SUPPORTING INFORMATION

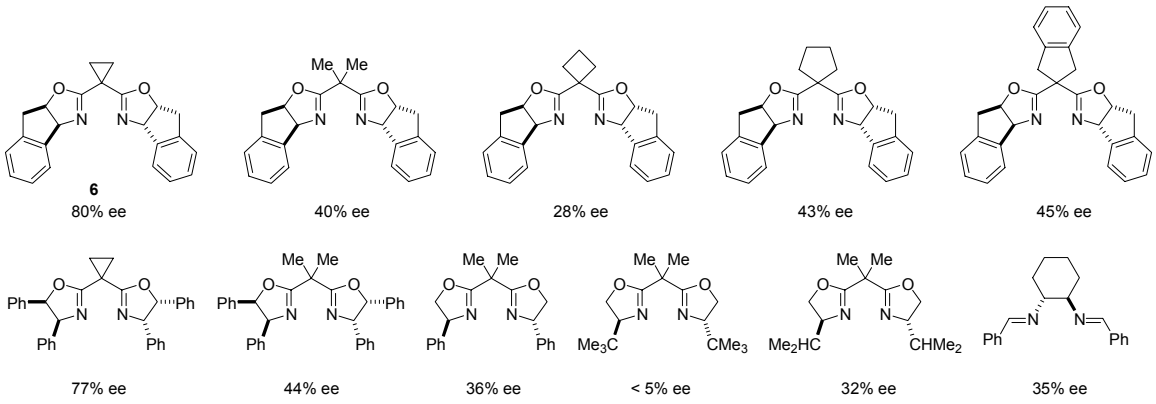
Experimental.

Experimental Procedures, Analytical Instrumentation and Data. ^{1}H NMR spectra were recorded on GE QE-300 (300 MHz) and Bruker AMX-400 (400 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) down field from TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublets of doublets, m=multiplet, br=broad), coupling constant(s), integration and peak assignment. ^{13}C NMR spectra were recorded on a GE QE-300 (75 MHz) and Bruker AMX-400 (100 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. Mass spectra were acquired on a Joel JMS-SX-102 spectrometer. HPLC analyses were carried out on Hewlett-Packard system model 1100. Rotations and elemental analysis were performed by Robertson Microlit Laboratories, Inc., Madison, New Jersey.

Typical Procedure for Enantioselective Michael Addition of 1 to 2: $Mg(OTf)_2*4H_2O$ (19.6 mg, 0.05 mMol, 0.05 equiv.) and ligand **6** (20.1 mg, 0.055 mMol, 0.055 equiv.) are combined in the reaction flask. 1 mL of $CHCl_3$ (hydrocarbon stabilized) is added and the mixture is stirred for 0.5-1h. 4 mL of $CHCl_3$ is added, followed by 200 mg of 4A molecular sieves, and the resulting mixture is stirred for an additional 90 min. Following this, nitrostyrene **2** (1 mMol, 1 equiv.) is added, followed by ketoester **1** (1.2 mMol, 1.2

equiv.) and N-methylmorpholine (6.6 μL, 0.06 mMol, 0.06 equiv.). Conversion and selectivity are determined by HPLC analysis. After the reaction is complete, 15 mL of hexane is added and stirred for 20 min. The solid is filtered off and the wet cake is washed with MTBE (5 mL). The combined filtrate is washed with 5 mL of aqueous H_3PO_4 (5%) and 5mL of brine, then dried over $MgSO_4$. The drying reagent is filtered and the solution is concentrated under reduced pressure. The product is purified by chromatography on silica gel using hexane/EtOAc (v. 80/20).

Ligands screened in the asymmetric conjugate addition reaction.



Ligand Preparation

Parent Ligand 9:[21a] A reaction vessel equipped with overhead stirrer, thermometer, and condenser, and N_2 inlet is charged with diethyl malonimidate dihydrochloride (1.527 kg, 6.61 mol). 14.5 L of dry THF is added, and once stirring is commenced, aminoindanol (1.793 kg, 12.02 mol) is added and washed in with 0.5 L of THF. The reaction is heated to 45–55 ^{o}C, until remaining aminoindanol is less than 10% by area (HPLC), and subsequent readings 30 min apart indicate a drop of less than 0.5 area%.

When the reaction is complete (4 h), the temperature is adjusted to < 5 ^{o}C. 0.5 N aqueous sodium bicarbonate [48 kg, 24 mol, prepared by dissolving 2.52 kg of $NaHCO_3$ (30 mol) in 61.5 kg of water] is added at such a rate that the internal temperature remains below 15 ^{o}C. The temperature is again brought to < 5 ^{o}C. By HPLC, <0.1 mg/mL of the product remains in the liquors. The product is filtered, and thoroughly washed twice with water (9 kg then 7.5 kg). The filter cake is dried in vacuo to yield 1.639 kg of parent ligand **9** (98 wt%, 1.606 kg assay, 81% yield) as a white crystalline solid.

Parent ligand 9: mp > 200 ^{o}C (lit.[1] 207-209 ^{o}C); ^{1}H ($CDCl_3$) δ 7.40-7.36 (m, 2H), 7.22-7.14 (m, 6H), 5.50 (d, *J* = 7.7 Hz, 2H), 5.27 (m, 2H), 3.32 (dd, *J* = 7.0, 18.0 Hz), 3.20 (m, 2H), 3.10 (dd, *J* = 1.5, 18.0 Hz). ^{13}C ($CDCl_3$) δ 161.4, 141.2, 139.2, 128.2, 127.1, 125.1, 124.9, 83.5, 76.6, 39.8, 28.9. $[\alpha]_D^{25}$ = -271.9^{o} (c 3.11, $CHCl_3$) (lit.[1] $[\alpha]_D^{25}$ = -352.7^{o} (c 3.0, $CHCl_3$)).

Anal. Cacld for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.12; H, 5.60; N, 8.54.

Ligand 6:[21a] A round bottom flask is charged with parent ligand **9** (1.491 kg, 98 wt%, 4.422 mol) followed by 11.3 L of THF, and stirring is commenced. Dibromoethane (0.780 L, 1.700 kg, 9.05 mol) is added. LiHMDS solution (1M in THF, 4.5 L, 4.5 mol) is then added over 30 min. The addition is mildly exothermic, and the internal temperature is maintained below 25 ^{o}C. Following the initial addition, the remainder of the LiHMDS solution (7.4 L) is added over 4 h.

The following morning, HPLC analysis shows little remaining starting material (<5%). 26.2 kg of a 20% aqueous ammonium chloride solution is added: the addition is mildly

exothermic, and the temperature increases slightly (23 ^{o}C). The mixture is transferred to a 100-L cylindrical flask, and washed in with 0.5 L of THF. The aqueous layer is drawn off, and the THF layer is washed with 29.1 kg of a 25% aqueous sodium chloride solution. The THF layer is then dried over 3 kg of magnesium sulfate. After 2.5 h, the mixture is filtered, and concentrated to a thick slurry. Ethanol (5 L) is added and the reaction reconcentrated.

The ethanol content of the reaction is adjusted to 6.5 L. The slurry is heated to 55–60 ^{o}C for 25 min. The heat is turned off, and the reaction cooled to ambient, then an ice/water bath is employed to lower the temperature to < 5 ^{o}C. The solid is collected by filtration and dried in vacuo at 32 ^{o}C to yield 1.342 kg (1.339 kg assay, 85% yield) of the product as a light green solid.

Ligand 6: mp = 165-166 ^{o}C; ^{1}H ($CDCl_3$) δ 7.47-7.44 (m, 2H), 7.28-7.22 (m, 4H), 5.53 (d, *J* = 8.0 Hz, 2H), 5.33 (m, 2H), 3.39 (dd, *J* = 6.6, 17.7 Hz, 2H), 3.20 (dd, *J* = 1.8, 17.8 Hz, 2H), 1.34 (m, 2H), 1.29 (m, 2H). ^{13}C ($CDCl_3$) δ 165.2, 141.3, 139.3, 128.0, 126.9, 125.2, 124.8, 83.2, 76.3, 39.8, 18.5, 16.0. $[\alpha]_D^{25}$ = -308.8^{o} (c 3.04, $CHCl_3$).

Anal. Cacld for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.51; H, 5.66; N, 7.86.

Nitrostyrene 2: A vessel is charged with 5-methoxypiperonal (4.208 kg, 18.0 mol). Acetic acid (24.0 kg) is added, followed by nitromethane (7.94 kg, 124 mol). Finally, ammonium acetate (3.37 kg, 43.7 mol) is added. Heating is commenced to 90–100 ^{o}C, during the course of which, the aldehyde is observed to go into solution then the nitrostyrene precipitates as a yellow solid.

After 4.5 h, heating is stopped and the reaction stirred overnight while cooling to ambient at which point the yellow solid is filtered. The wetcake is reslurried in 40.8 kg of water. After stirring overnight, the product is filtered and dried in vacuo at 50 ^{o}C with a N_2 bleed.

In order to remove residual acetic acid, the following wash was employed. A round bottom flask is charged with nitrostyrene (5.165 kg). 16.5 kg of ethyl acetate is added and stirring is commenced. 14.5 kg of methanol is then added, and the mixture is heated to 45–55 ^{o}C for 7 h. After cooling overnight, the solid is filtered and dried in vacuo at 57 ^{o}C until ^{1}H NMR indicates that <0.5 mol% HOAc remains. This procedure provides 4.616 kg of nitrostyrene **2** (88% assay, 4.061 kg assay, 89% recovery). This wash was performed in two batches. The combined yield of the two runs (corrected for purity) was 7.65 kg, which represents an 87% overall yield from 5-methoxypiperonal.

A sample was chromatographed. **Nitrostyrene 2**: mp > 200 ^{o}C. ^{1}H (DMSO-d_6, 300 MHz) δ 8.11 (d, *J* = 13.6 Hz, 1H), 7.96 (d, *J* = 13.6 Hz, 1H), 7.20 (d, *J* = 1.5 Hz, 1H), 7.15 (d, *J* = 1.5 Hz, 1H), 6.02 (s, 2H), 3.78 (s, 3H). ^{13}C (DMSO-d_6, 300 MHz) δ 148.4, 142.8, 139.1, 138.0, 136.0, 124.2, 111.3, 102.5, 101.9, 56.4. Anal. Cacld for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 54.34; H, 3.90; N, 5.77.

Ethyl 3,3-dimethylhexanoate (11): A reaction vessel is charged with THF (25.6 L), chlorotrimethylsilane (3.40 L, 26.5 mol), copper(I) iodide (429 g, 2.21 mol) and ethyl 3,3-dimethylacrylate (2.89 kg, 22.1 mol). The reaction mixture is stirred at room temperature for 15 min, then cooled to –15 ^{o}C with an ice/methanol bath. *n*-Propylmagnesium chloride (2M in diethyl ether, 13.3 L, 26.6 mol) is added over about 2

h with vigorous stirring such that the reaction temperature is maintained between –15 ^{o}C and –10 ^{o}C. During the addition, the reaction mixture becomes gray, then green, blue and finally black. The reaction temperature is kept below –10 ^{o}C. After the addition is finished, the reaction mixture is stirred at –15 ^{o}C to –10 ^{o}C.

When <3 area% (GC) of ethyl 3,3-dimethylacrylate remains, the reaction is slowly quenched with 8.2 kg of 20% aqueous ammonium chloride solution while maintaining the temperature between –15 ^{o}C and 0 ^{o}C. The mixture is then transferred to a vessel equipped with a mechanical stirrer and a nitrogen inlet. The reaction mixture is stirred under nitrogen and aqueous hydrochloric acid (1.28 L of concentrated hydrochloric acid in 11.5 L of water) is added and stirred for 0.5 h. Separation of layers affords 32.0 kg of a solution of **11** (11.3 wt% by GC, 3.62 kg assay, 95%) in THF which is stored at 0–10 ^{o}C. **Ethyl 3,3-dimethylhexanoate (11):** ^{1}H NMR ($CDCl_3$, 300MHz) δ 4.12 (q, *J*=7.0 Hz, 2H), 2.18 (s, 2H), 1.32-1.25 (m, 7H), 0.98 (s, 6H), 0.90 (m, 3H).

3,3-Dimethylhexanoic acid (12): A THF solution of ethyl 3,3-dimethylhexanoate (11.24 kg by assay) is concentrated to a 45 weight% (11.09 kg by assay) solution then charged to a vessel followed by ethanol (17.1 L), and a solution of 5.23 kg of sodium hydroxide in 17.1 L of water. The resulting mixture is stirred and heated to 72^{o}C.

After GC shows that <2 area% of ester **11** remains, the reaction mixture is cooled to room temperature. Most of the organic solvents are removed under reduced pressure, and the residue is slowly acidified with a solution of 22.0 L of 1:1 conc. HCl/water until the pH of the aqueous layer = 2–3. Ethyl acetate (23.5 L) is added and the mixture is stirred for 20 min. Following separation of layers, the aqueous layer is extracted twice with 14.7

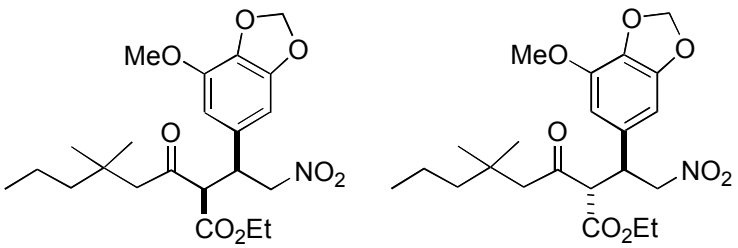
L of ethyl acetate. The EtOAc layers are combined and concentrated under reduced pressure, then chased with dry THF (24 L) until no ethyl acetate or ethanol peaks are observed by ^{1}H NMR, to yield 15.4 kg of a solution of 3,3-dimethylhexanoic acid (**12**) in THF (58.7 wt%, 9.04 kg assay, 97%). **3,3-Dimethylhexanoic acid (12):** ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.08 (s, 2H), 1.32–1.25 (m, 4H), 0.98 (s, 6H), 0.90(t, *J* = 7.0Hz, 3H).

Ethyl 5,5-dimethyl-3-oxo-octanoate (1): A vessel is charged with ethyl malonate, potassium salt (6.55 kg, 38.5 mol), and 22.0 L of THF. Magnesium chloride (3.66 kg, 38.5 mol) is added with cooling. The reaction mixture is stirred at 50 ^{o}C for 5 h under nitrogen, then allowed to cool to room temperature overnight.

A second reaction vessel is charged with 1,1'-carbonyldiimidazole (CDI, 4.87 kg, 30.0 mol) and 11 L of THF. A solution of 3,3-dimethylhexanoic acid (**12**) in THF (6.30 kg solution, 3.70 kg assay, 25.7 mol) is added to the stirred reaction mixture over 30 min at ambient temperature. After 15 additional min no starting material is observed by GC, and the solution is transferred to the malonate salt suspension over 10 min. After the addition is complete, the mixture is heated to 50 ^{o}C. The reaction is monitored by GC; after 2.5 h, < 0.5 area% of acyl imidazolide intermediate is observed. The reaction mixture is transferred over 20 min to a vessel containing a 33% aqueous phosphoric acid solution [10.9 kg of 85% phosphoric acid in 22 L of distilled water]. The mixture is stirred until all of the solid dissolves then the aqueous layer is separated.

A 20% aqueous $NaHSO_4$ solution (6.88 kg) is added to the organic solution. The mixture is vigorously stirred until <0.5 area% of acyl imidazolide is observed by GC in

the organic layer. Following separation, the organic layer is washed first with 17.3 kg of a 20% aqueous sodium carbonate solution then with 13.75 kg of a 20% aqueous sodium chloride solution to yield 32.43 kg of a solution of ethyl 5,5-dimethyl-3-oxo-octanoate (**1**) in THF (15.91 wt%, 5.16 kg assay, 93%). **Ethyl 5,5-dimethyl-3-oxo-octanoate (1):** ^{1}H NMR ($CDCl_3$, 300 MHz) ketoester/ enolester = 4/1 δ 12.1 (br s, 0.2H enolester), 4.92 (s, 0.2H, enolester), 4.19 (q, *J* = 7.0 Hz, 1.6H, ketoester), 4.18(q, *J* = 7.0 Hz, 0.4H, enolester), 3.40 (s, 1.6H, ketoester), 2.49 (s, 1.6H, ketoester), 2.06 (br s, 0.4H, enolester), 1.35–1.20 (m, 7H), 0.96 (s, 4.8H, ketoester), 0.95 (s, 1.2H, enolester), 0.87 (m, 3H); MS (DCI/NH_3) *m/z* 232 ($M + NH_4^+$).



Ethyl 5,5-dimethyl-2-[2-nitro-1-(4,5-methylenedioxy-3-methoxy-phenyl)ethyl]-3-oxooctanoate, 2: The solution of ketoester **1** in THF is turned over to $CHCl_3$ by first concentrating, then coevaporating with 58 L of $CHCl_3$.

A round bottom flask is charged with $Mg(OTf)_2$ (0.173 kg, 0.536 mol). Water (38 mL, 2.11 mol) is added over 30 min with vigorous stirring. Mixing is continued for 1 h, until homogenization is indicated by a sample KF of 15–25 wt% water. The gray powder $Mg(OTf)_2$ *4 H_2O is transferred to a round bottom flask. Ligand **6** (0.211 kg, 0.592 mol) is added, followed by 13 L of chloroform. The mixture is stirred for 2 h, then diluted

with 52 L of chloroform. 4A molecular sieves (2.60 kg) are added, and the reaction stirred for a further 20 min.

Nitrostyrene **2** (2.88 kg assay, 12.85 mol) is added, followed by ketoester **1** (5.5 L, 3.33 kg assay, 15.54 mol) and *N*-methylmorpholine (0.080 L, 0.73 mol). The reaction is then heated to 34–38 ^{o}C. After 19 h, chloroform is removed in vacuo to ⅓ to ½ volume. 50 L of hexane is added, followed after 10 min by 3.03 kg of activated charcoal. After stirring an additional 40 min the mixture is filtered and the cake washed with 15 L of 2:1 hexanes/chloroform. The resulting solution is washed with 3 kg of 5% aqueous H_3PO_4 then with 3 kg of water. The organic solution is concentrated under reduced pressure and chased with 30 L of THF to remove $CHCl_3$. The process provided 14.37 kg of a THF solution of nitroketone **3** (32.2 wt%, 4.63 kg assay, 82%, 88% ee).

A sample was chromatographed. **Nitroketone 3:** mixture of diastereomers. R_f=0.50(EtOAc/hexane =20:80); ^{1}H ($CDCl_3$, 300 MHz) δ 6.31 (m, 1H), 6.28 (m, 1H), 5.87 (m, 2H), 4.77–4.62 (m, 2H), 4.21–3.89 (m, 4H), 3.80 (s, 3H), 2.46 (d, *J* = 17.3 Hz, 0.5 H), 2.35 (d, *J* = 17.6 Hz, 0.5 H), 2.32 (d, *J* = 16.9 Hz, 0.5 H), 2.03 (d, *J* = 17.6 Hz, 0.5 H), 1.26–1.14 (m, 4H), 1.13–0.98 (m, 4H), 0.90 (s, 3H), 0.85–0.71 (m, 5H). MS (DCI/NH_3) *m/z* 455 (M + NH_4^+); Anal. Calcd for $C_{22}H_{31}NO_8$: C, 60.40; H, 7.14; N, 3.20. Found: C, 60.07; H, 7.03; N, 2.98. HPLC conditions: Zorbax RX-C8 column 4.6 x 250 mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v. 90:10 to 10:90 within 15 min.) at 1.5 mL/min., UV detection @210 nm, 35 ^{o}C. **3**: t_R: 15.0, 15.2 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/*i*-PrOH (v. 90:10) at 1.0 mL/min., UV detection @ 210 nm. t_R: [(2*S*, 1'*R*) and (2*R*, 1'*R*)] = 6.5, 7.2 min.; [(2*S*, 1'*S*) and (2*R*, 1'*S*)] = 7.8, 8.9 min.

Cyclic imine 13: A reactor equipped with a mechanical stirrer, a thermocouple, and nitrogen and hydrogen inlets is purged three times with nitrogen. Raney-nickel (6.6 kg) is washed four times with 7.5 L of water and charged to the reactor. After purging the reactor three times with nitrogen, a solution of nitroketone **3** in THF (15.35 kg, 27.5 wt%, 4.22 kg, 9.65 mol) is charged to the reactor, followed by H_3PO_4 in THF (100g, 0.87 mol, of 85 wt% H_3PO_4 in 4 kg of THF), and 25 kg of THF.

The reaction is stirred while the reactor is purged three times with hydrogen. The reaction pressure is kept between 40–50 psi. During the hydrogen purge, the reaction temperature increases to 30–35 ^oC. When the temperature holds steady for 5 min, the reaction is slowly heated to 50 ^oC. When HPLC indicates that <0.5 area% of nitroketone **3** remains in the reaction mixture, the reaction is cooled to room temperature. Raney-nickel is filtered off and the catalyst is washed with 30 kg of THF under nitrogen. The resulting THF solution of imine **13** is very air-sensitive and is carefully maintained under a nitrogen atmosphere in preparation for the next step.

Pyrrolidine 4: The solution of imine **13** in THF is concentrated under reduced pressure and chased with MeCN. When <0.5 area% of THF peak on GC is observed, the solution of imine **13** in MeCN is transferred under nitrogen to a reaction vessel equipped with mechanical stirrer, thermocouple and nitrogen inlet. 34 L of MeCN is added. $NaBH(OAc)_3$ (4.42 kg, 19.8 mol) is added slowly with stirring; the reaction temperature is maintained at 10–30 ^oC. After the addition is complete, the suspension is cooled to 5–10 ^oC. Hydrochloric acid (2.11 L) is slowly added at a rate such that gas evolution is

kept under control and the reaction temperature at 10–20 ^{o}C. At the end of the hydrochloric acid addition, the pH is 3–4. If the pH is above 4, extra hydrochloric acid can added until 2<pH<4. After the addition is complete, the reaction mixture is stirred at 20±5 ^{o}C. When the reaction is complete, potassium carbonate solution (6.33 kg of K_2CO_3 in 15.0 kg of water) is added to the reaction mixture over 20 min. The rate is adjusted to maintain the reaction temperature under 30 ^{o}C. At the end of the addition, the pH should be >8. After the addition is complete, the reaction mixture is stirred under nitrogen overnight. The layers are separated, yielding 42.6 kg of an MeCN solution of pyrrolidine **4** (7.24 wt%, 3.08 kg assay, 82%, 88–90% ee). The solution is stored at 0–10 ^{o}C.

The enantiomeric excess of the free base is assayed by forming the Cbz derivative, which is assayed by HPLC. Chiral HPLC sample preparation: 10 uL of amine solution is diluted with 990 ul of MTBE. CbzCl (100 uL) and 10% aqueous K_2CO_3 are added and shaken. 200 uL of the organic layer is diluted with 800 uL of hexane. Chiral HPLC conditions: Chiralpak® AD column; 90/10 hexane / EtOH; flow rate 1.0 mL/min.; 210nm; retention times: **Cbz-4**, 8.8 min, ***ent*-Cbz-4**, 11.1 min.

Pyrrolidine 4: ^{1}H NMR (CD_3OD/300 MHz) δ 6.50 (d, J = 1.8 Hz, 1H), 6.41 (d, J = 1.5 Hz, 1H), 5.93 (s, 2H), 4.21–4.17 (m, 2H), 3.88 (s, 3H), 3.53–3.36 (m, 3H), 3.03 (dd, J = 10.3, 6.6 Hz, 1H), 2.55 (t, J = 8.8 Hz, 1H), 1.69 (dd, J = 14.3, 1.8 Hz, 1H), 1.45 (dd, J = 14.4, 9.2 Hz, 1H), 1.30–1.18 (m, 4H), 1.22 (t, J = 7.0 Hz, 3H), 0.92 (s, 6H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 173.8, 148.9, 143.2, 137.2, 133.6, 106.7, 101.2, 100.8, 61.2, 60.8, 60.4, 56.4, 54.7, 49.9, 47.8, 45.0, 32.9, 27.5, 27.4, 17.0, 14.8,

14.2; $[\alpha]_D^{25}$=67.65° (c 1.00, $CHCl_3$); MS (DCI/NH_3) m/z 392 (amine+H); Anal. Cacld for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50; N, 3.58. Found: C, 67.20; H, 8.57; N, 3.54.

Pyrrolidine-tartrate salt 5: The solution of pyrrolidine **4** in MeCN (8.0 wt%, 81.1 kg, 6.50 kg assay) is concentrated to 15±2 L under reduced pressure. The residue is diluted with 71 L of *tert*-butyl methyl ether and transferred to a vessel equipped with a mechanical stirrer and a nitrogen inlet. K_2CO_3 solution (1.2 kg of K_2CO_3 in 10.8 kg of water) is added to remove residual HOAc. The mixture is stirred vigorously until no solids remain (about 1–2 hours). The organic layers are collected and washed twice with water (6 L then 3 L). The MTBE solution (63.75 kg) is collected (10.22 wt %, 6.5 kg assay).

The pyrrolidine solution is then concentrated to 15±2 L under reduced pressure. MTBE is chased with MeCN until no MTBE peaks are observed by GC or ^{1}H NMR (DMSO-D_6). To the resulting MeCN solution (10±1 L) is added 48.5 L of MeCN, and the mixture is stirred for 10 min. A MeOH solution of D-tartaric acid (1.24 kg of D-tartaric acid in 19.5 L of MeOH) is added over 10 min. The mixture is then heated to 65 °C and stirred until no solid is observed. The brown solution is allowed cool to 55 °C and seeded. When precipitation has begun, the reaction is allowed to cool to room temperature. The mixture is stirred at room temperature until <20 mg/mL product remains in the supernatant. The white solid is collected by filtration and washed sequentially with MeCN (12 L) and MTBE (12 L). The solid is dried in vacuo at 50 °C with a N_2 bleed for 2 days to yield 6.4 kg of salt **5** (assay 78.5 wt% pyrrolidine, 5.02 kg assay, 93.6 wt% salt, 77% yield, 96–97 % ee). **Pyrrolidine-tartrate salt 5:** ^{1}H NMR

(CD_3OD, 500 MHz) δ 6.55 (s, 4H), 5.91 (s, 4H), 4.37 (s, 2H), 4.15–4.07 (m, 4H), 3.87 (s, 6H), 3.85 (m, 2H), 3.67 (dd, *J* = 11.1, 8.4 Hz, 2H), 3.58 (td, *J* = 11.0, 8.4 Hz, 2H), 3.34 (t, *J* = 11.0 Hz, 2H), 2.99 (t, *J* = 11.0 Hz, 2H), 1.86 (dd, *J* = 15.2, 8.7 Hz, 2H), 1.73 (dd, *J* = 15.2, 2.3 Hz, 2H), 1.33–1.22 (m, 4H), 1.14 (t, *J* = 7.0 Hz, 6H), 0.95 (s, 6H), 0.94 (s, 6H), 0.91 (t, *J* = 6.5 Hz, 6H); ^{13}C NMR (DMSO-D_6, 300 MHz) δ 175.9, 171.0, 148.5, 143.1, 133.8, 133.4, 107.4, 101.4, 101.1, 90.0, 72.8, 60.5, 59.2, 58.1, 56.3, 51.4, 47.8, 44.2, 43.2, 32.4, 26.9, 26.8, 16.6, 14.8, 14.0; $[\alpha]_D^{25}$ = 47.15° (c 1.00, DMSO); MS (DCI/NH_3) *m/z* 392 (**6**+H); Anal. Cacld for $C_{44}H_{72}N_2O_{16}$: C, 61.79; H, 7.78; N, 3.00. Found: C, 61.72; H, 7.69; N, 2.87.

ABT-546: A flask is charged with 10L of THF and 20% aqueous K_2CO_3 (0.993 kg, 7.18 mol, dissolved in 4 L of water). Tartrate salt **5** (2.0 kg, 1.87 kg assay, 4.00 mol) is added and the mixture is stirred vigorously for 1.5 h, after which all of the solid has typically dissolved. The layers are separated, and the organic layer is assayed to contain 1.54 kg (98%) of the free base.

The THF layer is charged into a vessel and *N*,*N*-dibutylbromoacetamide (**15**, 1.053 kg, 3.93 mol) is added, followed by a 5% aqueous $NaHCO_3$ solution (0.528 kg dissolved in 10 L of water). The resulting mixture is heated to reflux for 2 h, after which another 0.105 kg of acetamide **15** is added. After another 1 h, another 0.105 kg of acetamide **15** is added. Reflux is continued until HPLC analysis indicates that less than 0.5 area% of the unalkylated pyrrolidine **4** remains (typically 5 h). The reaction is allowed to cool to ambient overnight at which point the level of the starting material is typically less than 0.15%. The layers are separated, and the organic layer is assayed to contain 2.19 kg

(99.4%) of the desired ester. **Ester:** ^{1}H NMR ($CDCl_3$, 300MHz) δ 6.60 (d, *J* = 1.5 Hz, 1H), 6.55 (d, *J* = 1.5 Hz, 1H), 5.92 (m, 2H), 4.16 (m, 2H), 3.89 (s, 3H), 3.73 (d, *J* = 13.7 Hz, 1H), 3.67 (m, 1H), 3.51 (dt, *J* = 7.7, 13.3 Hz), 3.34 (m, 1H), 3.19 (m, 1H), 3.11 (m, 1H), 2.98–2.85 (m, 2 H), 2.69 (dd, *J* = 5.5, 6.6 Hz), 1.68–1.43 (m, 4 H), 1.34 (m, 1H), 1.30–1.18 (m, includes t, *J* = 7.0 Hz, 5H), 1.15–1.09 (m, 1H), 0.97 (t, *J* = 7.0 Hz, 2H), 0.90–0.80 (m, 8H).

The THF solution of the ester is transferred into a reaction vessel. A 15% aqueous NaOH solution (0.312 kg, 7.8 mol in 1.768 L of water) is added, followed by 9.27 L of 95% EtOH. The reaction is heated to reflux for 2 h, at which point HPLC analysis indicates complete reaction. The reaction is cooled to 35–40 ^oC and treated with a solution of TsOH*H_2O (1.558 kg, 8.19 mol) in 2.73 L of water. The addition is mildly exothermic, and controlled so that the reaction temperature does not exceed 45 ^oC. The organic solvents are removed under reduced pressure, and the remaining mixture is diluted with 9.27 L of water and extracted twice with 9.27 L of *i*-PrOAc. The resulting organic layer is assayed to contain 2.06 kg (99.3%) of **ABT-546.**

ABT-546 tosylate salt: A solution of **ABT-546** in *i*-PrOAc (19.555 kg, 2.018 kg assay, assayed to contain 0.33 equiv TsOH) is concentrated under reduced pressure to 1/3 to 1/4 volume, and 6.3 L of *i*-PrOAc is added, followed by TsOH*H_2O (0.524 kg, 0.73 equiv). Stirring is continued until the acid has dissolved. HPLC assay indicates 1.05 equiv of TsOH. The resulting solution is azeotropically dried with *i*-PrOAc until < 6 mol% water remains. *i*-PrOAc is added to achieve the target *i*-PrOAc content (10.1 L) and the mixture is heated to 80 ^oC. 10.1 L of heptane is added over 35 min, maintaining

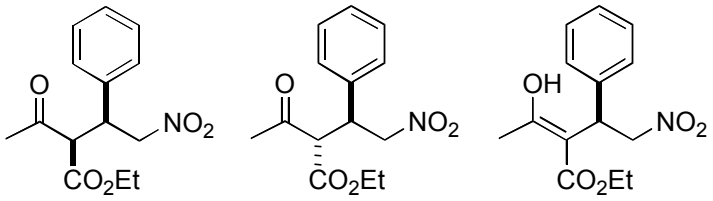
the temperature at 75–85 ^{o}C. Following the addition, the temperature is maintained for 50 min and the reaction is allowed to cool to ambient temperature overnight, at which point the liquor concentration is 6.1 mg/mL. The product is isolated by filtration and washed with 5.3 L of 3:1 heptane/ *i*-PrOAc. The salt is dried in vacuo at 50 ^{o}C overnight to yield 2.458 kg of an off-white solid. HPLC analysis typically indicates 1.02–1.04 equiv TsOH. The solid is loaded into a vessel and 12.3 L of water is added. The slurry is stirred for 3 h then filtered and washed with 4.15 L of water, and dried in vacuo at 50 ^{o}C with a N_2 bleed for two days. The process yields 2.328 kg of **ABT-546 tosylate salt** (99.2 wt%, 1.00 equiv TsOH, 89% yield). **ABT-546 tosylate salt:** mp 185–186 ^{o}C; ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.71 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.55 (br s, 1H), 6.39, (d, J = 1.1 Hz, 1H), 5.93 (s, 2H), 4.5–4.25 (m, 2H), 4.13 (br s, 1H), 3.96 (m, 2H), 3.70 (s, 3H), 3.60 (br s, 1H), 3.34–2.99 (m, 5H), 2.32 (s, 3H), 2.00 (m, 1H), 1.75 (m, 1H), 1.48–1.33 (m, 4H), 1.32–1.0 (m, 10 H), 0.89 (t, J = 7.0 Hz, 3H), 0.83–0.76 (m, 11H); ^{13}C NMR ($CDCl_3$, 300MHz) δ 173.5, 163.4, 148.9, 143.8, 142.0, 139.9, 134.6, 128.6, 126.0, 107.3, 101.5, 100.8, 90.4, 57.0, 56.4, 46.9, 45.9, 44.9, 32.7, 30.5, 29.4, 26.6, 26.4, 21.3, 20.1, 19.8, 17.0, 14.7, 13.8, 13.7. $[\alpha]_D^{25} = 21.7^{o}$ (c 3.02, $CHCl_3$). Anal. Cacld for $C_{37}H_{56}N_2O_9S$: C, 63.04; H, 8.01; N, 3.97. Found: C, 62.90; H, 8.00; N, 3.96.

Typical Procedure for Enantioselective Michael Addition of 1,3-Diacrbonyl Compounds to Niroalkenes. Preparation of 18a: $Mg(OTf)_2.4H_2O$ (19.6 mg, 0.05 mmol, 0.05 equiv) and ligand **6** (20.1 mg, 0.055 mmol, 0.055 equiv) were combined in the reaction flask. 1 mL of $CHCl_3$ (hydrocarbon stablized) was added and the mixture was stirred for 0.5–1h. 4 mL of $CHCl_3$ was added, followed by 200 mg of 4A molecular

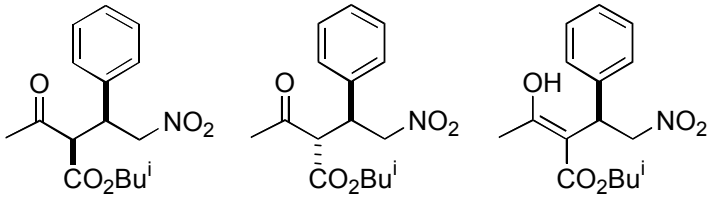
sieves, and the resulting mixture was stirred for an additional 90 min. Following this, nitrostyrene (149 mg, 1 mmol, 1 equiv) was added, followed by ethyl acetoacetate (**17**, 144 mg, 1.2 mmol, 1.2 equiv) and *N*-methylmorpholine (6.6 μL, 0.06 mmol, 0.06 equiv). Conversion and selectivity were determined by HPLC analysis. After the reaction was complete, 15 mL of hexane was added and stirred for 20 min. The solid was filtered off and the wet cake was washed with MTBE (5 mL). The combined filtrate was washed with 5 mL of aqueous H_3PO_4 (5% v/v) and 5mL of brine, then dried over $MgSO_4$. The drying reagent was removed by filtration and the solution was concentrated under reduced pressure. The product was purified by chromatography on silica gel using hexane/EtOAc (v. 80/20).

By ^{1}H NMR, Michael adducts **18a-18f** of ketoesters with nitrostyrenes appear as a 1:1 mixture of two compounds with are diastereomeric at the ester-bearing stereocenter, in addition to a varying amount of the enol tautomer. For the purposes of determining selectivity, chiral HPLC conditions were developed which separated the four diastereomers. In the case of **18e**, the two diastereomeric compounds were separable by reverse phase HPLC.

The absolute stereochemistry of adducts **18b** and **18k** was established by conversion to known compounds (vide infra). The sense of induction of the other adducts was assigned by analogy.

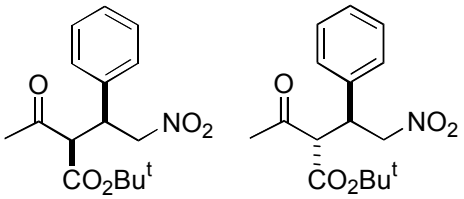


Ethyl 2-acetyl-4-nitro-3-phenylbutyrate, 18a: mixture of diastereomers and enol tautomer. R_f=0.4 (EtOAc/hexane=20:80); mp. 74-76°C;. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.32-7.19(m, 5H, $C_6\underline{H}_5$-), 4.85-4.74(m, 2H, -$C\underline{H}_2NO_2$), 4.28-3.92(m, 4H), {[2.32(s, 1.3H), 2.28(s, 0.4H), 2.06(s, 1.3H)], $C\underline{H}_3CO$-} {[1.29(t, J=7.0Hz, 0.4H), 1.28(t, J=7.0Hz, 1.3H), 1.02(t, J=7.1Hz, 1.3H)], $OCH_2C\underline{H}_3$}; MS (DCI/NH_3) *m/z* 279 (M + NH_4^+); Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.13; N, 5.01. Found: C, 60.00; H, 6.10; N, 4.78. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents $H_2\underline{O}$ (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **18a**: t_R: 12.7 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/ethanol (v. 90:10) at 0.8 mL/min., UV detection @ 210 nm. t_R: [(2*S*, 3*R*) and (2*R*, 3*R*)] = 8.4, 11.4 min.; [(2*S*, 3*S*) and (2*R*, 3*S*)]= 10.4, 13.2 min.

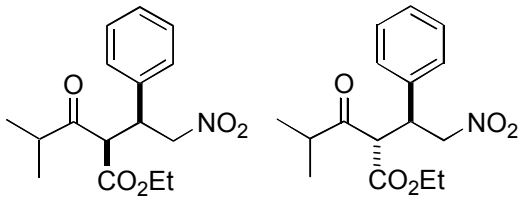


2'-Methylpropyl 2-acetyl-4-nitro-3-phenylbutyrate, 18b: mixture of diastereomers and enol tautomer. R_f=0.5 (EtOAc/hexane=20:80); oil; ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.32-7.18(m, 5H, $C_6\underline{H}_5$-), 4.90-4.74(m, 2H, -$C\underline{H}_2NO_2$), 4.28-3.90(m, 3H), 3.76-3.63(m, 1H), {[2.32(s, 1.2H), 2.28(s, 0.6H), 2.07(s, 1.2H)], $C\underline{H}_3CO$} 2.00-1.90(m, 0.5H), 1.80-1.66(m, 0.5H), {[0.96 -0.91(m, 4.5H), 0.78(d, J=6.6Hz, 1.5H)], $CH(C\underline{H}_3)_2$}; MS (DCI/NH_3) *m/z* 325 (M + NH_4^+) Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.25; H, 6.79 ; N, 4.35. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **18b**: t_R: 14.1 min.; Chiral

HPLC conditions: Chiralcel AD column with hexane/ethanol (v. 90:10) at 0.8 mL/min., UV detection @ 210 nm. t_R: [(2*S*, 3*R*) and (2*R*, 3*R*)] = 7.8, 10.3 min.; [(2*S*, 3*S*) and (2*R*, 3*S*)] = 9.2, 14.4 min.

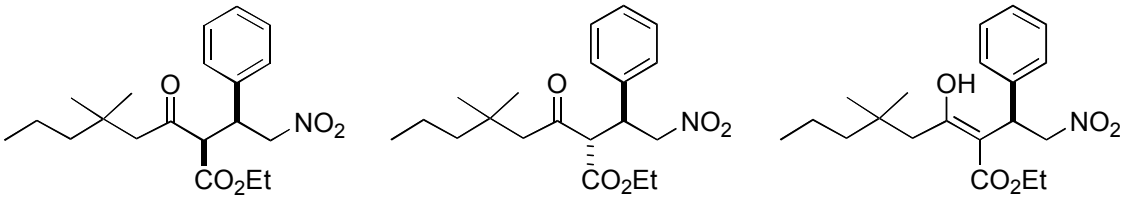


1',1'-Dimethylethyl 2-acetyl-4-nitro-3-phenylbutyrate, 18c: mixture of diastereomers. R_f=0.45 (EtOAc/hexane=20:80); mp. 123-126°C;. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.35-7.16(m, 5H, Ph-), 4.90-4.64(m, 2H), 4.23-4.10(m, 1H), 4.02(d, J=9.7Hz, 0.7H), 3.93(d, J=9.5Hz, 0.3H), 2.31(s, 2.1H), 2.06(s, 0.9H), 1.48(s, 2.7H), 1.17(s, 6.3H); MS (DCI/NH_3) *m/z* 325 (M + NH_4^+); Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.84; N, 4.51. Found: C, 62.07; H, 6.84; N, 4.51. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **18c**: t_R: 14.1 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/ethanol (v. 90:10) at 0.8 mL/min., UV detection @ 210 nm. t_R: [(2*S*, 3*R*) and (2*R*, 3*R*)] = 8.0, 9.7 min.; [(2*S*, 3*S*) and (2*R*, 3*S*)] = 8.9, 11.1 min.



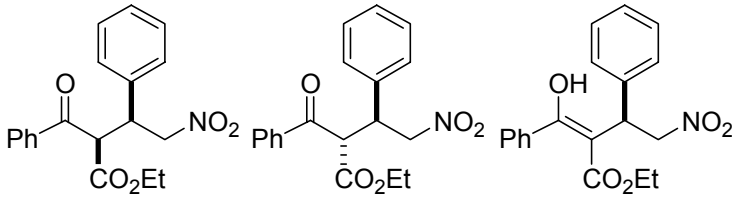
Ethyl 4-methyl-2-(2-nitro-1-phenylethyl)-3-oxopentanoate, 18d: mixture of diastereomers. R_f=0.5 (EtOAc/hexane=20:80); mp. 65-68°C;. ^{1}H NMR ($CDCl_3$/300 MHz)

δ 7.31-7.19(m, 5H), 4.90-4.73(m, 2H), 4.29-4.10(m, 3H), 3.98(q, J=7.0Hz, 1H), 2.74(m, 0.5H), 2.45(m, 0.5H), 1.27(t, J=6.9Hz, 1.5H), 1.10-0.7(m, 6.0H), 0.69(d, J=6.9Hz, 1.5H); MS (DCI/NH_3) *m/z* 325 (M + NH_4^+); Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.34 ; H, 6.93; N, 4.48. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **18d**: t_R: 14.0 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/i-PrOH (v. 95:5) at 1.0 mL/min., UV detection @ 210 nm. t_R: [(2*S*, 1'*R*) and (2*R*, 1'*R*)] = 7.0, 8.2 min.; [(2*S*, 1'*S*) and (2*R*, 1'*S*)] = 9.7, 10.1 min.

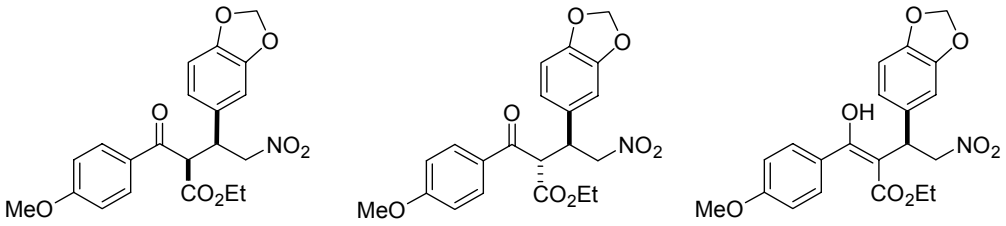


Ethyl 5,5-dimethyl-2-(2-nitro-1-phenylethyl)-3-oxooctanoate, 18e: mixture of diastereomers and enol tautomer. R_f=0.65 (EtOAc/hexane=20:80); oil; ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.33-7.18(m, 5H), 4.92-4.75(m, 2H), 4.30-3.92(m, 4H), 2.56-2.34(m, 2H), 1.34-0.76(m, 16H); MS (DCI/NH_3) *m/z* 381 (M + NH_4^+); Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.36; H, 8.56 ; N, 3.22. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **18e**: t_R: 16.4, 16.5 min.; Chiral HPLC conditions: Chiralcel AD column with

hexane/i-PrOH (v. 95:5) at 1.0 mL/min., UV detection @ 210 nm. t_R: [(2*S*, 1'*R*) and (2*R*, 1'*R*)] = 7.8, 10.4 min.; [(2*S*, 1'*S*) and (2*R*, 1'*S*)] = 9.2, 14.4 min.



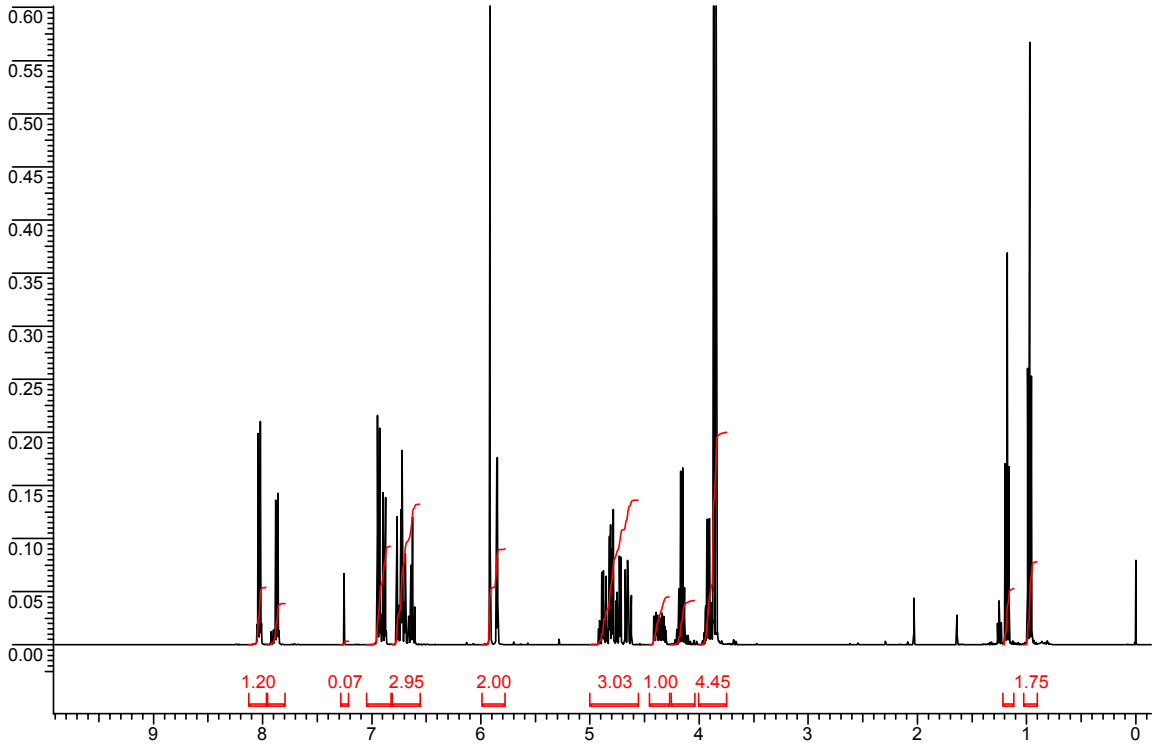
Ethyl 2-phenylcarbonyl-4-nitro-3-phenylbutyrate, 18f: The product was purified by flash column chromatography (25% EtOAc/hexanes, R_f = 0.08), and was obtained as a white solid (1.91 g, 83% yield). Enantiomeric excesses (ee's) was measured by chiral HPLC (Chiralpack AD column, 95:5 hexane/EtOH mobile phase, 1 mL/min flow rate, 210 nm). The ee was determined to be 87% for both pairs of enantiomers, $[\alpha]_D^{25}$ –2.31 (*c* = 1.03, $CHCl_3$). Mp 95.6 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-8.02 (m, 1.4 H), 7.85-7.82 (m, 0.6 H), 7.61-7.58 (m, 0.7 H), 7.55-7.51 (m, 0.3 H), 7.49-7.45 (m, 1.4 H), 7.42-7.38 (m, 0.6 H), (7.33-7.15 (m, 5 H), 4.94-4.89 (m, 1.5 H), 4.82-4.73 (m, 1.5 H), 4.51-4.40 (m, 1 H), 4.17 (q, *J* = 7.2 Hz, 0.6 H), 3.90-3.82 (m, 1.4 H), 1.17 (t, *J* = 7.2 Hz, 0.9 H), 0.89 (t, *J* = 7.2 Hz, 2.1 H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): δ 192.1, 167.2, 166.4, 152.0, 136.4, 135.9, 135.7, 135.5, 133.9, 133.5, 128.6(3), 128.5(9), 128.5(8), 128.4, 128.2, 128.0, 127.9(7), 127.8, 127.6, 77.9, 62.3, 62.0, 57.1, 56.5, 43.3, 43.3, 14.2, 13.9. Elemental Analysis, Calc'd: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.60; H, 5.61; N, 4.10.



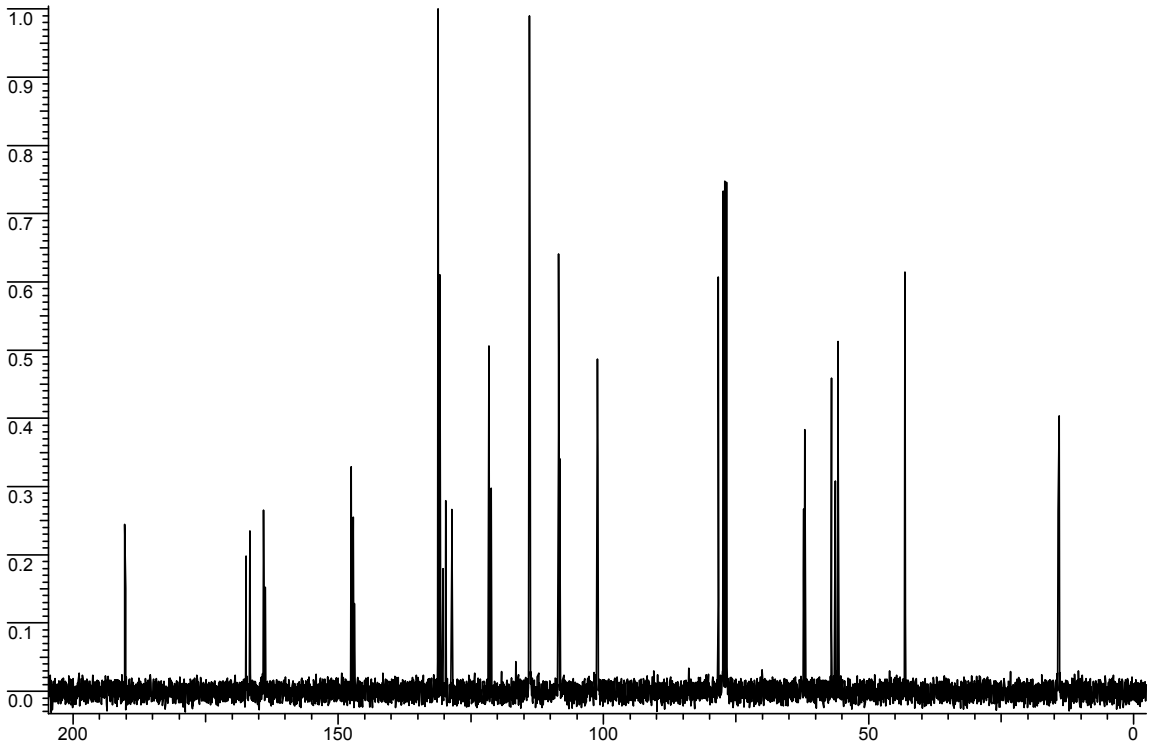
Ethyl 3-Benzo[1,3]dioxol-5-yl-2-(-4-methoxy-benzoyl)-4-nitro-butyrate, 18g:

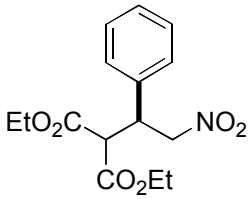
The product was purified by flash column chromatography (10% EtOAc/hexanes, R_f = 0.14), and obtained as a viscous yellow oil (2.04 g, 94% yield). Ee's were measured by chiral HPLC (80:20 EtOH/hexanes mobile phase, 1 mL/min flow rate, 210 nm, major enantiomer: 14.2, 26.2 min; minor enantiomer: 16.4, 20.1 min). The ee was determined to be 70% for both sets of diastereomers, $[\alpha]_D^{25}$ –19.20 (*c* = 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-8.02 (m, 1.2 H), 7.88-7.86 (m, 0.8 H), 6.95-6.92 (m, 1.2 H), 6.90-6.88 (m, 0.8 H), 6.77-6.61 (m, 3 H), 5.92 (s, 1.2 H), 5.85 (dd, *J* = 1.2, 4.0 Hz, 0.8 H), 4.92-4.63 (m, 3 H), 4.42-4.31 (m, 1 H), 4.21-4.14 (m, 1 H), 3.95-3.85 (m, 4 H), 1.18 (t, *J* = 7.0 Hz, 1.2 H), 0.97 (t, *J* = 7.0 Hz, 1.8 H). ^{13}C {^{1}H} NMR ($CDCl_3$, 100 MHz): δ 190.2, 190.0, 167.3, 166.6, 163.9, 163.6, 147.5, 147.0, 146.8, 131.1, 130.8, 130.2, 129.6, 128.5, 128.4(7), 121.5, 121.1, 113.8, 113.7, 108.3(4), 108.3(1), 108.1, 101.1, 101.0, 78.2, 62.2, 61.9, 56.9, 56.1, 55.7, 55.6, 43.1, 14.2, 14.0. FAB HRMS: Calcd. For $C_{21}H_{22}NO_8$ (M + H): 416.1345. Observed: 416.1337.

1H NMR of Ethyl 3-Benzo[1,3]dioxol-5-yl-2-(-4-methoxy-benzoyl)-4-nitro-butyrate, 18g (400 MHz, $CDCl_3$):



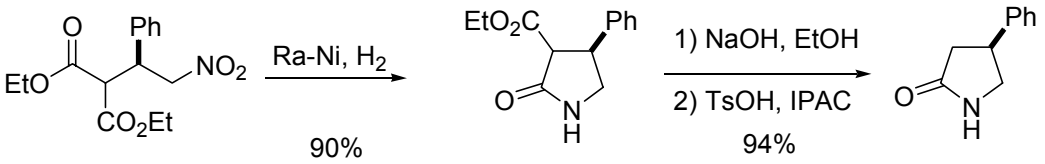
13C NMR of Ethyl 3-Benzo[1,3]dioxol-5-yl-2-(-4-methoxy-benzoyl)-4-nitro-butyrate, 18g (400 MHz, $CDCl_3$):





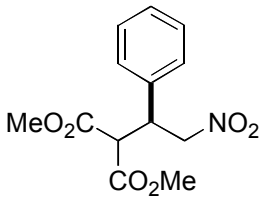
Ethyl 2-carboethoxy-4-nitro-3-phenylbutyrate, 21a: R_f=0.4 (EtOAc/hexane = 20:80); mp. 55-57°C;. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.34-7.20(m, 5H), 4.93(dd, J=13.3, 5.1Hz, 1H), 4.85(dd, J=13.3, 9.2Hz, 1H), 4.30-4.16(m, 3H), 4.0(q, J=7.3Hz, 2H), 3.82(d, J=9.2Hz), 1.27(t, J=7.0Hz, 3H), 1.04(t, J=7.0Hz, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 167.4, 166.8, 136.2, 128.9, 128.3, 128.0, 77.6, 62.1, 61.9, 55.0, 43.0, 14.0, 13.7; MS (DCI/NH_3) *m/z* 325 (M+NH_3); $[\alpha]_D^{25}$=7.09° (c 1.00, $CHCl_3$); Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19; N, 4.53. Found: C, 58.18; H, 5.89; N, 4.29. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v.

95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **21a**: t_R: 13.6 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/EtOH (v. 95:5) at 1.0 mL/min., UV detection @ 210 nm. t_R: (*R*) = 10.1 min.; (*S*)= 8.5 min.



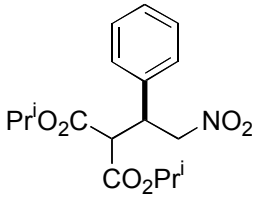
21a (99% ee after recrystallization) **22** **23**

Absolute stereochemistry of adduct 21a: The absolute stereochemistry of adduct **21a** was determined by conversion to 4-phenyl-2-pyrrolidone. The nitroester was hydrogenated to form the lactam which was decarboxylated (1. NaOH; 2. TsOH). (*R*)-4-Phenylpyrrolidinone (**23**) thus obtained had a rotation of $[\alpha]_D^{25}$ = +35.2 (*c* 1.02 MeOH) (lit. $[\alpha]_D^{25}$ = -33.8 (*c* 0.89 MeOH) for the (*S*)-isomer. Meyers, A. I.; Snyder, L. *J. Org. Chem*. **1993**, *58*, 36-42).

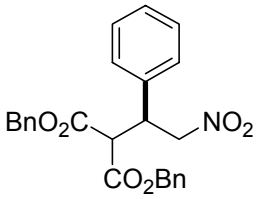


Methyl 2-carbomethoxy-4-nitro-3-phenylbutyrate, 21b: R_f=0.3 (EtOAc/ hexane = 20:80); mp. 63-65°C;. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.36-7.21(m, 5H), 4.93(dd, J=13.2, 5.5Hz, 1H), 4.85(dd, J=13.2, 8.5Hz, 1H), 4.25(td, J=8.8, 5.5Hz, 1H), 3.87(d, J=8.8Hz, 1H), 3.76(s, 3H), 3.56(s, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 167.8, 167.2, 136.1, 129.0, 128.4, 127.8, 77.4, 54.7, 53.0, 52.8, 42.9; ; $[\alpha]_D^{25}$=4.40° (c 1.02, $CHCl_3$); Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.50; H, 5.38; N, 4.89. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents

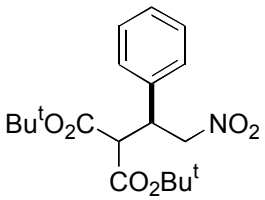
H_2O (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **21b**: t_R: 12.3 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/i-PrOH (v. 90:10) at 1.0 mL/min., UV detection @ 210 nm. t_R: (*R*) = 15.3 min.; (*S*)= 11.8 min.



1-Methylethyl 2-(1-methylethoxycarbo)-4-nitro-3-phenylbutyrate, 21c: R_f=0.5 (EtOAc/hexane=20:80); mp. 53-55^{o}C;. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.34-7.22(m, 5H), 5.09(m, 1H), 4.93(dd, J=12.9, 4.8Hz, 1H), 4.87-4.79(m, 2H), 4.20(td, J=8.8, 4.8Hz, 1H), 3.78(d, J=9.6Hz), 1.24(d, J=6.2Hz, 6H), 1.07(d, J=6.2Hz, 3H), 1.01(d, J=6.6Hz, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 167.0, 166.3, 136.3, 128.8, 128.2, 128.1, 77.9, 69.9, 69.5, 55.1, 42.9, 21.6, 21.4, 21.2; MS (DCI/NH_3) *m/z* 267 (M + NH_4^+); $[\alpha]_D^{25}$=8.17^o (c 1.01, $CHCl_3$); Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.45; H, 6.74; N, 4.05. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **21c**: t_R: 14.7 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/i-PrOH (v. 90:10) at 1.0 mL/min., UV detection @ 210 nm. t_R: (*R*) = 15.2 min.; (*S*)= 8.1 min.

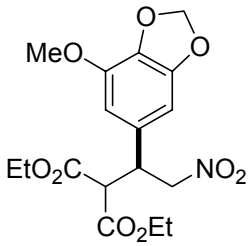


Phenylmethyl 2-(1-carbophenylmethoxy)-4-nitro-3-phenylbutyrate, 21d: R_f = 0.6 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.35-7.23 (m, 11H), 7.18-7.15 (m, 2H), 7.10-7.06 (m, 2H), 5.18 (d, J = 12.1 Hz, 1H), 5.14 (d, J = 12.1 Hz, 1H), 4.94 (s, 2H), 4.85-4.83 (m, 2H), 4.25 (ddd, *J* = 6.2, 7.7, 8.8 Hz, 1H), 3.94, (d, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$/75 MHz) δ 167.1, 166.5, 136.0, 134.7, 134.6, 129.0, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 127.9, 77.4, 67.8, 67.6, 55.0, 42.9; $[\alpha]_D^{25}$ = -4.82^o (c 1.03, $CHCl_3$); Anal. Calcd for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N, 3.23. Found: C, 68.65; H, 5.25; N, 3.24; Chiral HPLC conditions: Chiralcel AD column with hexane/i-PrOH (v. 90:10) at 1.0 mL/min., UV detection @ 210 nm. t_R: (*R*) = 19.8 min.; (*S*) = 21.2 min.

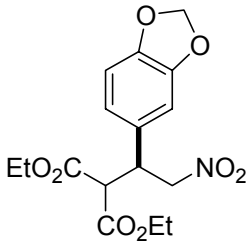


1,1-Dimethylethyl 2-(1,1-dimethylethoxycarbo)-4-nitro-3-phenylbutyrate, 21e: R_f = 0.5 (EtOAc/hexane = 20:80); mp. 115-117^{o}C;. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.31-7.22(m, 5H), 4.94(dd, J=12.9, 4.4Hz, 1H), 4.79(dd, J=12.9, 9.6Hz, 1H), 4.12(td, J=9.7, 4.4Hz, 1H), 3.62(d, J=9.9Hz, 1H), 1.49(s, 9H), 1.25(s, 9H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 166.9, 165.0, 136.5, 128.7, 128.3, 128.1, 82.8, 82.3, 78.2 , 56.4, 43.0, 27.8, 27.4; $[\alpha]_D^{25}$=3.86^o (c 1.03, $CHCl_3$); Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83.

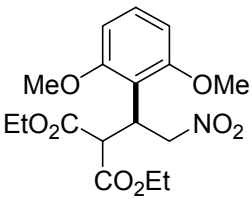
Found: C, 62.17; H, 7.27; N, 3.52. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **21e**: t_R: 15.8 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/i-PrOH (v. 90:10) at 1.0 mL/min., UV detection @ 210 nm. t_R: (*R*) = 14.4 min.; (*S*) = 7.0 min.



Ethyl 2-carboethoxy-4-nitro-3-(3-methoxy-4,5-methtylenedioxyphenyl)butyrate, 21j: R_f = 0.2 (30% EtOAc/hexanes), mp = 95-97 ^oC; ^1H NMR ($CDCl_3$/300 MHz) δ 6.41 (d, *J* = 1.8 Hz, 1H), 6.40 (d, *J* = 1.6 Hz, 1H), 5.95 (s, 2H), 4.88 (dd, *J* = 5.2, 12.9 Hz, 1H), 4.82 (dd, *J* = 9.0, 13.0 Hz, 1H), 4.28-4.18 (m, 2H), 4.16-4.04 (m, 3H), 3.87 (s, 3H), 3.77 (d, J = 9.2 Hz, 1H), 1.28 (t, J = 7.2 Hz), 1.13 (t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$/75 MHz) δ 167.3, 166.6, 149.1, 143.5, 135.0, 130.4, 108.0, 101.7, 101.6, 77.7, 62.1, 61.8, 56.5, 54.9, 42.9, 13.9, 13.8; MS (DCI/NH_3) *m/z* 401 ($M + NH_4^+$); $[\alpha]_D^{25}$=3.63^o (c 1.02, $CHCl_3$); Anal. Calcd for $C_{17}H_{21}NO_9$: C, 53.26; H, 5.52; N, 3.65. Found: C, 52.99; H, 5.41; N, 3.47.

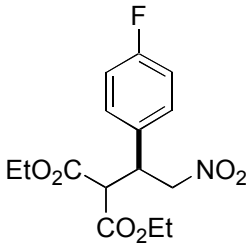


Ethyl 2-carboethoxy-4-nitro-3-(4,5-methtylenedioxyphenyl)butyrate, 21k: R_f = 0.3 (30% EtOAc/hexanes), mp = 82-84 ^oC; ^1H NMR ($CDCl_3$/300 MHz) δ 6.75-6.67 (m, 3H), 5.95 (s, 2H), 4.88 (dd, J = 4.8, 12.9 Hz, 1H), 4.79 (dd, J = 9.2, 12.9 Hz, 1H), 4.26-4.18 (m, 2H), 4.17-4.11 (m, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.75 (d, J = 9.2 Hz, 1H), 1.27 (t, J = 7.4 Hz, 3H), 1.12 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 167.4, 166.7, 148.0, 147.5, 129.7, 121.5, 108.5, 108.3, 101.2, 77.8, 62.1, 61.9, 55.0, 42.7, 14.0, 13.8 ppm; MS (DCI/NH_3) *m/z* 371 (M + NH_4^+); $[\alpha]_D^{25}$=4.85^o (c 1.01, $CHCl_3$); Anal. Calcd for $C_{16}H_{19}NO_8$: C, 54.39; H, 5.42; N, 3.96. Found: C, 54.37; H, 5.33; N, 3.69.

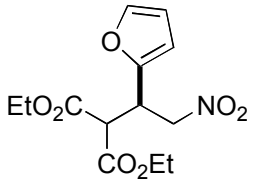


Ethyl 2-carboethoxy-4-nitro-3-(2,6-dimethoxyphenyl)butyrate, 21l: R_f=0.4 (EtOAc/hexane=20:80); oil;. ^1H NMR ($CDCl_3$/300 MHz) δ 7.21(t, J=8.3Hz, 1H), 6.51(d, J=8.4Hz, 2H), 5.08-4.96(m, 1H), 4.93(d, J=8.4Hz, 1H), 4.84(dd, J=11.8, 4.8Hz, 1H), 4.30-4.16(m, 3H), 3.92-3.81(m, 3H), 3.83(s, 6H), 1.29(t, J=7.0Hz, 3H), 0.94(t, J=7.2Hz, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 168.3, 167.2, 158.8, 129.6, 112.4, 104.2, 76.6, 61.8, 61.2, 55.8, 52.5, 33.2, 14.0, 13.6; MS (DCI/NH_3) *m/z* 387 (M + NH_4^+); $[\alpha]_D^{25}$=14.10^o (c 1.00, $CHCl_3$); HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents

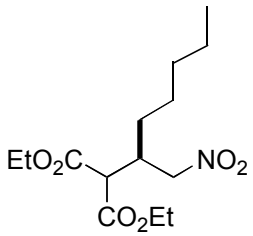
H_2O (0.1wt% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **21l**: t_R: 13.6 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/i-PrOH (v. 95:5) at 1.0 mL/min., UV detection @ 210 nm. t_R: (*R*) = 6.6 min.; (*S*)= 5.9 min. Anal. Calcd for $C_{17}H_{23}NO_8$: C, 55.28; H, 6.28; N, 3.79. Found: C, 55.15; H, 6.18; N, 3.60.



Ethyl 2-carboethoxy-4-nitro-3-(4-fluorophenyl)butyrate, 21m: R_f=0.6 (EtOAc/hexane=20:80); oil;. ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.31-7.22(m, 2H), 7.04-6.98(m, 2H), 4.93(dd, J=13.2, 4.87Hz, 1H), 4.82(dd, J=12.9, 9.6Hz, 1H), 4.29-4.16(m, 3H), 4.06(q, J=7.4Hz, 2H), 3.82(d, J=9.5Hz, 1H), 1.25(t, J=7.0Hz, 3H), 1.06(t, J=7.0hz, 3H); ^{13}C NMR ($CDCl_3$/300 MHz) δ 167.1, 166.5, 163.9, 160.6, 132.0, 131.9, 129.8, 129.7, 115.8, 115.5, 77.5, 62.0, 61.7, 54.7, 42.1, 13.7, 13.5; MS (DCI/NH_3) *m/z* 345 (M + NH_4^+); $[\alpha]_D^{25}$=6.60^o (c 1.03, $CHCl_3$); Anal. Calcd for $C_{15}H_{18}FNO_6$: C, 55.04; H, 5.54; N, 4.28; F, 5.80. Found: C, 55.12; H, 5.61; N, 4.17; F, 6.05. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **21m**: t_R: 13.6 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/EtOH (v. 90:10) at 1.0 mL/min., UV detection @ 210 nm. t_R: (*R*) = 16.8 min.; (*S*)= 12.2 min.

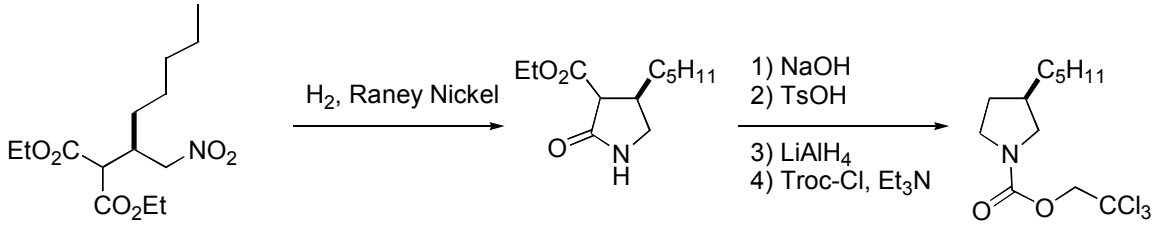


Ethyl 2-carboethoxy-3-(2-furyl)-4-nitro-butyrate, 21n: ^{1}H NMR ($CDCl_3$/300 MHz) δ 7.35 (dd, J=1.8, 0.7Hz, 1H), 6.29 (dd, J=3.3, 1.8Hz, 1H), 6.22 (dt, J=3.3, 0.8 Hz, 1H), 4.39 (td, J=7.8, 5.2Hz, 1H), 4.22 (q, J=6.9Hz, 2H), 4.15 (q, J=7.3Hz, 2H), 3.90 (d, J=8.0Hz, 1H), 1.27 (t, J=7.0Hz, 3H), 1.20 (t, J=7.3Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$/300 MHz) δ 167.1, 166.5, 163.9, 160.6, 132.0, 131.9, 129.8, 129.7, 115.8, 115.5, 77.5, 62.0, 61.7, 54.7, 42.1, 13.7, 13.5 ppm; $[\alpha]_D^{25}$= -4.04^{o} (c 1.03, $CHCl_3$); Anal. Cacld for $C_{13}H_{17}NO_7$: C, 52.17; H, 5.73; N, 4.68. Found: C, 52.23; H, 5.79; N, 4.60. Chiral HPLC conditions: Chiralcel AD column with hexane/EtOH (v. 90:10) at 1.0 mL/min., UV detection @ 210 nm. t_R: (*R*) = 7.6 min.; (*S*)= 8.1 min.

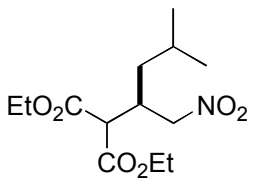


Ethyl 2-carboethoxy-3-(nitromethyloctanoate, 21o: R_f=0.5 (EtOAc/hexane = 20:80); oil; ^{1}H NMR ($CDCl_3$/300 MHz) δ 4.71(dd, J=13.3, 4.8Hz, 1H), 4.54(dd, J=13.3, 7.0Hz, 1H), 4.23(q, J=7.0Hz, 2H), 4.22(q, J=7.0Hz, 2H), 3.63(d, J=5.9Hz, 1H), 3.02-2.91(m, 1H), 1.50-1.30(m, 8H), 1.28(t, J=7.0Hz, 6H), 0.88(t, J=6.6Hz, 3H); ^{13}C NMR ($CDCl_3$/300 MHz) δ 170.0, 167.8, 77.00, 61.9, 61.7, 52.6, 36.9, 31.4, 30.0, 26.2, 22.3, 14.0, 13.9; MS (DCI/NH_3) *m/z* 321 (M + NH_4^+); $[\alpha]_D^{25}$=4.82 (c 1.00, $CHCl_3$); Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.53; H, 8.31; N, 4.62;. Found: C, 55.65; H, 8.16; N, 4.64.

HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1v.% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **21o**: t_R: 15.3 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/i-PrOH (v. 98:2) at 1.0 mL/min., UV detection @ 210 nm. t_R: (*R*) = 6.7 min.; (*S*)= 7.2 min.



Absolute stereochemistry of adduct 21o: The absolute stereochemistry of adduct **26o** was determined by conversion to the Troc-protected pyrrolidine. Hydrogenation (H_2/Raney nickel) was followed by saponification (NaOH) and decarboxylation (TsOH) to form the pyrrolidinone. $LiAlH_4$ reduction delivered the pyrrolidine which was protected with Troc-Cl (Et_3N) to form the carbamate, whose rotation had the same sign [+15.4^o (c 1.0, $CHCl_3$)] as reported in the literature ($[a]^{22}_D$ = 19.8^o (c 1.12, $CHCl_3$); Denmark, S. E.; Marcin, L. R. *J. Org. Chem*. **1995**, *60*, 3221-3235).



Ethyl 2-carboethoxy-5-methyl-3-nitromethylhexanoate, 21p: R_f=0.35 (EtOAc/hexane = 20:80); oil; ^{1}H NMR ($CDCl_3$/300 MHz) δ 4.71 (dd, J=13.2, 5.1Hz, 1H), 4.53 (dd, J=13.3, 6.6Hz, 1H), 4.23 (q, J=7.0Hz, 2H), 4.22 (q, J=7.0Hz, 2H), 3.62 (d,

J=5.5 Hz, 1H), 3.02-2.91 (m, 1H), 1.73-1.60 (m, 1H), 1.33 (t, J=7.4 Hz, 6H), 0.94 (d, J=6.6 Hz, 3H), 0.92 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$/75 MHz) δ 168.0, 167.8, 77.0, 61.9, 61.7, 52.7, 39.0, 34.9, 25.1, 22.4, 22.2,, 14.0; MS (DCI/NH_3) *m/z* 307 ($M + NH_4^+$); $[\alpha]_D^{25}$=6.58^o (c 0.99, $CHCl_3$); Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84;. Found: C, 54.20; H, 7.93; N, 4.91. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm with solvents H_2O (0.1wt% H_3PO_4)/MeCN (from v. 95:5 to 10:90 within 15 min.) at 1.0 mL/min., UV detection @210 nm. **21p**: t_R: 14.6 min.; Chiral HPLC conditions: Chiralcel AD column with hexane/i-PrOH (v. 98:2) at 0.6 mL/min., UV detection @ 210 nm. t_R: (*R*) = 9.6 min.; (*S*)= 10.3 min.

Typical Procedure for Enantioselective Michael Addition Reaction, Products 21f-i: $Mg(OTf)_2$*$4H_2O$ (138.5 mg, 0.35 mmol, 0.052 equiv.) and ligand 8 (135.0 mg, 0.49 mmol, 0.057 equiv) were combined in the reaction vessel. 7 mL of $CHCl_3$ was added and the mixture was stirred for 1 h. 27 mL of $CHCl_3$ was added, followed by 200 mg of 4 A molecular sieves, and the resulting mixture was stirred for an additional 1.5 h. Nitrostyrene (1.00 g, 6.70 mmol, 1.00 equiv.) was added, followed by the malonate reagent (8.06 mmol, 1.20 equiv.) and morpholine (37.0 μL, 0.424 mmol, 0.063 equiv.). The reaction was stirred until no further conversion was observed by HPLC analysis (**21f**, 44 h; **21g**, 8 d; **21h**, 10 d; **21i**, 67 h). 100 mL of hexanes were added and the mixture stirred for 20 min. The solids were removed by vacuum filtration through Celite, and the wet cake was washed with dichloromethane (35 mL). The combined filtrate was washed with 67 mL of aqueous HCl (5% v/v), then dried over $MgSO_4$. The drying reagent was

removed by vacuum filtration through Celite and the solution was concentrated under reduced pressure. Enantioselectivity of the reactions was determined by chiral HPLC (Chiralcel OJ column, 4.6 x 250 mm, isocratic, 80:20 hexane:ethanol, flow rate 1mL/min, column temperature 25 ^{o}C) and are as follows, with respective retention times: **21f**, 46% ee, 12.2 min (major), 20.0 min (minor); **21g**, 89% ee, 15.3 min (minor), 17.7 min (major); **21h**, 41% ee, 8.2 min (major), 10.4 min (minor); **21i**, 56% ee. 4.1 min (major), 6.8 min (minor).

Products **21f-i** were purified by chromatography (2% to 20% EtOAc/hexanes) to provide analytically pure products. **21f**, 1.54 g (71%); **21g**, 1.74 g, (83%); **21h**, 1.22 g (50%); **21i**, 2.40 g (84%).

Product **21i** was somewhat unstable to chromatography, with some reversion to nitrostyrene and diethyl-2-[N-Boc-amino]malonate.

Typical Procedure for Racemic Michael Addition Reactions: $MgCl_2$ (59.8 mg, 1.00 mmol, 1.00 equiv) and 5 mL of $CHCl_3$ were added to a reaction vessel, followed by 200 mg of 4 A molecular sieves, and the resulting mixture was stirred for 1.5 h. Nitrostyrene (149 mg, 1.00 mmol, 1.00 equiv) was added, followed by the malonate reagent (1.20 mmol, 1.20 equiv) and triethylamine (0.278 ml, 2.0 mmol, 2.0 equiv). The reaction was stirred until complete, as determined by HPLC (**21f**, **21g**, and **21h**, 6.5 h; **21i**, 11 d). Hexanes (15 mL) was added, and the mixture was stirred for 20 min. The solids were removed by vacuum filtration through Celite, and the wet cake was washed with dichloromethane (5 mL). The combined filtrate was washed with aqueous HCl (10 mL , 5% v/v), then dried over $MgSO_4$. The drying reagent was removed by vacuum filtration

through Celite, and the solution was concentrated under reduced pressure. The products were purified by chromatography for use as HPLC standards.

Characterization:

2-methyl derivative (21f): ^{1}H NMR ($CDCl_3$) δ 7.34-7.28 (om, 2.9 H), 7.21-7.17 (m, 2.0 H), 5.07 (d, *J* = 1.6 Hz, 1.0 H), 5.05 (s), 4.26 (q, *J* = 7.1 Hz, 2.1 H), 4.2 (overlapping m, 3.0 H), 1.34 (s, 3.0 H), 1.29 (t, *J* = 7.2 Hz, 3.0 H), 1.26 (t, *J* = 7.2 Hz, 2.9 H) ppm; ^{13}C{^{1}H}NMR ($CDCl_3$) δ 171.0 (s), 170.3 (s), 135.1 (s), 129.0 (s), 128.7 (s), 128.4 (s), 77.7 (s), 62.1 (s), 61.9 (s), 56.7 (s), 48.2 (s), 20.3 (s), 13.93 (s), 13.91 (s) ppm. $[\alpha]_D^{25} = -26.14^{o}$ (c 1.04, $CHCl_3$); Anal calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.41; H, 6.49; N, 4.26

2-methoxy derivative (21g): ^{1}H NMR ($CDCl_3$) δ 7.29-7.28 (om, 4.6 H), 5.25 (dd, *J* = 3.6, 13.6 Hz, 1.1 H), 4.85 (dd, *J* = 10.0, 13.6 Hz, 1.1 H), 4.28 (dd, *J* = 4.0, 10.0 Hz, 1.0 H), 3.86 (s, 3.0 H), 3.60 (s, 3.0 H), 3.49 (s, 3.0 H) ppm; ^{13}C{^{1}H}NMR ($CDCl_3$) δ 167.9 (s), 167.4 (s), 135.1 (s), 129.3 (s), 128.44 (s), 128.41 (s), 86.0 (s), 76.8 (s), 56.1 (s), 52.9 (s), 52.3 (s), 48.8 (s) ppm. $[\alpha]_D^{25} = 4.86^{o}$ (c 1.04, $CHCl_3$); Anal calcd for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.30; H, 5.54; N, 4.42.

2-acetamido derivative (21h): ^{1}H NMR ($CDCl_3$) δ 7.31-7.28 (m, 3.0 H), 7.21-7.19 (m, 2.0 H), 6.70 (s, 1.0 H), 5.52 (m, 1.1 H), 4.70 (dd, *J* = 11.8, 18.2 Hz, 1.1 H), 4.69 (m, 0.9 H), 4.28 (m, 2.0 H), 4.17 (dq, *J* = 7.1, 10.7 Hz, 1.1 H), 4.05 (dq, *J* = 7.1, 10.7 Hz, 1.1 H), 2.12 (s, 3.0 H), 1.27 (t, *J* = 7.2 Hz, 3.0 H), 1.25 (t, *J* = 7.2 Hz, 3.0 H) ppm; ^{13}C{^{1}H}NMR

($CDCl_3$) δ 170.1 (s), 166.5 (s), 165.7 (s), 133.9 (s), 128.83 (s), 128.78 (s), 128.71 (s), 76.9 (s), 67.2 (s), 63.6 (s), 62.8 (s), 48.3 (s), 23.1 (s), 13.9 (s), 13.8 (s) ppm. $[\alpha]_D^{25} = -26.33^o$ (c 1.01, $CHCl_3$); Anal calcd for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.65. Found: C, 55.52; H, 5.80; N, 7.58.

2-*tert*-butoxycarbamato derivative (21i): ^1H NMR ($CDCl_3$) δ 7.28-7.25 (m, 3.1 H), 7.24-7.21 (m, 1.9 H), 5.92 (s, 0.9 H), 5.49 (dd, *J* = 3.2, 12.8 Hz, 1.0 H), 4.72 (t, *J* = 12.8 Hz, 1.0 H), 4.63 (dd, *J* = 3.0, 11.8 Hz, 1.0 H), 4.27 (m, 2.0 H), 4.13 (dq, *J* = 7.2, 10.8 Hz, 1.1 H), 3.99 (dq, *J* = 7.2, 10.8 Hz, 1.0 H), 1.49 (s, 9.0 H), 1.27 (t, *J* = 7.2 Hz, 3.0 H), 1.21 (t, *J* = 7.2 Hz, 2.9 H) ppm; $^{13}C\{^1H\}$NMR ($CDCl_3$) δ 165.9 (s), 165.7 (s), 154.3 (s), 133.8 (s), 128.6 (s), 128.42 (s), 128.38 (s), 81.2 (s), 77.0 (s), 67.6 (s), 63.5 (s), 62.8 (s), 48.4 (s), 28.4 (s), 14.3 (s), 14.2 (s) ppm. Anal calcd for $C_{20}H_{28}N_2O_8$: C, 56.59; H, 6.65; N, 6.60. Found: C, 56.62; H, 6.62; N, 6.40.

Synthesis of Rolipram

3-Cyclopentyloxy-4-methoxy-benzaldehyde

To a flask containing isovanillin (**25**) (15.0 g, 98 mMol) was added DMF (100 mL), cyclopentyl bromide (13.7 mL, 128 mMol) and K_2CO_3 (20.4 g, 148 mMol). The reaction mixture was then heated to 100 ^oC and stirred under N_2 until no isovanillin was observed by HPLC. The mixture was then cooled to room temperature. 200 mL of saturated aqueous ammonium chloride solution was added. The mixture was stirred for 10 min and was then extracted with ethyl acetate (3 x 150 mL). The organic extracts were

combined and washed with water (2 x 50 mL) and concentrated. The crude product (20.9 g, 97% yield) was obtained and used in the next step.

^{1}H NMR ($CDCl_3$/300 MHz) δ 9.84 (s, 1H); 7.44 (dd, J=8.1, 1.8Hz, 1H), 7.39 (d, J=1.9Hz, 1H), 6.97(d, J=8.1Hz, 1H), 4.90-4.82 (m, 1H), 3.95(s, 3H), 2.08-1.80(m, 6H), 1.70-1.54(m, 2H) ppm; MS (DCI/NH_3) m/z 238 ($M+NH_4$), 221(M+H); HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm; solvent, 5/95 MeCN/H_2O (w. 0.1% H_3PO_4) to 90/10 in 15 min.; flow rate, 1.0 mL/min.; uv, 210 nm; Retention time: isovanillin 7.6 min; product: 12.6 min.

Synthesis of 3-Cyclopentyloxy-4-methoxy-β-nitrostyrene (26):

To a flask containing the above crude 3-cyclopentyloxy-4-methoxy-benzaldehyde (20.9 g, 95 mMol) was added ammonium acetate (12.7 g, 0.165mol), nitromethane (25.7 mL, 0.475 mol) and acetic acid (90 mL). The mixture was stirred and heated to 90 ^oC for 2 hours during which yellow solid precipitated. The reaction was monitored by HPLC. When the reaction was complete, the mixture was cooled to ambient. 100 mL of distilled water was added to the brown mixture and stirred for 1h. The solid was filtered and washed with water (3 x 100 mL). It was then dried under vacuum at 50^oC for 3 days. 22.5 g (90% yield) of 3-cyclopetanyloxy-4-methoxy-β-nitrostyrene (**26**) was obtained.

^{1}H NMR ($CDCl_3$/300 MHz) δ 7.96 (d, J=13.6Hz, 1H), 7.52(d, J=13.6Hz, 1H), 7.15(dd, J=8.5, 2.3Hz, 1H), 7.02(d, J=2.2Hz, 1H), 6.90(d, J=8.5Hz, 1H), 4.84-4.76(m, 1H), 3.90(s, 3H), 2.04-1.80(m, 6H), 1.70-1.56(m, 2H) ppm; ^{13}C NMR ($CDCl_3$/300 MHz) δ 153.8, 148.1, 139.5, 134.9, 124.2, 122.5, 113.7, 111.7, 84.2, 59.5, 36.2, 27.5 ppm; MS (DCI/NH_3) m/z 281 ($M+NH_4$); Calc. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.91; H, 6.46; N, 5.36. HPLC conditions: Zorbax-XDB-C8 RX column 4.6x250mm;

solvent, 5/95 MeCN/H_2O (w. 0.1% H_3PO_4) to 90/10 in 15 min.; flow rate, 1.0 mL/min.; 210 nm; Retention time: **26**, 14.1min.

Nitroketone (*R*)-27:

Under N_2, to a flask equipped with a stirring bar and a thermometer, was added $Mg(OTf)_2$*$4H_2O$ (Aldrich, 600 mg, 1.50 mMol), *ent*-**6** (600 mg, 1.65 mMol) and $CHCl_3$ (hydrocarbon stabilized) (60 mL). The mixture was stirred for 0.5 hour and turned cloudy. MS-4A (6.0 mg) was added and the mixture was stirred at ambient for an additional 30 min. Nitrostyene **26** (7.89 g, 30 mMol), diethyl malonate (5.76 g, 36 mMol), and $CHCl_3$ (90 mL) were then added and stirred for an additional 10 min before N-methylmorpholine (182.0 mg, 1.80 mMol) was added. The reaction mixture was stirred at room temperature and monitored with HPLC. When the reaction was complete, MS-4A were filtered off and the wet cake was washed with MTBE (2x30 mL). The majority of the solvents were removed under reduced pressure. The residue was then dissolved in 300 mL of MTBE and washed with 5wt% H_3PO_4 aqueous (30 mL) and H_2O (2x30 mL). The solution was reconcentrated. The final crystalline product (12.1 g, 95% yield) was obtained from MTBE/heptane (1/4 v.) in 97% ee. (*R*)-**27**: ($R_{f.}$, 0.3, EtOAc/hexane=20/80), ^{1}H NMR ($CDCl_3$/300 MHz) δ 6.80-6.73 (m, 3H), 4.88 (dd, J=12.8, 5.5Hz, 1H), 4.80 (dd, J=12.9, 4.4Hz, 1H), 4.76-4.70 (m, 1H), 4.28-4.10 (m, 3H), 4.03(q, J=7.0Hz, 2H), 3.82(s, 3H), 3.81(d, J=9.6Hz, 1H), 2.00-1.78(m, 5H), 1.68-1.58(m, 3H), 1.27(t, J=7.3Hz, 3H), 0.90(t, J=7.0Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$/300 MHz) δ 167.5, 166.9, 149.9, 147.7, 128.3, 120.1, 114.8, 112.0, 80.4, 78.0, 62.1, 61.8, 55.9, 55.0, 42.6, 32.7, 24.0, 14.0, 13.8 ppm; MS (DCI/NH_3) *m/z* 441 (M + NH_4^+); Anal. Calc. for $C_{21}H_{29}NO_8$: C, 59.56.; H, 6.90.; N, 3.31. Found: C, 59.52.; H, 6.86.; N, 3.26. HPLC

conditions: Zorbax-XDB-C8 RX column 4.6x250mm; solvent, 5/95 MeCN/H_2O (w. 0.1% H_3PO_4) to 90/10 in 15 min.; flow rate, 1.0 mL/min.; uv, 210 nm; Retention time, 14.6min.; Chiral HPLC conditions: Chiralpak® AD column, solvent, hexane/EtOH = 90/10; flow rate, 1.0 mL/min.; uv, 210nm; retention time: (*S*)-isomer, 7.1 min; (*R*)-isomer, 9.8 min.

Hydrogenation of (*R*)-27: A reaction vessel equipped with a mechanical stirrer, a thermocouple, and nitrogen and hydrogen inlets is purged three times with nitrogen. Raney-nickel (18.0g) is washed water (2 x 50 mL) and charged to the reaction vessel. It was purged again three times with nitrogen. A solution of **(*R*)-27** (12.0g, 28.4 mMol) in THF (100 mL) was charged to the reactor, followed by H_3PO_4 (85%, 327 mg, 2.84 mMol). The reactor was purged three times with hydrogen while stirring. The reaction pressure was kept between 40-50 psi. It was then slowly heated to 50 ^oC. After the mixture had stirred under hydrogen (40-50 psi.) at 50 ^oC for 2 hours, the reaction was allowed to settle and was purged three times with nitrogen. A sample was withdrawn and checked by HPLC. After the reaction had finished, Raney-Ni was filtered off under N_2. The wet cake was washed with THF (2x 30 mL). The combined organic solution was then concentrated to afford pyrrolidone (*R*)-**28** as a slight yellow oil. It was used directly in the next step. ^1H NMR ($CDCl_3$/300 MHz) δ 6.80-6.73 (m, 4H), 4.78-4.72 (m, 1H), 4.30-4.20 (m, 2H), 4.02 (m, 1H), 3.82 (s, 3H), 3.79 (t, J=8.4Hz, 1H), 3.52 (d, J=10.0Hz, 1H), 3.40 (dd, J=9.1, 8.4Hz, 1H), 2.00-1.78 (m, 7H), 1.68-1.58 (m, 2H), 1.27 (t, J=7.3Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$/300 MHz) δ 173.8, 170.4, 150.6, 149.0, 133.3, 120.0, 115.1, 113.4, 91.5, 81.7, 62.9, 57.2, 56.6, 48.8, 45.2, 33.9, 25.1, 15.3 ppm; MS (DCI/NH_3) *m/z* 365 (M + NH_4^+); same HPLC conditions as above. Retention time for **28** is 13.1 min.

Synthesis of (*R*)-Rolipram, (*R*)-24: Under N_2, to a flask containing the above pyrrolidone (*R*)-**28** was added 50 mL of EtOH and 50 mL of aqueous NaOH (10%) solution. The mixture was heated to reflux for 2 hours (The reaction was monitored with HPLC, same conditions as above the retention time for acid product is 9.2 min.). After the reaction was complete, the reaction was allowed to cool down. Ethanol solvent was removed under reduced pressure. The residue was acidified with 10% HCl till pH=2-3. It was then extracted with i-PrOAc (3 x 100mL). The extracts were combined and washed with brine (2 x 20 mL). It was then concentrated to volume of ~ 50 mL. 10 mg of $TsOH.H_2O$ was added. The solution was heated to reflux till no starting material was observed on HPLC (about 15 hours). It was then cooled and concentrated. The final crystalline product (7.1 g, 90% yield) was obtained by recrystallization with $MeOH/H_2O$. **(*R*)-Rolipram, (*R*)-24:** Mp: 132-134^oC. (lit. mp:) ^1H NMR ($CDCl_3$/300 MHz) δ 7.44(s, 1H), 6.85-6.76(m, 3H), 4.56-4.4(m, 1H), 3.82(s, 3H), 3.75(td, J=8.1, 0.8Hz, 1H), 3.53-3.51(m, 1H), 3.40(dd, J=9.1, 7.4Hz, 1H), 2.70(dd, J=16.9, 8.8Hz, 1H), 2.49(dd, J=16.9, 8.8Hz, 1H), 2.00-1.78(m, 7H), 1.68-1.58(m, 2H) ppm; ^{13}C NMR ($CDCl_3$/300 MHz) δ 179.2, 150.1, 148.8, 135.7, 119.8, 114.9, 113.2, 81.6, 57.1, 50.9, 40.9, 39.4, 33.8, 25.0, 21.3 ppm; $[\alpha]_D^{25}$= -30.8^o (c, 1.01. MeOH) (lit. $[\alpha]_D^{25}$= -30.2^o). Same HPLC conditions as above. The retention time for (*R*)-rolipram is 10.3 min.

(*S*)-Rolipram was prepared using the same procedure. mp: 133.0-134.0 ^oC, $[\alpha]_D^{25}$=30.1^o.

Experimental for the Kinetics analyses.

General experimental: Reactions were run as in the general experimental, with sufficient $CHCl_3$ added to generate the desired concentration. Samples were pulled at specific times and quenched into a solution of 5% HOAc in MeCN, then filtered. Conversions were determined by HPLC analysis (Zorbax Sb-C8 short column (7.5 mm), 35 ^oC, 1.5 mL/min, 210 nm, 90:10 → 10:90 0.1% H_3PO_4:MeCN over 7.5 min, hold 2.5 min.) using purified reference standards to determine relative response factors; the conversion was calculated according to the equation:

Conv. = area product/(area product + (area SM*resp. factor)).

Reactions were repeated two or more times. The conversions or logs thereof were plotted against time on Microsoft Excel, and linear fits were obtained to give rates.

Ethyl acetoacetate + nitrostyrene

Varying ketoester ($[nitrostyrene]_0$ = 0.1 M; [catalyst] = 0.005 M)

$[ketoester]_0$	init. rates ($x10^{-4}$M/min)	Ave. init. rate($x10^{-4}$M/min)
0.06M	8.16, 8.06, 8.67	8.30 ± 0.27
0.12M	9.50, 10.2, 9.34	9.68 ± 0.37
0.18M	9.76, 10.0	9.88 ± 0.12
0.24M	9.42, 9.72, 8.91	9.35 ± 0.33
0.30M	9.36, 9.27	9.32 ± 0.45
0.48M	7.48, 7.95, 7.26	7.56 ± 0.29
1.0M	5.15, 5.20, 4.99	5.11 ± 0.09

Varying catalyst ($[nitrostyrene]_0$ = 0.1 M; $[ketoester]_0$ = 0.12 M)

[catalyst]	init. rates ($x10^{-4}$M/min)	Ave. init. rate($x10^{-4}$M/min)
0.0010M	1.81, 1.70, 1.90	1.80 ± 0.08
0.0025M	4.69, 4.68, 4.77	4.71 ± 0.04
0.005M	8.89, 8.98, 8.98	8.95 ± 0.04

0.010M	17.2, 17.4, 17.5	17.4 ± 0.1

Order in nitrostyrene (pseudo-first order, $[nitrostyrene]_0$ = 0.1 M, $[ketoester]_0$ = 1.0 M, [catalyst] = 0.005 M)

Description	Reaction 1	Reaction 2	Reaction 3
10 min (% conv.)	5.15	5.20	4.99
20 min (% conv.)	9.37	9.51	9.27
30 min (% conv.)	13.3	13.7	13.2
60 min (% conv.)	24.0	24.6	23.8
120 min (% conv.)	41.3	42.3	40.9
186 min (% conv.)	55.4	56.5	55.0
300 min (% conv.)	72.5	73.5	72.1
425 min (% conv.)	83.3	84.2	82.9
Rate eqn (Ln[nitrostyrene]/ [nitrostyrene]) vs. time	Y = 0.00421x + 0.01576 R^2 = 0.9971	Y = 0.00434x + 0.01581 R^2 = 0.9972	Y = 0.00416x + 0.01580 R^2 = 0.9997

Average equation: Y = (4.24 ± 0.08 x10^{-3}) x + 0.01579 ± 0.00002

$k_{obs} = k[ketoester]^0[catalyst]^1$

k = (4.24 x10^{-3}/s)/[1][0.005M] = 0.848$M^{-1}s^{-1}$.

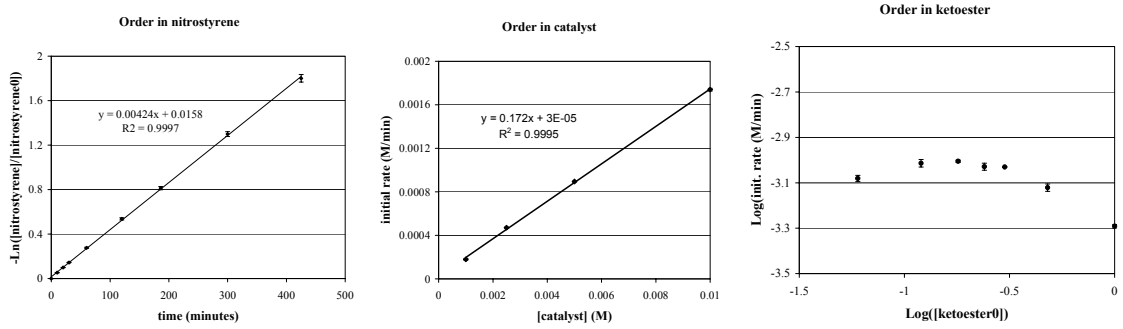


Figure. Kinetics of the reaction of ethyl acetoacetate (**17**) with nitrostyrene using pseudo-first order conditions in acetoacetate

Diethyl malonate + nitrostyrene

Varying malonate ($[nitrostyrene]_0$ = 0.1 M; [catalyst] = 0.005 M)

$[malonate]_0$	init. rates (x10^{-4}M/min)	Ave. init. rate(x10^{-4}M/min)
0.06M	6.01, 5.91, 6.07, 5.96	5.99 ± 0.07
0.12M	9.36, 8.60, 8.88	8.95 ± 0.31

0.24M	12.32, 12.00, 11.64	11.99 ± 0.28
0.48M	15.52, 15.96, 14.72	15.40 ± 0.51
0.96M	22.08, 22.60, 21.80, 20.72	21.80 ± 0.79

Varying catalyst ([nitrostyrene]$_0$ = 0.1 M; [malonate]$_0$ = 0.12 M)

[catalyst]	init. rates (x10^{-4}M/min)	Ave. init. rate(x10^{-4}M/min)
0.0010M	1.40, 1.41, 1.28	1.36 ± 0.06
0.0025M	3.56, 3.55, 3.34	3.48 ± 0.10
0.005M	7.44, 7.14, 6.80	7.13 ± 0.26
0.010M	15.6, 15.0, 15.4	15.33 ± 0.25

Varying nitrostyrene ([malonate]$_0$ = 0.24 M; [catalyst] = 0.005 M)

[malonate]$_0$	init. rates (x10^{-4}M/min)	Ave. init. rate(x10^{-4}M/min)
0.025M	5.03, 4.55, 4.97	4.94 ± 0.31
0.050M	7.88, 6.08, 7.89	7.28 ± 0.85
0.10M	12.1, 10.4, 11.7	11.4 ± 0.73
0.20M	18.3, 16.2, 18.5	17.7 ± 1.04

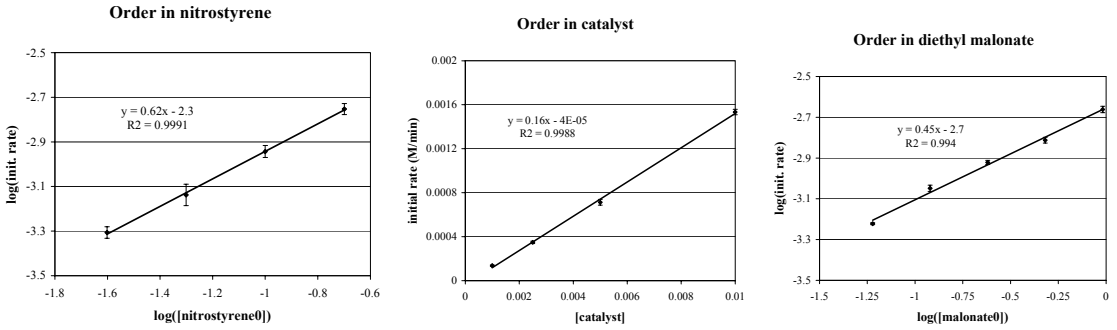


Figure. Kinetics for the addition of diethyl malonate to nitrostyrene.

References:

1) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815-3818.