	156.62	49.875	156.97	95.197

2-Methyl-2-(4-methylpentyl)but-3-enoate (5). IR (neat): 2948 (s), 2867 (m), 1741 (s), 1646 (w), 1476 (m), 1438 (w), 1376 (w), 1269 (w), 1199 (m), 1155 (m), 1010 (w), 916 (w) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 6.02 (1H, dd, J = 10.8, 17.6 Hz, $\text{CH}=\text{CH}_2$), 5.08 (2H, m, $\text{CH}=\text{CH}_2$), 3.68 (3H, s, CH_3), 1.68 (1H, m, $\text{CHH}(\text{CH}_2)_2$), 1.53 (2H, m, aliphatic CH), 1.27 (3H, s, $\text{C}(\text{CH}_3)(\text{CO}_2\text{CH}_3)$), 1.19 (4H, m, aliphatic CH), 0.85 (6H, d, J = 6.8 Hz, $(\text{CH}_3)_2\text{CH}$). ^{13}C NMR (100 MHz, CDCl_3): δ 176.6, 142.0, 113.5, 52.0, 48.8, 39.5, 39.4, 27.9, 22.7, 22.7, 22.5, 20.7. Anal Calcd for $\text{C}_{12}\text{H}_{22}\text{O}_2$: C, 72.68; H, 11.18. Found: C, 72.74; H, 11.41. $[\alpha]_{\text{D}}^{20}$ -9.61° (c = 0.340, CHCl_3) for an optically enriched sample of 88% ee.

The optical purity of the allylic substitution is determined by hydrolysis to the corresponding carboxylic acid. Treatment of the product in 0.5 mL THF with 0.5 mL 1 M LiOH at reflux for 12 h, acid/base work-up followed by silica gel chromatography (3:1 pentane/ Et_2O) delivers the desired carboxylic acid.

2-Methyl-2-(4-methylpentyl)but-3-enoic acid. IR (neat): 3088 (w), 1954 (s), 2911 (m), 2874 (m), 2654 (w), 1706 (s), 1645 (w), 1467 (m), 1418 (w), 1278 (m), 1210 (w), 1161 (w), 1008 (w), 923 (m) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 10.79 (1H, br s, HO_2C), 6.03 (1H, m, $\text{CH}=\text{CH}_2$), 5.13 (2H, m, $\text{CH}=\text{CH}_2$), 1.74-1.48 (3H, m, aliphatic CH), 1.29 (3H, s, $\text{C}(\text{CH}_3)(\text{CO}_2\text{H})$), 1.27-1.15 (4H, m, aliphatic CH), 0.86 (6H, d, $J = 6.4$ Hz, $(\text{CH}_3)_2\text{CH}$). ^{13}C NMR (100 MHz, CDCl_3): δ 182.4, 141.3, 114.1, 48.6, 39.4, 27.9, 22.7, 22.7, 22.4, 20.3. HRMS Calcd for $\text{C}_{11}\text{H}_{20}\text{O}_2$: 184.1463. Found: 184.1466.

The carboxylic acid is subjected to chiral GLC analysis (β -dex, 140 $^\circ\text{C}$, 15 psi); chromatograms are illustrated below:

Authentic Racemic

From Catalytic Reaction

Peak	Ret time (min)	Area (%)	Ret time (min)	Area (%)
1	74.71	49.827	74.576	94.013
2	77.85	50.133	79.249	5.987

Methyl-2-(4-acetoxybutyl)-2-methylbut-3-enoate (6). IR (neat): 2949 (m), 2867 (m), 1753 (s), 1470 (w), 1438 (w), 1369 (m), 1237 (s), 1136 (m), 1042 (m) cm^{-1} . ^1H NMR (400 MHz,

CDCl₃): δ 5.99 (1H, dd, J = 10.8, 17.6 Hz, CH=CH₂), 5.09 (2H, m, CH=CH₂), 4.04 (2H, t, J = 6.8 Hz, CH₂OAc), 3.68 (3H, s, CH₃O₂C), 2.04 (3H, s, OC(O)CH₃), 1.78-1.2 (6H, m, alkyl CH), 1.27 (3H, s, C(CH₃)(CO₂CH₃)). ¹³C NMR (100 MHz, CDCl₃, sample is an 8:1 mixture of S_N2':S_N2): δ 176.3, 171.3, 141.6, 113.8, 64.4, 52.1, 48.7, 38.8, 29.1, 28.6, 28.3, 26.0, 25.8, 21.2, 21.1, 20.6. HRMS Calcd For C₁₂H₂₀O₄: 228.1362. Found: 228.1367. $[\alpha]_D^{20}$ -6.65° (c = 0.400, CHCl₃) for an optically enriched sample of 77% ee.

The optical purity of the sample is determined conversion to the derived di-Mosher ester.⁶ Treatment of the product in 1 mL Et₂O at 0 °C with 6 equivalents of LiAlH₄ for 30 min delivers a diol, which is esterified according to published procedure.⁷

3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid 5-methyl-5-(3,3,3-trifluoro-2-methoxy-2-phenylpropionyloxymethyl)-hept-6-enyl ester. IR (neat): 3062 (m), 2962 (s), 2855 (m), 1747 (s), 1508 (w), 1451 (m), 1275 (s), 1174 (s), 1124 (s), 1086 (m), 1029 (s), 916 (m) cm⁻¹. ¹H NMR (400 MHz, C₆D₆, data for a racemic sample): δ 7.66 (4H, m, ArH), 7.08 (6H, m, ArH), 5.41 (1H, m, CH=CH₂), 4.83 (2H, m, CH=CH₂), 3.87 (4H, m, OCH₂), 3.41 (6H, m, CH₃O), 1.40-0.84, 6H, m, alkyl CH₂), 0.754 (3H, s, (CH₃)(alkyl)C), 0.734 (3H, s, (CH₃)(alkyl)C). ¹³C NMR (100 MHz, CDCl₃, data for a racemic sample): δ 166.7, 166.6, 142.4, 142.3, 132.5, 132.4, 129.8, 128.6, 128.5, 127.6, 127.4, 127.4, 124.9, 122.0, 114.6, 114.5, 84.9, 84.6, 72.8, 66.3, 55.5, 40.1, 36.8, 36.7, 29.8, 29.0, 20.6, 20.6, 20.2. HRMS Calcd for C₂₉H₃₂F₆O₆: 590.2103. Found: 590.2095.

The optical purity of the allylic substitution is determined by ¹H NMR (400 MHz, CDCl₃): δ 0.754 (3H, s, (CH₃)(alkyl)C), 0.734 (3H, s, (CH₃)(alkyl)C); the spectrum are illustrated below:

⁶ Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

⁷ Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165-7166.

Authentic Racemic

From Catalytic Reaction

Authentic Racemic

From Catalytic Reaction

Peak	Ret time (ppm)	Area (%)	Ret time (ppm)	Area (%)
1	0.753	1.33	0.753	2.30
2	0.733	1.70	0.733	0.30

Methyl-2-isopropyl-2-methylbut-3-enoate (7). IR (neat): 2955 (s), 2931 (s), 2879 (m), 1733 (s), 1657 (w), 1633 (w), 1458 (w), 1434 (m), 1406 (w), 1373 (w), 1259 (m), 1150 (m), 1112 (m), 1017 (w), 927 (m) ^{-1}cm . ^1H NMR (400 MHz, CDCl_3): δ 6.0 (1H, dd, $J = 10.8, 17.6$ Hz, $\text{CH}=\text{CH}_2$), 5.15 (1H, dd, $J = 1.2, 10.8$ Hz, $\text{CH}=\text{CHH}$), 5.08 (1H, dd, $J = 0.8, 17.6$ Hz, $\text{CH}=\text{CHH}$), 3.68 (3H, s, CH_3O), 2.14 (1H, dq, $J = 6.8, 6.8$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.17, (3H, s, $(\text{CH}_3)\text{C}(\text{CO}_2\text{Me})$), 0.83 (3H, d, $J = 6.8$ Hz, $(\text{CH}_3)_2\text{CH}$), 0.82 (3H, d, $J = 6.8$ Hz, $(\text{CH}_3)_2\text{CH}$). ^{13}C NMR (100 MHz, CDCl_3): δ 176.6, 141.1, 114.6, 52.7, 52.0, 34.9, 17.9, 17.4, 14.5. HRMS Calcd for $\text{C}_9\text{H}_{16}\text{O}_2$: 156.1150. Found: 156.1150. $[\alpha]_{\text{D}}^{20} -31.9^\circ$ ($c = 0.233$, CHCl_3) for an optically enriched sample of 54% ee.

The optical purity of the sample is determined conversion to the derived Mosher ester.⁶ Treatment of the product in 1 mL Et_2O at 0 $^\circ\text{C}$ with 3 equivalents of LiAlH_4 for 30 min delivers a diol, which is esterified according to published procedure.⁷

The optical purity of the allylic substitution is determined by ^1H NMR (400 MHz, CDCl_3): δ 0.976 (3H, s, $(\text{CH}_3)(\text{alkyl})\text{C}$), 0.961 (3H, s, $(\text{CH}_3)(\text{alkyl})\text{C}$); the spectrum are illustrated below:

From Catalytic Reaction

Authentic Racemic

From Catalytic Reaction

***t*-Butyl-2-ethyl-2-methylbut-3-enoate (8).** IR (neat): 2974 (m), 2920 (s), 2861 (m), 1728 (s), 1461 (m), 1372 (m), 1266 (m), 1153 (m) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 5.99 (1H, dd, $J = 10.4, 18.0$ Hz, $\text{CH}=\text{CH}_2$), 5.06 (2H, m, $\text{CH}=\text{CH}_2$), 1.73 (1H, m, CH_3CHH), 1.55 (1H, m, CH_3CHH), 1.44 (9H, s, $(\text{CH}_3)_3\text{CO}$), 1.20 (3H, s, $(\text{CH}_3)(\text{CO}_2t\text{-Bu})\text{C}$), 0.848 (3H, dd, $J = 7.2, 7.2$ Hz, CH_3CH_2). ^{13}C NMR (100 MHz, CDCl_3): δ 175.3, 142.5, 113.2, 80.4, 49.6, 32.2, 28.2, 20.1, 9.1. Anal Calcd for $\text{C}_{11}\text{H}_{20}\text{O}_2$: C, 71.70; H, 10.94. Found: C, 71.97; H, 10.69. $[\alpha]_D^{20} -6.36^\circ$ ($c = 0.673$, CHCl_3) for an optically enriched sample of >98% ee.

The optical purity of the allylic substitution is determined by conversion to the corresponding carboxylic acid. Treatment of the desired product in 0.5 mL CH_2Cl_2 with 5 equivalents of TFA for 2 h, concentration of the reaction followed by silica gel chromatography (3:1 pentane/ Et_2O) delivers the desired carboxylic acid.

The carboxylic acid is subjected to chiral GLC analysis (β -dex, 85 °C, 15 psi); chromatograms are illustrated below:

Authentic Racemic

From Catalytic Reaction

Peak	Ret time (min)	Area (%)	Ret time (min)	Area (%)
1	152.29	46.287		
2	156.04	53.713	156.01	1.00

***t*-Butyl-2-acetoxybutyl-2-methylbut-3-enoate (9).** IR (neat): 3087 (w), 2974 (s), 2943 (s), 2873 (m), 1745 (s), 1728 (s), 1640 (w), 1457 (m), 1407 (w), 1369 (m), 1243 (s), 1143 (s), 1042 (m), 929 (m), 853 (m) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 5.98 (1H, m, $\text{CH}=\text{CH}_2$), 5.06 (2H, m, $\text{CH}=\text{CH}_2$), 4.05 (2H, t, $J = 6.8$ Hz, CHOAc), 2.03 (3H, s, OC(O)CH_3), 1.78-1.3 (6H, m, alkyl CH), 1.44 (9H, s, $(\text{CH}_3)_3\text{CO}$), 1.22 (3H, s, $(\text{CH}_3)(\text{CO}_2t\text{-Bu})\text{C}$). ^{13}C NMR (100 MHz, CDCl_3): δ 175.0, 171.3, 142.3, 113.3, 80.5, 64.5, 49.2, 38.9, 29.2, 28.1, 21.3, 21.1, 20.7. Anal Calcd for $\text{C}_{15}\text{H}_{26}\text{O}_4$: C, 66.64; H, 9.69. Found: C, 66.90; H, 9.42. HRMS Calcd for $\text{C}_{15}\text{H}_{26}\text{O}_4$ $[\text{M}+1]$: 271.1831. Found: 271.1913. $[\alpha]_D^{20} -9.95$ ($c = 0.347$, CHCl_3) for an optically enriched sample of 83% ee.

The optical purity of the allylic substitution is determined by conversion to the derived Mosher ester.⁶ Treatment of the product in 1 mL Et_2O at 0 °C with 6 equivalents of LiAlH_4 for 30 min delivers a diol, which is esterified according to published procedure.⁷

The optical purity of the sample is determined by ¹H NMR (400 MHz, CDCl₃): δ 0.754 (3H, s, (CH₃)(alkyl)C), 0.734 (3H, s, (CH₃)(alkyl)C); the spectrum are illustrated below:

From Catalytic Reaction

*Authentic Racemic**From Catalytic Reaction*

Peak	Ret time (ppm)	Area (%)	Ret time (ppm)	Area (%)
1	0.754	1.33	0.754	2.62
2	0.734	1.70	0.734	0.25

(S)-(+)-Methyl-2-ethyl-2-phenylbut-3-enoate (13). IR (neat): 3039 (w), 2983 (m), 2952 (m), 2877 (w), 1736 (s), 1500 (w), 1451 (w), 1432 (w), 1246 (s), 1159 (w), 1134 (m), 998 (m), 923 (m) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.33 (2H, m, ArH), 7.24 (3H, m, ArH), 6.38 (1H, dd, $J = 10.8, 17.6$ Hz), 5.31 (1H, dd, $J = 0.4, 11.2$ Hz), 5.02 (1H, dd, $J = 0.4, 17.6$ Hz), 3.69 (3H, s, CH_3O), 2.22 (1H, dq, $J = 7.2, 14.8$, Hz, CHHCH_3), 2.13 (1H, dq, $J = 7.6, 14.4$ Hz, CHHCH_3), 0.84 (3H, dd, $J = 7.6, 7.6$ Hz, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 175.0, 142.0, 139.6, 128.4, 127.4, 126.9, 116.3, 58.2, 52.3, 29.6, 9.4. HRMS Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: 204.1150. Found: 204.1145. $[\alpha]_D^{20} +11.2$ ($c = 0.647$, CHCl_3) for and optically enriched sample of 86% ee.

The optical purity of the sample is determined by chiral GLC analysis (CD-GTA, 80 $^\circ\text{C}$, 15 psi); the chromatograms are illustrated below:

Authentic Racemic

From Catalytic Reaction

Peak	Ret time (min)	Area (%)	Ret time (min)	Area (%)
1	119.46	49.022	119.29	93.132
2	125.40	50.978	127.72	6.868

Methyl-2-methyl-2-phenylbut-3-enoate (14). IR (neat): 3093 (w), 3074 (w), 3031 (w), 2987 (m), 2955 (m), 1734 (s), 1646 (w), 1608 (w), 1508 (m), 1451 (m), 1250 (s), 1193 (s), 1136 (s), 1080 (m), 922 (m) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.33 (2H, m, ArH), 7.25 (3H, m, ArH), 6.40 (1H, dd, $J = 10.4, 17.2$ Hz, CH=CH₂), 5.29 (1H, dd, $J = 0.80, 10.4$ Hz, CH=CHH), 5.15 (1H, dd, $J = 0.8, 17.6$ Hz, CH=CHH), 3.71 (3H, s, CH₃O), 1.64 (3H, s, CH₃C). ^{13}C NMR (100 MHz, CDCl_3): δ 175.4, 143.6, 141.0, 128.6, 127.0, 126.5, 115.2, 54.0, 52.5, 23.7. Anal Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2$: C, 75.76; H, 7.42. Found: C, 75.66; H, 7.41. $[\alpha]_{\text{D}}^{20} -6.81^\circ$ ($c = 0.467$, CHCl_3) for an optically enriched sample of 94% ee.

The optical purity of the allylic substitution is determined by chiral HPLC analysis (OJ, 99.5:0.5 Hexane/IPA, 1.0 mL/min); the chromatograms are illustrated below:

Authentic Racemic

From Catalytic Reaction

Peak	Ret time (min)	Area (%)	Ret time (min)	Area (%)
1	12.46	47.87	12.63	97.224
2	14.59	52.133	14.97	2.776

(S)-(+)-Tert-Butyl-2-ethyl-2-phenylbut-3-enoate (15). IR (neat): 3100 (w), 3062 (w), 2974 (s), 2936 (m), 2886 (w), 1728 (s), 1501 (w), 1470 (m), 1243 (s), 1168 (s), 1130 (s), 1042 (w), 998 (w), 922 (m), 859 (m), 765 (w), 746 (w) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.29 (2H, m, ArH), 7.23 (2H, m, ArH), 6.35 (1H, dd, $J = 10.8, 17.6$ Hz, $\text{CH}=\text{CH}_2$), 5.25 (1H, dd, $J = 1.2, 11.2$ Hz, $\text{CH}=\text{CHH}$), 4.97 (1H, dd, $J = 1.2, 17.6$ Hz, $\text{CH}=\text{CHH}$), 2.15 (1H, dq, $J = 7.6, 14.0$ Hz, CHHCH_3), 2.06 (1H, dq, $J = 7.2, 13.6$ Hz, CHHCH_3), 1.39 (9H, s, $(\text{CH}_3)_3\text{CO}$), 0.84 (3H, dd, $J = 7.2$ Hz, CH_3CH_2). ^{13}C NMR (100 MHz, CDCl_3): δ 173.6, 142.7, 140.3, 128.1, 127.4, 126.6, 115.7, 81.0, 58.5, 29.5, 28.0, 9.5. HRMS Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2$ $[\text{M}+1]$: 247.1620. Found: 247.1698. $[\alpha]_D^{20} +14.3^\circ$ ($c = 0.493$, CHCl_3) for an optically enriched sample of 79% ee.

The optical purity of the allylic substitution is determined by conversion to the corresponding methyl ester. Treatment of the desired product in 0.5 mL CH_2Cl_2 with 5 equivalents of TFA for 2 h, concentration of the reaction followed by silica gel chromatography (3:1 pentane/ Et_2O) delivers the desired carboxylic acid. The carboxylic acid is then treated with 3 equivalents of iodomethane and 5 equivalents K_2CO_3 in 0.5 mL DMF for 4 h. The reaction is quenched by addition of 1 mL of H_2O and subsequently extracted 5 times with Et_2O . The organics are dried

over MgSO_4 , filtered, concentrated and the residue is purified by silica gel chromatography (50:1 pentane/ Et_2O).

The optical purity of the sample is determined by removal of the chiral GLC analysis (CD-GTA, 80 °C, 15 psi); the chromatograms are illustrated below:

Authentic Racemic

From Catalytic Reaction

Peak	Ret time (min)	Area (%)	Ret time (min)	Area (%)
1	119.46	49.022	120.68	89.321
2	125.40	50.978	129.25	10.679

***Tert*-Butyl-2-methyl-2-phenylbut-3-enoate (16).** IR (neat): 3087 (w), 3062 (w), 2980 (s), 2936 (w), 1728 (s), 1508 (w), 1451 (w), 1369 (m), 1250 (s), 1162 (s), 1130 (s), 1079 (w), 922 (m), 853 (m) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.27 (5H, m, ArH), 6.37 (1H, dd, J = 10.8, 17.6 Hz, $\text{CH}=\text{CH}_2$), 5.25 (1H, dd, J = 1.2, 10.8 Hz, $\text{CH}=\text{CHH}$), 5.13 (1H, dd, J = 1.2, 17.6 Hz, $\text{CH}=\text{CHH}$), 1.58 (3H, s, CH_3), 1.41 (9H, s, $(\text{CH}_3)_3\text{CO}$). ^{13}C NMR (100 MHz, CDCl_3): δ 1.74.0, 144.3, 141.7, 128.4, 126.7, 126.5, 114.6, 81.1, 54.4, 28.0, 23.6. HRMS Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$ $[\text{M}+1]$: 233.1463. Found: 233.1543. $[\alpha]_{\text{D}}^{20}$ -3.05° (c = 0.747, CHCl_3) for an optically enriched sample of 89% ee.

The optical purity of the allylic substitution is determined by conversion to the corresponding methyl ester. Treatment of the desired product in 0.5 mL CH_2Cl_2 with 5 equivalents of TFA for 2 h, concentration of the reaction followed by silica gel chromatography (3:1 pentane/ Et_2O) delivers the desired carboxylic acid. The carboxylic acid is then treated with 3 equivalents of iodomethane and 5 equivalents K_2CO_3 in 0.5 mL DMF for 4 h. The reaction is quenched by addition of 1 mL of H_2O and subsequently extracted 5 times with Et_2O . The organics are dried over MgSO_4 , filtered, concentrated and the residue is purified by silica gel chromatography (50:1 pentane/ Et_2O).

The optical purity of the allylic substitution is determined by chiral HPLC analysis (OJ, 99.5:0.5 Hexane/IPA, 1.0 mL/min); the chromatograms are illustrated below:

Authentic Racemic

From Catalytic Reaction

Peak	Ret time (min)	Area (%)	Ret time (min)	Area (%)
1	12.46	47.87	14.14	94.622
2	14.59	52.133	16.87	5.378

(R)-(+)-Methyl-2-formyl-2-phenylbutyrate (18). A solution of (*S*)-(+)-methyl-2-ethyl-2-phenylbut-3-enoate (**13**) (23.0 mg, 0.11 mmol), NaHCO_3 (2.4 mg, 0.028 mmol) and MeOH (1.1 mL) in 5.5 mL CH_2Cl_2 is allowed to cool to -78°C with a dry ice/acetone bath. Ozone is bubbled through the reaction mixture for 30 min, and after this time N_2 is bubbled through the solution and methylsulfide (24 μL , 0.33 mmol) is added. The reaction is allowed to warm to room temperature and stir for 1 h. The reaction is then concentrated and purified by silica gel chromatography (100% pentane to 50:1 pentane/ Et_2O , R_f of the product in 50:1 pentane/ Et_2O = 0.15) to yield a clear oil (20 mg, 0.097 mmol, 88%). IR (neat): 3058 (w), 3033 (w), 2978 (s),

2947 (s), 2891 (m), 2848 (m), 2755 (w), 1748 (s), 1739 (s), 1733 (s), 1728 (s), 1722 (s), 1716 (s), 1596 (w), 1497 (m), 1448 (m), 1392 (w), 1342 (w), 1299 (w), 1243 (s), 1138 (m), 1020 (m), 989 (w) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 9.91 (1H, d, $J = 0.8$ Hz, HC(O)), 7.39 (2H, m, ArH), 7.32 (1H, m, ArH), 7.21 (2H, m, ArH), 3.82 (3H, s, CH_3O), 2.38 (1H, dq, 7.2, 13.6 Hz, CHHCH_3), 2.16 (1H, ddq, $J = 0.8$, 7.2, 13.6 Hz, CHHCH_3), 0.91 (3H, dd, $J = 7.2$, 7.2 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 196.9, 172.0, 135.7, 129.3, 128.3, 127.6, 66.7, 52.7, 25.6, 9.7. HRMS Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_3$ [$\text{M}+1$]: 207.0943. Found: 207.1025. $[\alpha]_{\text{D}}^{20} +146^\circ$ ($c = 0.367$, CHCl_3).

(S)-(+)-4-Ethyl-4-phenyl-pent-2-enedioic acid 1-ethyl ester 5-methyl ester (19). A modified procedure was followed.⁸ To a solution of triethylphosphonoacetate (42 μL , 0.21 mmol) and LiCl (8.9 mg, 0.21 mmol) in 0.5 mL CH_3CN , DBU (28 μL , 0.19 mmol) is added dropwise. After one hour a solution of **18** in 0.5 mL CH_3CN is added dropwise over 20 min. The reaction is allowed to stir for 4 h and after this time the reaction is concentrated. The reaction is purified by silica gel chromatography (20:1 Hexanes/EtOAc, $R_f = 0.12$) to yield a clear oil (17 mg, 0.062 mmol, 65%). IR (neat): 3068 (w), 3032 (w), 2976 (s), 2909 (w), 2891 (w), 1738 (s), 1714 (s), 1659 (s), 1604 (w), 1505 (m), 1463 (m), 1371 (m), 1322 (s), 1273 (s), 1236 (s), 1181 (s), 1119 (m), 1040 (s), 997 (m), 868 (m) cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 7.47 (1H, d, $J = 16.4$ Hz, $\text{CH}=\text{CH}$), 7.34 (2H, m, ArH), 7.27 (1H, m, ArH), 7.22 (2H, m, ArH), 5.65 (1H, d, $J = 16.0$ Hz, $\text{CH}=\text{CH}$), 4.20 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 3.72 (3H, s, CH_3O), 2.31 (1H, dq, $J = 7.2$, 14.8 Hz, $\text{C}(\text{CHHCH}_3)(\text{Ph})$), 2.15 (1H, dq, $J = 7.2$, 14.8 Hz, $\text{C}(\text{CHHCH}_3)(\text{Ph})$), 1.29 (3H, t, $J = 7.2$ Hz, OCH_2CH_3), 0.89 (3H, dd, $J = 7.2$, 7.2 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 173.8, 166.6, 149.3, 140.7, 128.7, 127.5, 127.3, 122.7, 60.7, 57.8, 52.6, 29.9, 14.4, 9.5. Analysis Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4$: C, 69.54; H, 7.30. Found: C, 67.84; H, 7.59. $[\alpha]_{\text{D}}^{20} +10.1^\circ$ ($c = 0.513$, CHCl_3). **Proof of stereochemistry:** literature value $[\alpha]_{\text{D}}^{20} +11$ ($c = 1$, CHCl_3) is assigned to the *S* enantiomers of **13**.

(S)-(+)-Methyl-2-(benzylaminomethyl)-2-phenylbutyrate (20). A modified procedure was

⁸ a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essinfeld, A. P.; Masamune, S.; Rousch, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 25, 2183-2186. b) Fadel, A.; Garcia-Argote, S. *Tetrahedron Lett.* **1996**, 7, 1159-1166.

followed.⁹ To a solution of (*R*)-(+)-methyl-2-formyl-2-phenylbutyrate (**18**) (2.0 mg, 0.024 mmol) and benzylamine (8.0 μ L, 0.072 mmol) in 1.2 mL 1,2-dichloroethane, NaBH(OAc)₃ (25 mg, 0.12 mmol) and acetic acid (1.4 μ L, 0.024 mmol) are added. The reaction is allowed to stir for 24 h, after which time 0.5 mL NaHCO₃ is added. The mixture is extracted three times with 0.5 mL CH₂Cl₂. The organics are dried over MgSO₄, filtered, evaporated and purified by silica gel chromatography (1:1 Pentane/Et₂O, *R_f* of the product = 0.61) to yield a viscous yellow oil (6.9 mg, 0.023 mmol, 97%). IR (neat): 3343 (m), 3099 (w), 3068 (m), 3037 (m), 2970 (s), 2945 (s), 2884 (m), 2841 (m), 1952 (w), 1885 (w), 1744 (s), 1603 (w), 1493 (m), 1462 (m), 1334 (w), 1242 (s), 1119 (s), 1033 (m), 917 (w), 868 (w), 733 (m), 708 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.22 (10H, m, ArH), 3.75 (2H, s, NHCH₂Ph), 3.65 (3H, s, CH₃O), 3.16, 3.11, 2.23 (1H, dq, *J* = 7.6, 14.0 Hz, CHHCH₃), 2.11 (1H, dq, *J* = 7.6, 14.0 Hz, CHHCH₃), 0.75 (3H, dd, *J* = 7.6, 7.6 Hz, CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 175.9, 141.6, 140.7, 128.5, 128.4, 128.1, 127.0, 126.9, 126.8, 55.6, 54.3, 52.3, 52.1, 26.6, 8.9. HRMS Calcd for C₁₉H₂₃NO₂: 297.1729. Found: 297.1727. [α]_D²⁰ +18.5° (*c* = 1.59, CHCl₃).

3-Ethyl-3-methyldihydrofuran-2-one (17). To a solution of methyl-2-ethyl-2-methylbut-3-enoate (**2**) (5.0 mg, 0.035 mmol) in mL 100 μ L THF, 9-BBN (13 mg, 0.053 mmol) is added. The reaction is allowed to stir for 12 h. After this time the is allowed to cool to 0 °C with an ice bath and 70 μ L EtOH/THF (1:1), 70 μ L 2M NaOH and 70 μ L 30% H₂O₂ are added. After 1 h, the reaction is extracted five times with 0.5 mL Et₂O, the organics are dried over MgSO₄, filtered and evaporated. The reaction mixture is purified by silica gel chromatography (5:1 Pentane/Et₂O) to yield a clear oil (2.0 mg, 0.016 mmol, 44%). ¹H NMR (400 MHz, CDCl₃): δ 4.25 (2H, t, *J* = 7.2 Hz, OCH₂), 2.21 (1H, dt, *J* = 7.6, 12.8 Hz, OCH₂CHH), 2.00 (1H, dt, *J* = 6.8, 12.8 Hz, OCH₂CHH), 1.63 (2H, q, *J* = 7.6 Hz, CH₂CH₃), 1.24 (3H, s, C(CH₃)(Et)), 0.95 (3H, t, *J* = 7.6 Hz, CH₂CH₃).

Ligand Optimization Studies: Libraries of ligands were synthesized on solid support following published procedures.¹⁰ All solid phase reactions are performed in Bio-Spin Chromatography Columns (1.2 mL capacity, from Bio-Rad, cat.# 732-6008).

Library Screen I. The screening was carried out using the conversion of **1** to **2** as the model reaction. Each reaction was run using 5 mol % (CuOTf)₂•C₆H₆, 20 mol % chiral ligand on solid

⁹ Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849-3862.

¹⁰ a) For the ligand optimization protocol: Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1668-1671. b) Procedure for the synthesis of the ligands on solid support: Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690-4691.

support and 3 equivalents Et_2Zn in THF at $-30\text{ }^\circ\text{C}$ for 12 h.

Chart 1. *Ligand Screen for AA_1 Optimization ($\text{AA}_2 = \text{Phe}$).* The library indicated Gln(Trt) and Hfe are optimal AA_1 's. The screening was continued with Gln(Trt) due to the high cost of Hfe.

Amino Acid	Conv (%)	ee (%)
Val	95	35
D-Val	<5	—
Aib	20	<5
Ala	30	49
D-Ala	<5	—
Cha	80	52
Chg	>98	34
Tle	36	−11
Ile	>98	31
Leu	64	46
Nle	69	52
Lys(Boc)	50	46
Gln(Trt)	56	59
Glu(OBut)	52	44
D-Glu(OBut)	28	14
Glu(OBzl)	36	30
Arg(Tos)	>98	54
Asn(Trt)	>98	47
Asp(OBut)	52	51
Cys(Trt)	>98	9
Met	>98	48
Ser(But)	46	51
Ser(Bzl)	30	34
Phg	>98	47
Phe	53	32
D-Phe	19	<5

Hfe	>98	61
Tyr(Bzl)	28	<5
Tyr(But)	49	35
Thr	36	-15
Thr(Bzl)	>98	40
Thr(But)	>98	26
Thr(Trt)	<5	–
His(Trt)	18	3
Trp(Boc)	12	40
Gly	<5	–

Chart 2. *Ligand Screen for AA₂ Optimization (AA₁ = Gln(Trt)).* The library indicated that there were a number of optimal amino acids for the AA₂ position. The best examples were synthesized in solution and it was found that Tyr(OBn) is optimal.

Amino Acid	Conv (%)	ee (%)
Val	18	50
D-Val	9	<5
Aib	19	<5
Ala	25	4
D-Ala	29	<5
Cha	29	26
Chg	34	14
Tle	37	<5
Ile	30	21
Leu	45	54
Nle	20	10
Pro	25	<5
Gln(Trt)	25	<5
Glu(OBut)	45	45
D-Glu(OBut)	38	<5
Glu(OBzl)	18	5
Arg(Tos)	63	31
Asn(Trt)	23	<5
Asp(OBut)	43	25
Cys(Trt)	49	50
Met	82	70
Ser(But)	20	<5
Ser(Bzl)	22	<5

Phg	50	44
Phe	68	69
D-Phe	21	-7
Hfe	19	34
Tyr(Bzl)	66	63
Tyr(But)	25	58
Thr	14	6
Thr(Bzl)	18	<5
Thr(But)	13	<5
Thr(Trt)	26	<5
His(Trt)	15	<5
Trp(Boc)	17	43
Gly	16	4

Chart 3. *Ligand Screen for Schiff Base Optimization* ($AA_1 = \text{Gln(Trt)}$, $AA_2 = \text{Tyr(OBn)}$). The screening data indicated salicyl aldehyde (**1**) and 5-methoxysalicyl aldehyde (**14**) are optimal.

Aldehyde	ee (%)
1	91
2	88
3	13
4	39
5	17
6	55
7	13

8	71
9	91
10	17
11	29
12	87
13	88
14	92
15	70

Library Screen II. The screening was carried out using the conversion of **12a** to **13** as the model reaction. Each reaction was run using 5 mol % $(\text{CuOTf})_2 \cdot \text{C}_6\text{H}_6$, 20 mol % chiral ligand on solid support and 3 equivalents Et_2Zn in THF at -15°C for 24 h. The conversion and $S_N2':S_N2$ ratio was only determined by 400 MHz ^1H NMR for the reactions with the highest enantioselectivity.

Chart 4. *Ligand Screen for AA_1 Optimization ($\text{AA}_2 = \text{Phe}$).* The library indicated that Val, Thr(*Ot*-Bu) and Thr(Obzl) were optimal. The screening was continued with Tyr(Bzl).

Amino Acid	ee (%)	Conv (%)	$S_N2':S_N2$
Val	47	12	>20:1
D-Val	10		
Aib	2		
Ala	19		
D-Ala	<5		
Cha	13		
Chg	17		
Tle	10		
Ile	44	35	>20:1
Leu	28		
Nle	22		
Lys(Boc)	23		

Gln(Trt)	28		
Glu(OBut)	29		
D-Glu(OBut)	8		
Glu(OBzl)	<5		
Arg(Tos)	35		
Asn(Trt)	<5		
Asp(OBut)	30		
Cys(Trt)	28		
Met	31		
Ser(But)	25		
Ser(Bzl)	26		
Phg	31		
Phe	27		
D-Phe	11		
Hfe	28		
Tyr(Bzl)	21		
Tyr(But)	22		
Thr	11		
Thr(Bzl)	46	>98	>20:1
Thr(But)	44	>98	>20:1
Thr(Trt)	24		
His(Trt)	11		
Trp(Boc)	30		
Gly	31		

Chart 5. *Ligand Screen for AA₂ Optimization (AA₁ = Thr(OBzl)).* The library indicated that Trp(Boc) was optimal.

Amino Acid	ee (%)	Conv (%)	S _N 2':S _N 2
Val	32		
D-Val	-25		
Aib	2		
Ala	16		
D-Ala	-39	30	1:1
Cha	27		
Chg	22		
Tle	27		
Ile	22		

Leu	35		
Nle	20		
Lys(Boc)	35		
Gln(Trt)	−11		
Glu(OBut)	21		
D-Glu(OBut)	−10		
Glu(OBzl)	18		
Arg(Tos)	59	39	3:1
Asn(Trt)	−4		
Asp(OBut)	3		
Cys(Trt)	3		
Met	18		
Ser(But)	4		
Ser(Bzl)	16		
Phg	40		
Phe	39	>98	>20:1
D-Phe	−16		
Hfe	22		
Tyr(Bzl)	42	>98	>20:1
Tyr(But)	41	>98	>20:1
Thr	<5		
Thr(Bzl)	<5		
Thr(But)	<5		
Tyr(Me)	41		
His(Trt)	<5		
Trp(Boc)	49	79	>20:1
Gly	<5		

Chart 6. *Ligand Screen for Schiff Base Optimization* ($AA_1 = \text{Thr}(\text{OBzl})$, $AA_2 = \text{Trp}(\text{Boc})$). The library indicated that 1-naphthylsilylaldhyde (**2**) is optimal. At this point a number of ligands were synthesized in solution that contained the amino acids the libraries indicated were best. It was found that a ligand containing 1-naphthylsilylaldhyde-Thr(*O**t*-Bu)-Trp(Boc) was optimal.

Aldehyde	ee (%)
1	56
2	58
3	54
4	22
5	-17
6	44
7	13
8	15
9	<5
10	52
11	42
12	14
13	30
14	42
15	54

16	43
17	33

Chart 7. *Ligand Screen for terminus optimization.* Twelve ligands with various termini were synthesized in solution. The library indicated a benzyl terminus is optimal.

Amine	ee (%)
1	79
2	29
3	70
4	74
5	79
6	67
7	84
8	83
9	84
10	76
11	84
12	76