Supporting Information

Highly Enantioselective, Catalytic Conjugate Addition of Cyanide to α,β -Unsaturated Imides

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General Methods

Unless otherwise stated, all reagents were purchased from Aldrich or Strem and used without further purification. Solvents were purified and dried using standard methods: toluene and benzene were distilled from sodium; THF was distilled from sodium/benzophenone ketyl; isopropanol was distilled from magnesium onto activated 3 Å molecular sieves. Trimethylsilyl cyanide (TMSCN) was distilled prior to use. CAUTION! Trimethylsilyl cyanide and hydrogen cyanide are severe poisons and should only be used with great caution in a well-ventilated fume hood. A potassium carbonate trap was used to trap any residual hydrogen cyanide when concentrating reaction solutions. Flash chromatography was performed using silica gel 60 (230–400 mesh) from EM Science. All ^1H NMR and ^{13}C NMR spectra were recorded on Inova 600, Bruker AM 500, or AM 400 FT spectrometers at ambient temperature. IR spectra were recorded on a Matteson FTIR 3000. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. Chiral GC analysis was performed on a Hewlett-Packard 5890 gas chromatograph. Chiral HPLC analysis was performed on a Hewlett-Packard 1050 HPLC.

Catalyst Preparation (1a):¹ In a flame dried 100 mL round-bottom flask equipped with a stir bar were combined (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (1.52 g, 2.78 mmol) and CH_2Cl_2 (20 mL, freshly distilled from CaH_2). At ambient temperature, diethyl aluminum chloride (1.8 M solution in toluene, 1.54 mL, 2.78 mmol) was added slowly to the stirring solution. After stirring for 2 h, the reaction mixture was concentrated in *vacuo* and the resulting yellow solid was rinsed with 100 mL of hexanes. The solid was dried in *vacuo* to yield **1a** (1.59 g, 95% yield) as a yellow solid. mp >350 °C (dec); IR (KBr) 2966, 2953, 2867, 1640, 1544, 848 cm^{-1} ; ^1H NMR (400 MHz, C_6D_6) δ 7.84 (s, 2H), 7.77 (s, 2H), 7.61 (s, 2H), 3.51 (m, 1H), 1.93 (s, 1H), 1.91 (s, 18H), 1.39 (s, 18H), 1.36 (m, 4H), 0.59 (m, 4H); ^{13}C NMR [^1H] (100 MHz, CD_2Cl_2) δ 162.7, 141.2, 139.3, 131.4, 128.7, 128.4, 118.7, 64.6 (broad), 35.9, 34.4, 31.6, 30.0, 28.2, 24.1. Anal. Calcd for $\text{C}_{36}\text{H}_{52}\text{AlClN}_2\text{O}_2$; C, 71.20; H, 8.42; Al, 4.44; Cl, 5.84; N, 4.61. Found: C, 71.05; H, 8.63; Al, 4.49; Cl, 5.73; N, 4.56.

General procedure for conjugate cyanide addition (Method A): Aluminum complex **1a** (60.7 mg, 0.1 mmol) and the imide **2** (1 mmol) were combined in a 25 mL Schlenk flask under N_2 . Toluene (0.4 mL) and TMSCN (333 μL , 2.5 mmol) were added by syringe and the mixture was heated gently with a heat gun until the yellow solution became homogeneous. The reaction flask was then placed in a water bath at ambient temperature and isopropanol (193 μL , 2.5 mmol) was added dropwise over 2 min. The system was sealed and the mixture was stirred for the specified length of time. Solvents were removed in *vacuo* with a K_2CO_3 solution trap. The residue was purified by flash chromatography to afford pure product **3**.

General procedure for conjugate cyanide addition (Method B): Aluminum complex **1a** (45.5 mg, 0.075 mmol) and the imide **2** (0.5 mmol) were combined in a 25 mL Schlenk flask under N_2 . Toluene (0.4

¹ Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316.

mL) and TMSCN¹ (267 μ L, 2 mmol) were added by syringe and the mixture was heated gently with a heat gun until it became a homogeneous yellow solution. The reaction flask was then heated to 45 °C and isopropanol (154 μ L, 2 mmol) was added dropwise over 20 sec. The system was sealed and the mixture was stirred for the specified length of time at 45 °C. Solvents were removed in *vacuo* with a K₂CO₃ solution trap. The residue was purified by flash chromatography to afford pure product **3**.

***N*-[3-(*R*)-Cyano-butryl]-benzamide (**3a**):** Method A. Reaction time: 26 h. The crude residue was purified by flash chromatography (3:1 hexanes:ethyl acetate) to afford *N*-[3-(*R*)-cyano-butryl]-benzamide (200 mg, 92%) as a white solid. The ee was determined to be 98% (p S-7) by HPLC analysis using a Pirkle L-Leucine column (Regis), 254 nm, 7% ethanol in hexane, 1 mL/min, *t_r*(minor) = 39.5 min, *t_r*(major) = 41.9); [α]_D²⁵ = -11.9 (*c* = 1.0, CHCl₃); *R_f* = 0.14 (3:1 hexanes:ethyl acetate); mp 118.4 °C; IR (thin film, cm⁻¹) 3295, 3251, 2961, 2922, 1693, 1674, 1509, 1466, 1257, 1247, 1071, 1019; ¹H NMR (400 MHz, CDCl₃) δ 1.45 (d, 3H, *J* = 7.3 Hz), 3.2 (m, 1H), 3.3 (m, 1H), 3.45 (dd, 1H, *J* = 17.9 Hz, *J* = 7 Hz), 7.54 (t, 2H, *J* = 7 Hz), 7.63 (t, 1H, *J* = 6 Hz), 7.85 (dd, 2H, *J* = 8.4 Hz, *J* = 1.5 Hz), 8.88 (s, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 17.8, 20.9, 41.7, 120.9, 127.7, 129.2, 132.0, 133.7, 163.6, 172.1.

***N*-[3-(*R*)-Cyano-pentanoyl]-benzamide (**3b**):** Method A. Reaction time: 26 h. The crude residue was purified by flash chromatography (3:1 hexanes:ethyl acetate) to afford *N*-[3-(*R*)-cyano-pentanoyl]-benzamide (222 mg, 95%) as a white solid. The ee was determined to be 97% (p S-8) by HPLC analysis using a Pirkle L-Leucine column (Regis), 254 nm, 7% ethanol in hexane, 1 mL/min, *t_r*(minor) = 30.9 min, *t_r*(major) = 32.9); [α]_D²⁴ = 7.8 (*c* = 1.0, CHCl₃); *R_f* = 0.17 (3:1 hexanes:ethyl acetate); mp 95 °C; IR (thin film, cm⁻¹) 3285, 2968, 2934, 1714, 1683, 1503, 1466, 1386, 1256, 1213, 1194, 1096, 1072; ¹H NMR (400 MHz, CDCl₃) δ 1.17 (t, 3H, 7.3 Hz), 1.78, (m, 2H), 3.10 (m, 1H), 3.32 (dd, 1H, *J* = 18 Hz, *J* = 5.4 Hz), 3.48 (dd, 1H, *J* = 18.6 Hz, *J* = 9.2 Hz), 7.57 (t, 2H, 7.8 Hz), 7.66 (t, 1H, 7.3 Hz), 7.98 (d, 2H, *J* = 7.3 Hz), 9.62 (s, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 11.5, 25.2, 28.3, 40.1, 121.3, 127.9, 129.1, 131.9, 133.6, 166.0, 173.2.

***N*-[3-(*R*)-Cyano-hexanoyl]-benzamide (**3c**):** Method A. Reaction time: 26 h. The crude residue was purified by flash chromatography (3:1 hexanes:ethyl acetate) to afford *N*-[3-(*R*)-cyano-hexanoyl]-benzamide (220 mg, 90%) as a white solid. The ee was determined to be 97% (p S-9) by HPLC analysis using a Pirkle L-Leucine column (Regis), 254 nm, 7% ethanol in hexane, 1 mL/min, *t_r*(minor) = 27.2 min, *t_r*(major) = 28.9); [α]_D²⁴ = 0.4 (*c* = 1.0, CHCl₃); *R_f* = 0.2 (3:1 hexanes:ethyl acetate); IR (thin film, cm⁻¹) mp 105.8 °C; IR (thin film, cm⁻¹) 3290, 2960, 1714, 1701, 1685, 1671, 1507, 1466, 1458, 1395, 1387, 1260, 1241, 1197, 1104; ¹H NMR (400 MHz, CDCl₃) δ 0.98 (t, 3H, *J* = 7 Hz), 2.42-2.8 (m, 4H), 3.14 (m, 1H), 3.3 (dd, 1H, *J* = 18.7 Hz, *J* = 5 Hz), 3.45 (dd, 1H, *J* = 18.3 Hz, *J* = 8.8 Hz), 7.54 (t, 2H, *J* = 8.1 Hz), 7.6 (t, 1H, *J* = 6.2 Hz), 7.93 (dd, 2H, *J* = 8 Hz, *J* = 1.1 Hz), 9.38 (s, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 13.4, 20.3, 26.5, 33.8, 40.3, 121.4, 127.9, 129.1, 132.0, 133.6, 165.9, 173.0.

***N*-[3-(*R*)-Cyano-4-methyl-pentanoyl]-benzamide (**3d**):** Method A. Reaction time: 26 h. The crude residue was purified by flash chromatography (3:1 hexanes:ethyl acetate) to afford *N*-[3-(*R*)-cyano-4-methyl-pentanoyl]-benzamide (221 mg, 91%) as a white solid. The ee was determined to be 94% (p S-10) by HPLC analysis using a Pirkle L-Leucine column (Regis), 254 nm, 7% ethanol in hexane, 1 mL/min, *t_r*(minor) = 27.1 min, *t_r*(major) = 29.3); [α]_D²⁵ = 18.0 (*c* = 1.0, CHCl₃); *R_f* = 0.2 (3:1 hexanes:ethyl acetate); mp 103.0 °C; IR (thin film, cm⁻¹) 2974, 1708, 1683, 1639, 1597, 1500, 1467, 1431, 1380, 1241, 1209; ¹H NMR (400 MHz, CDCl₃) δ 1.14 (dd, 6H, *J* = 6.8 Hz, *J* = 3 Hz), 2.0 (m, 1H), 3.12 (m, 1H), 3.28 (dd, 1H, *J* = 18.6 Hz, *J* = 4.3 Hz), 3.45 (dd, 1H, *J* = 18 Hz, *J* = 10 Hz), 7.54 (t, 2H, *J* = 7.3 Hz),

7.64 (t, 1H, J = 7.3 Hz), 7.88 (dd, 2H, J = 8.3 Hz, J = 1.5 Hz), 8.95 (s, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 18.6, 20.9, 29.9, 33.8, 38.5, 120.3, 127.7, 129.2, 132.0, 133.7, 165.7, 173.8.

***N*-[3-(*R*)-Cyano-5-methyl-hexanoyl]-benzamide (3e):** Method A. Reaction time: 26 h. The crude residue was purified by flash chromatography (3:1 hexanes:ethyl acetate) to afford *N*-[3-(*R*)-cyano-5-methyl-hexanoyl]-benzamide (240 mg, 93%) as a white solid. The ee was determined to be 96% (p S-11) by HPLC analysis using a Pirkle L-Leucine column (Regis), 254 nm, 7% EtOH in hexane, 1 mL/min, t_r (minor) = 22.9 min, t_r (major) = 24.3; $[\alpha]_D^{25}$ 1.19 (c = 1.01, CHCl_3); R_f = 0.3 (3:1 hexanes:ethyl acetate); mp 113.1 °C; IR (thin film, cm^{-1}) 3270, 2962, 1714, 1682, 1505, 1470, 1385, 1250, 1212, 1195, 1188, 910; ^1H NMR (400 MHz, CDCl_3) δ 0.98 (dd, 6 H, J = 6.6 Hz, 2.9 Hz), 1.42 (m, 1H), 1.78 (m, 1H), 1.92 (m, 1H), 3.2 (m, 1H), 3.25-3.43 (m, 2H), 7.54 (t, 2 H, J = 8 Hz), 7.63 (t, 1 H, J = 7.3 Hz), 7.88 (dd, 2 H, J = 8.8 Hz, 1.5 Hz), 9.03 (1H); ^{13}C NMR (400 MHz, CDCl_3) δ 21.3, 22.9, 24.9, 26.1, 40.7, 121.5, 127.7, 129.2, 132.0, 133.6, 165.7, 172.5.

***N*-[3-(*R*)-Cyano-7-hexenoyl]-benzamide (3f):** Method A (0.25 mmol scale). Reaction time: 48 h. The crude residue was purified by flash chromatography (3:1 hexanes:ethyl acetate) to afford *N*-[3-(*R*)-cyano-7-hexenoyl]-benzamide (69 mg, 96%) as a clear oil. The ee was determined to be 95% (p S-12) by HPLC analysis using a Pirkle L-Leucine column (Regis), 254 nm, 7% ethanol in hexane, 1 mL/min, t_r (minor) = 27.8 min, t_r (major) = 29.7; $[\alpha]_D^{25}$ = 3.1 (c = 1.0, CHCl_3); R_f = 0.3 (3:1 hexanes:ethyl acetate); IR (thin film, cm^{-1}) 1712, 1679, 1466, 1382, 1247, 1207, 1071; ^1H NMR (400 MHz, CDCl_3) δ 1.5-1.8 (m, 4H), 2.1 (m, 2 H), 3.1 (m, 1H), 3.3 (m, 1H), 3.4 (m, 1H), 5.0 (t, 2H, J = 10 Hz), 7.5 (t, 2H, J = 8 Hz), 7.6 (t, 1H, J = 7 Hz), 7.9 (d, 2H, J = 8 Hz), 9.4 (1H); ^{13}C NMR (400 MHz, CDCl_3) δ 26.1, 26.6, 31.2, 32.9, 40.4, 115.5, 121.4, 127.9, 129.1, 131.9, 133.6, 137.5, 165.9, 173.0.

***N*-[3-(*R*)-Cyano-4,4-dimethyl-pentanoyl]-benzamide (3g):** Method B. Reaction time: 48 h. The crude residue was purified by flash chromatography (3:1 hexanes:ethyl acetate) to afford *N*-[3-(*R*)-cyano-4,4-dimethyl-pentanoyl]-benzamide (117 mg, 90%) as a white solid. The ee was determined to be 97% (p S-13) by HPLC analysis using a Pirkle L-Leucine column (Regis), 254 nm, 7% EtOH in hexane, 1 mL/min, t_r (minor) = 26.0 min, t_r (major) = 28.7; $[\alpha]_D^{25}$ = 18.1 (c = 1.0, CHCl_3); R_f = 0.26 (3:1 hexanes:ethyl acetate); mp 118.4 °C; IR (thin film, cm^{-1}) 3288, 2966, 2919, 1711, 1677, 1469, 1383, 1243; ^1H NMR (400 MHz, CDCl_3) δ 1.14 (s, 9H), 3.01 (dd, 1H, J = 10.6 Hz, J = 4Hz), 3.3-3.4 (m, 2H), 7.53 (t, 2H, J = 7.3 Hz), 7.6 (t, 1H, J = 6.2 Hz), 7.9 (m, 2H), 9.03 (s, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 27.3, 32.9, 36.6, 38.4, 120.8, 127.7, 129.2, 132.1, 133.6, 165.8, 173.1.

***N*-(4-Benzyloxy-3-(*R*)-cyano-butyl)-benzamide (3h):** Method B. Reaction time: 48 h. The crude residue was purified by flash chromatography (3:1 hexanes:ethyl acetate) to afford *N*-(4-benzyloxy-3-(*R*)-cyano-butyl)-benzamide (117 mg, 70%) as a clear oil. The ee was determined to be 87% (p S-14) by HPLC analysis using a Pirkle L-Leucine column (Regis), 254 nm, 7% ethanol in hexane, 1 mL/min, t_r (minor) = 52.7 min, t_r (major) = 56.4; $[\alpha]_D^{25}$ = 19 (c = 1.0, CHCl_3); R_f = 0.09 (3:1 hexanes:ethyl acetate); IR (thin film, cm^{-1}) 3288, 2929, 2869, 1715, 1686, 1504, 1469, 1382, 1243, 1207, 1104; ^1H NMR (400 MHz, CDCl_3) δ 3.42 (m, 1H), 3.49 (t, 2H, J = 4.8 Hz), 3.7 (t, 2H, J = 5.5 Hz), 7.3-7.4 (m, 5H), 7.5 (t, 2H, J =

8Hz), 7.65 (t, 1H, J = 7 Hz), 7.9 (m, 2H), 9.15 (s, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 27.6, 37.3, 68.4, 73.4, 119.8, 127.8, 128.0, 128.5, 129.1, 132.0, 133.6, 137.1, 165.8, 172.6.

Synthesis of γ -Amino Acid **5**

3-(S)-Cyano-5-methyl-hexanoic acid (4): *N*-[3-(S)-Cyano-5-methyl-hexanoyl]-benzamide (1.26 g, 4.88 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. A solution of NaOH (1 N, 5.52 mL, 5.52 mmol) was added dropwise over 1 min and the mixture was then stirred at 0 °C for 30 min. The mixture was then allowed to warm to room temperature and stirring was continued for 8 h. The solution was then concentrated by rotary evaporation to approximately half of the original volume and saturated sat. NaHCO_3 (10 mL) was added. The aqueous phase was washed with CH_2Cl_2 (3x125 mL), acidified to a pH of 2 and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated by rotary evaporation to afford a clear oil (733 mg, 94%) contaminated with ca. 5% benzoic acid. $[\alpha]^{25}_{\text{D}} = 16.7$ ($c = 0.5$, CHCl_3); IR (thin film, cm^{-1}) 2963, 2932, 2875, 1732, 1470, 1415, 1174; ^1H NMR (400 MHz, CDCl_3) δ 0.97 (t, 6H, J = 6.6 Hz), 1.38 (m, 1H), 1.69 (m, 1H), 1.86 (m, 1H), 2.59-2.81 (m, 2H) 3.05 (m, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ : 21.2, 22.8, 25.5, 26.0, 36.8, 40.6, 120.8, 175.7. For the purposes of analysis, the acid was converted to the methyl ester by treatment of 5 mg of the acid with trimethylsilyldiazomethane (1 mL) in MeOH (2 mL). The solution was stirred for five min. The solvent was removed by rotary evaporation. The ee of the ester was determined to be 97% (p S-15) by chiral GC analysis of a CH_2Cl_2 solution of the residue (γ -TA, isothermal 90 °C, $t_{\text{r}}(\text{minor}) = 23.9$ min, $t_{\text{r}}(\text{major}) = 42.1$).

3-(S)-Aminomethyl-5-methyl-hexanoic acid (5):² 3-(S)-Cyano-5-methyl-hexanoic acid (756 mg, 4.88 mmol) was combined with PtO_2 (46.4 mg, 0.2 mmol, 5 mol%), H_2O (20 mL), HCl (conc., 2 mL) and the mixture was placed in a pressure bomb under H_2 (500 psi). After 6 h, the mixture was filtered through Celite and concentrated to a clear oil. The residue was dissolved in ethanol. Ethyl acetate was added and the solution was cooled to 4 °C for 30 min. The mixture was filtered through Celite and concentrated to afford **5** as a clear oil (821 mg, 92%). $[\alpha]^{24}_{\text{D}} = 7.0$ ($c = 1.03$, H_2O); IR (thin film, cm^{-1}) 3219, 3120, 2995, 1721, 1409, 1390, 1228, 1192; ^1H NMR (400 MHz, CD_3OD) δ 0.94 (dd, 6H, J = 9.5 Hz), 1.26 (t, 2H, J = 7 Hz), 1.69 (m, 1H), 2.2 (m, 1H), 2.42 (t, 2H, J = 6 Hz), 2.96 (m, 2H); ^{13}C NMR (400 MHz, CD_3OD) δ 22.5, 23.2, 26.1, 32.6, 37.1, 42.0, 44.5, 175.8. For the purposes of analysis, the acid was converted to the methyl ester and the amine was trifluoroacetylated as follows: the acid **5** (5 mg) was dissolved in a methanolic solution of HCl (1 N, 2 mL) and stirred at 65 °C for 4 h. The solvent was removed by rotary evaporation. The crude residue was then dissolved in CH_2Cl_2 (3 mL) and refluxed with trifluoroacetic acid (1 mL) for 2 min. The solution was filtered through a plug of silica. The ee of the trifluoroacetamide methyl ester was determined to be 96% (p S-16) by chiral GC analysis (γ -TA, isothermal 110 °C, $t_{\text{r}}(\text{minor}) = 14.8$ min, $t_{\text{r}}(\text{major}) = 19.4$).

Synthesis of β -Amino Acid **8**

3-(R)-Cyano hexanoic acid (6): *N*-[3-(R)-Cyano-hexanoyl]-benzamide (500 mg, 2.05 mmol) was dissolved in THF (8.8 mL) and cooled to 0 °C. A solution of NaOH (1 N, 3 mL, 3 mmol) was added dropwise over 1 min and the mixture was

² (a) Silverman, et al. U.S. Patent 6 262 120, 2001. (b) Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, B. S.; Franklin, L. C.; Granger, E. J.; Karrick, G.; *Org. Process Dev.* **1997**, *1*, 26-38.

stirred at 0 °C for 30 min. The mixture was allowed to warm to room temperature and stirring was continued for 8 h. The solution was then concentrated by rotary evaporation to approximately half of the original volume and saturated sat. NaHCO₃ (10 mL) was added. The aqueous phase was washed with CH₂Cl₂ (3x125 mL), acidified to a pH of 2 and extracted with CH₂Cl₂ (3x50 mL). The combined organic phases were dried (Na₂SO₄) and concentrated by rotary evaporation to afford a clear oil (283 mg, 93%) contaminated with ca. 5% benzoic acid. $[\alpha]^{25}_D = 1.3$ ($c = 1.1$, CHCl₃); IR (thin film, cm⁻¹) 2966, 2245, 1714, 1466, 1414, 1263, 1238, 1174; ¹H NMR (400 MHz, CDCl₃) δ 0.97 (t, 3H, J = 7 Hz), 1.4-1.8 (m, 4H), 2.65 (m, 1H), 2.75 (m, 1H), 3.01 (m, 1H), 10.5 (s, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 13.4, 20.2, 27.1, 33.7, 36.3, 120.8, 175.3. For the purposes of analysis, the acid was converted to the methyl ester by treatment of 5 mg of the acid with trimethylsilyldiazomethane (1 mL) in MeOH (2 mL). The solution was stirred for five min. The solvent was removed by rotary evaporation. The ee of the ester was determined to be 96% (p S-17) by chiral GC analysis of a CH₂Cl₂ solution of the residue (γ -TA, isothermal 90 °C, t_r (major) = 18.5 min, t_r (minor) = 20.57).

(2-(*R*)-Cyano-pentyl)-carbamic acid *tert*-butyl ester (7): Nitrile Acid (283 mg, 1.9 mmol) was combined with triethylamine (0.558 mL, 4 mmol) and dissolved in ^tBuOH (2.5 mL). Diphenyl phosphoryl azide (0.862 mL, 1.276 mmol) was added and the mixture was heated to 75 °C for 3 h. The solvent was removed in *vacuo* to afford a yellow oil. The crude residue was purified by flash chromatography (CH₂Cl₂) to afford 2(*R*)-cyano-pentyl)-carbamic acid *tert*-butyl ester (302 mg, 75%). $[\alpha]^{24}_D = 23.9$ ($c = 1.5$, CHCl₃); IR (thin film, cm⁻¹) 3354, 2967, 2935, 2876, 2241, 1709, 1522, 1458, 1275, 1253, 1173; ¹H NMR (400 MHz, CDCl₃) δ 0.98 (t, 3H, J = 5 Hz), 1.4 (s, 9H), 1.4-1.5 (m, 4H), 2.84 (m, 1H), 3.2 (m, 1H), 3.4 (m, 1H), 4.9 (m, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 13.5, 20.2, 28.3, 31.4, 32.9, 42.2, 80.1, 121.1, 155.7. For the purposes of analysis, the N-Boc carbamate was converted to the trifluoroacetamide by treatment of 5 mg of the carbamate with HCl (conc., 0.3 mL) for 5 min. The solvent was removed in *vacuo*. The residue was dissolved in CH₂Cl₂ (3 mL) and trifluoroacetic anhydride (1 mL) and the mixture was refluxed for 5 min. The ee of the amide was determined to be 96% (p S-18) by chiral GC analysis (γ -TA, isothermal 120 °C, t_r (minor) = 11.5 min, t_r (major) = 14.9).

2-(*R*)-Aminomethyl-pentanoic acid (8):³ 2-(*R*)-Cyano-pentyl)-carbamic acid *tert*-butyl ester (298 mg, 1.42 mmol) was dissolved in HCl (conc., 3 mL) and stirred for 10 min. The mixture was then washed with CH₂Cl₂ (2x50 mL) and heated to 100 °C for 2.5 h. The solvent was removed in *vacuo* to afford a white solid. The solid contains ammonium chloride as a byproduct of nitrile hydrolysis (302 mg, 97%). $[\alpha]^{28}_D = 1.3$ ($c = 1.0$, H₂O); IR (thin film, cm⁻¹) 3178, 3142, 3099, 3041, 2966, 2932, 2874, 1714, 1406, 1226.8, 1194. ¹H NMR (400 MHz, CD₃OD) δ 0.98 (t, 3H, J = 7 Hz), 1.4 (m, 2H), 1.6 (m, 2H), 1.65 (m, 2H), 2.75 (m, 1H), 3.05 (m, 1H), 3.15 (m, 1H); ¹³C NMR (400 MHz, CD₃OD) δ 14.2, 20.9, 32.9, 41.3, 43.6, 176.2. For the purposes of analysis, the acid was converted to the methyl ester and the amine was converted to the trifluoroacetamide. The β -acid (5mg) was treated with trimethylsilyldiazomethane (1 mL) in MeOH (2 mL). The solution was stirred for five min. The solvent was removed by rotary evaporation. The crude residue was then dissolved in CH₂Cl₂ (3 mL) and refluxed with trifluoroacetic acid (1 mL) for 2 min. The solution was filtered through a plug of silica. The ee of the trifluoroacetamide methyl ester was determined to be 94% (p S-19) by chiral GC analysis. 94% ee (γ -TA, isothermal 90 °C, t_r (minor) = 18.1 min, t_r (major) = 20.7).

³ Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A.; *Org. Lett.* **2000**, 2, 3527-3530.

Spectroscopic Data For Imidate Complex

(salen)Al-imidate complex (**1d**) derived from imide **3a**: ^1H NMR (400 MHz, C_6D_6) δ 8.18 (s, 2H), 7.90 (s, 1H), 7.85 (s, 1H), 7.64 (s, 1H), 7.58 (s, 1H), 7.45 (s, 1H), 7.10-6.90 (m, 4H), 6.80 (d, 1H, $J = 7$ Hz), 6.01 (d, 1H, $J = 16$ Hz), 3.73 (m, 1H), 2.40 (m, 1H), 1.83 (s, 9H), 1.71 (m, 2H), 1.61 (s, 9H), 1.40 (s, 9H), 1.36 (m, 2H), 1.32 (s, 9H), 1.29 (d, 3H, $J = 7$ Hz), 1.1-0.6 (m, 4H); ^{13}C NMR (400 MHz, C_6D_6) δ 179.9, 179.1, 165.8, 165.0, 164.2, 161.2, 144.8, 141.7, 141.1, 137.1, 136.9, 136.7, 136.3, 132.7, 131.4, 130.5, 129.9, 128.7, 126.3, 125.0, 121.8, 119.0, 68.3, 63.1, 36.2, 35.6, 34.2, 34.0, 31.9, 31.7, 30.7, 30.3, 29.9, 29.2, 27.9, 27.0, 24.5, 23.8, 18.0, 17.8.

Plot of Initial Rate vs. $[\text{1a}]^2$

Reaction of substrate **3c** using Method A (see Table 1 of main document). Catalyst loadings range from 5.0 to 17.5 mol%. Rate data were collected by dividing the reaction mixture into 7 ^1H NMR tubes and then quenching each tube at different times by dilution with CD_2Cl_2 . Reaction progress was monitored over the first 20% of each reaction by integration of starting material and product ^1H NMR resonances.

Chiral HPLC Analysis: Pirkle Covalent L-Leucine 7% EtOH/Hex, 1.0 mL/min

Signal 1: DAD1 E, Sig=254, Ref=550.100

Sorted By	Signal
Multiplier	1.0000
Dilution	1.0000

Peak #	Retention Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	39.509		0.0000	50.1834	44.9416	
2	41.939		0.0000	5.48808	0.0000	
3	41.939		1.6559	4639.42378	47.29840	55.0584

Totals: 8535.34326 107.16989

Racemic Product

Signal 1: DAD1 E, Sig=254, Ref=550.100

Sorted By	Signal
Multiplier	1.0000
Dilution	1.0000

Peak #	Retention Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.865		0.7613	50.2133	1.10612	0.3270
2	41.486		1.6399	5401.21631	54.89413	99.6730

Totals: 5451.75164 56.00025

Reaction Product

Chiral HPLC Analysis: Pirkle Covalent L-Leucine 7% EtOH/Hex, 1.0 mL/min

Area Percent Report

Sorted By	: Signal
Multiplier	: 1.0000
Dilution	: 1.0000

Signal 1: DAD1 E, Sig=254.4 Ref=550.100

Peak #	Retention Time [min]	Width [min]	Area [a.u.]	Height [a.u.]	Area %
1	30.931	0.2232	2406.53	31.3872	51.1632
2	31.412	0.2232	2406.53	31.3872	51.1632

Totals : 4620.73828 69.60159

Results obtained with enhanced integrator!

Racemic Product

Area Percent Report

Sorted By	: Signal
Multiplier	: 1.0000
Dilution	: 1.0000

Signal 1: DAD1 E, Sig=254.4 Ref=550.100

Peak #	Retention Time [min]	Width [min]	Area [a.u.]	Height [a.u.]	Area %
1	32.719	0.2253	4475.05615	60.81981	98.7996
2	33.797	0.2253	4475.05615	60.81981	98.7996

Totals : 4529.42926 62.08948

Results obtained with enhanced integrator!

Reaction Product

Chiral HPLC Analysis: Pirkle Covalent L-Leucine
7% EtOH/Hex, 1.0 mL/min

Racemic Product

Reaction Product

Area Percent Report

Sorted By	Signal
Multiplicator	1.0000
Dilution	1.0000

Peak	Retention Time (min)	Area	Height	Area %
1	27.222	116.8163	46.1488	1.0000
2	28.867	107.8187	53.8111	1.0000
3	29.653	44.36234	0.0000	1.0000

Totals : 1.119764 268.6874

Area Percent Report

Sorted By	Signal
Multiplicator	1.0000
Dilution	1.0000

Peak	Retention Time (min)	Area	Height	Area %
1	28.552	17.45265	4.42454	1.0000
2	29.650	1421.15267	27.43543	98.7731

Totals : 1438.60291 23.88773

Chiral HPLC Analysis: Pirkle Covalent L-Leucine
7% EtOH/Hex, 1.0 mL/min

Racemic Product

Reaction Product

Area Percent Report

Sorted By	Signal
Multiplier	1.0000
Dilution	1.0000

Signal 1: DAD E, Sig=254, Ref=550.100

Peak	RetTime	Type	Width	Area	Height	Area%
1	27.140	MF	0.9136	1892.69141	34.52958	48.2785
2	29.255	FM	1.0541	2027.67261	32.05218	51.7215
Totals:				3920.36401	66.58075	

Results obtained with enhanced integrator!

Area Percent Report

Sorted By	Signal
Multipliers	1.0000
Dilution	1.0000

Signal 1: DAD E, Sig=254, Ref=550.100

Peak	RetTime	Type	Width	Area	Height	Area%
1	27.945	MF	0.8240	126.19723	2.52351	3.0672
2	29.943	FM	1.0672	3384.16211	62.28344	96.9328
Totals:				4114.35934	64.85595	

Results obtained with enhanced integrator!

Chiral HPLC Analysis: Pirkle Covalent L-Leucine
7% EtOH/Hex, 1.0 mL/min

Racemic Product

Reaction Product

Chiral HPLC Analysis:
Pirkle Covalent L-Leucine
7% EtOH/Hex, 1.0 mL/min

Chiral HPLC Analysis: Pirkle Covalent L-Leucine
7% EtOH/Hex, 1.0 mL/min

Racemic Product

Reaction Product

Chiral HPLC Analysis: Pirkle Covalent

L-Leucine

7% EtOH/Hex, 1.0 mL/min

Signal 1: DAD1 E, Sig=354.4 Ref=450.100

Peak	Retention Time [min]	Width [min]	Area [mAU]	Height [mAU]	Area
1	52.697	1.8323	179.1031	2.18081	47.0358
2	56.441	1.7334	221.8395	2.14418	52.9642

Totals : 471.4555 4.3499

Results obtained with enhanced integrator!

Racemic Product

Signal 1: DAD1 E, Sig=354.4 Ref=450.100

Peak	Retention Time [min]	Width [min]	Area [mAU]	Height [mAU]	Area
1	52.948	1.4156	400.4553	4.71526	6.9382
2	54.479	1.8912	5371.80615	47.34139	93.0518

Totals : 5772.30168 52.05555

Results obtained with enhanced integrator!

Reaction Product

Chiral GC Analysis: γ -TA

90° Isotherm

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	23.880	178795	2591	MM	1.150	49.6778
2	42.154	181115	1252	MM	2.411	50.3222

Total area = 359910

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	24.384	14208	369	MM	0.641	1.3515
2	37.954	1037054	3899	MM	4.433	98.6485

Total area = 1051262

Racemic Product

Reaction Product

Chiral GC Analysis: γ -TA

110° Isotherm

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	14.824	97406	3629	MM	0.447	50.1125
2	19.422	96968	2339	MM	0.691	49.8875

Total area = 194374

Racemic Product

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	14.894	2297	94	MM	0.406	1.2782
2	19.267	177413	3653	MM	0.810	98.7218

Total area = 179710

Reaction Product

Chiral GC Analysis: γ -TA
90° Isotherm

Racemic Product

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	18.530	114668	2715	MM	0.704	49.7039
2	20.527	116034	2221	MM	0.871	50.2961

Total area = 230702

Reaction Product

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	17.668	409447	5435	MM	1.256	97.8164
2	21.063	9140	145	MM	1.052	2.1836

Chiral GC Analysis: γ -TA
120° Isotherm

Racemic Product

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	11.549	128294	4815	MM	0.444	50.2602
2	14.891	126965	3291	MM	0.643	49.7398

Total area = 255258

Reaction Product

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	12.057	1482	111	MM	0.222	1.8729
2	15.060	77663	2416	MM	0.536	98.1271

Total area = 79146

Chiral GC Analysis: γ -TA
90° Isotherm

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	18.082	253341	5757	MM	0.733	49.3710
2	20.681	259796	4381	MM	0.988	50.6290

Total area = 513137

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	18.982	6055	361	MM	0.280	2.9926
2	20.880	196277	3775	MM	0.867	97.0074