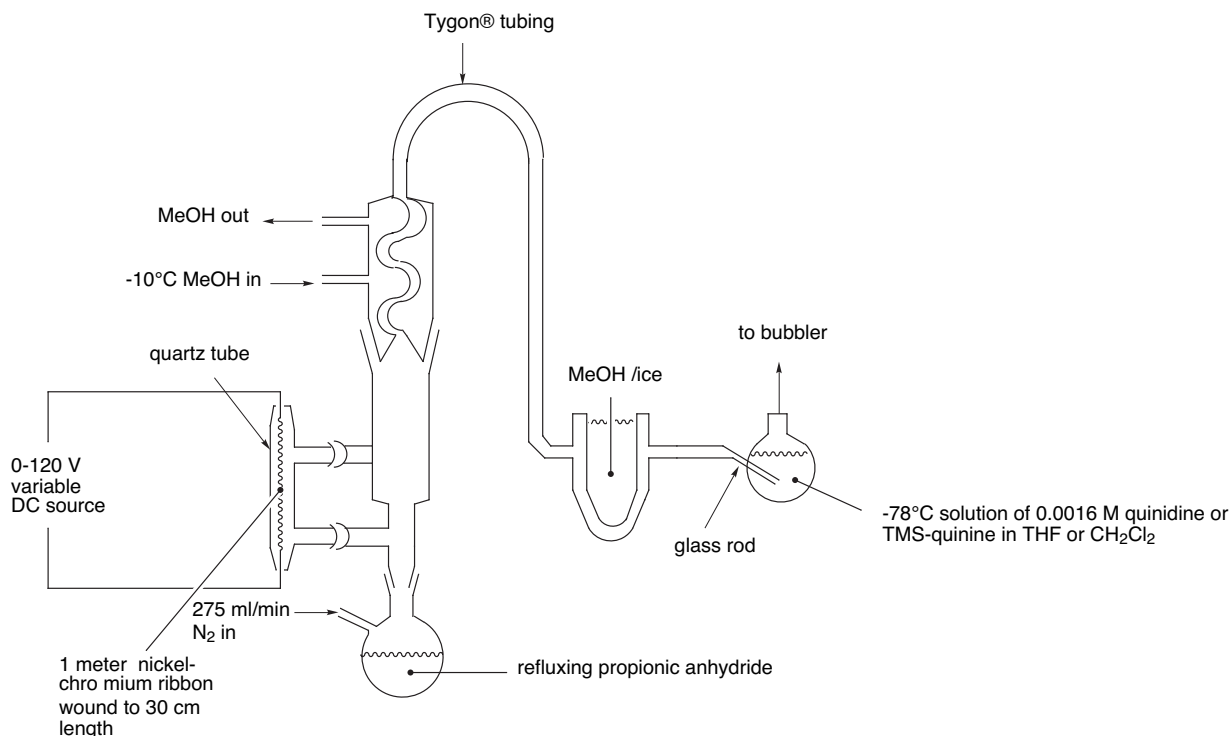


One-Pot, Catalytic, Asymmetric Syntheses of Polypropionates Supporting Material

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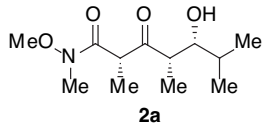
Formation and asymmetric dimerization of methylketene from propionic anhydride: The still pot of the pyrolysis apparatus (Fig. 1) was charged with 250 mL of propionic anhydride. The variable DC source was adjusted so the nickel-chromium wire glowed red (~40V), and the propionic anhydride solution was brought to reflux (**Caution:** To avoid the possibility of fire or explosion, it is essential that the system be maintained under a positive pressure of nitrogen during the entire process). The outlet from the pyrolysis device was passed through a -78°C solution of 10.0 mg (0.031 mmol) of quinidine in 20 mL THF or CH₂Cl₂. The reaction was conducted for the appropriate amount of time to yield 10 mmol of methylketene dimer per hour. This unpurified reaction mixture can be used directly in the following reaction, or the dimer could be isolated from CH₂Cl₂ by removal of the solvent under reduced pressure. The yield and optical purity could be confirmed by conversion of the dimer into the β-ketoamide as described earlier.¹

Figure 1. Pyrolysis device.



Representative opening and aldol reaction of methylketene dimer: To a solution of 0.150 mL (0.125 g, 2.04 mmol) of *N,O*-dimethylhydroxylamine in 10 mL of tetrahydrofuran (THF) at -78°C was added, dropwise, 0.800 mL (2.00 mmol) of a 2.5 M solution of *n*-BuLi in hexanes. After stirring for 30 min, the solution was added via cannula to a -78°C solution of 0.230 g (2.05 mmol) of the methylketene dimer in 10 mL THF. This solution was stirred for 3 min at -78°C, and then 2.2 mmol of the aldehyde was added neat. After 40 min at -78°C, the reaction was quenched by the addition via cannula of a rapidly stirred mixture of deionized water (55 mL) and 1 M HCl (10 mL). The mixture was then warmed to room temperature, separated, the aqueous layer washed two times with CH₂Cl₂ (20 mL), the combined organic layers were dried (Na₂SO₄), and the solvents were removed in vacuo. Flash chromatography (SiO₂, EtOAc/hexanes) afforded the pure aldol adducts.

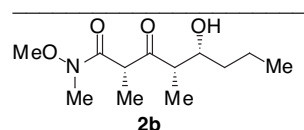
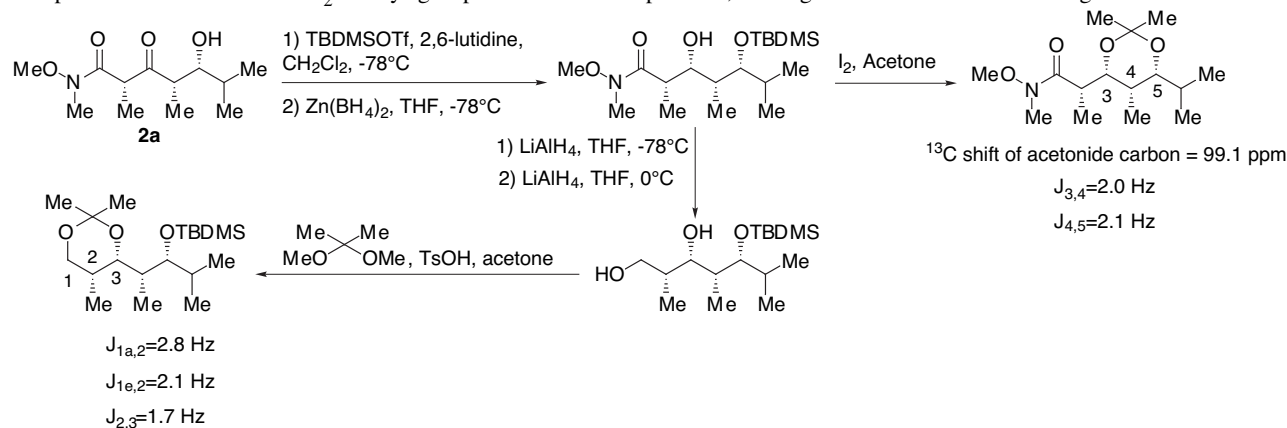
Data for aldol adducts:



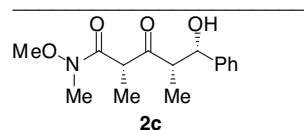
[2S,4S,5R]-5-Hydroxy-N-methoxy-3-oxo-N,2,4,6-tetramethylheptanamide (2a) : Capillary GC analysis (AT1701, 30 m, 7.2 psi, 150°C isothermal) of the unpurified reaction mixture showed a 95:5 mixture of *syn,syn:syn,anti*-diastereomers ($R_{t\text{ syn,syn}} = 37.2$ min; $R_{t\text{ anti,syn}} = 38.3$ min), data for *syn,syn*-diastereomer (**2a**): $[\alpha]_D^{25} = -25.5^\circ (c\ 1.025, \text{CH}_2\text{Cl}_2)$; IR (neat film) 3490, 2960, 2940, 2875, 1710, 1660, 1460, 1380, 990; ¹H NMR (CDCl₃, 400 MHz) δ 3.93 (q, 1H, *J*=7.0 Hz), 3.68 (3H, s), 3.49 (apt. dt, 1H, *J*=8.8, 2.4 Hz), 3.19 (s, 3H), 2.88 (qd, 1H, *J*=7.2, 2.2 Hz), 2.80 (d, 1H, *J*=2.6 Hz), 1.68-1.61 (m, 1H), 1.33 (d, 3H, *J*=7.0 Hz), 1.09 (d, 3H, *J*=7.2 Hz), 0.99 (d, 3H, *J*=6.5 Hz), 0.82 (d, 3H, *J*=6.7 Hz); ¹³C (CDCl₃, 100.7 MHz) δ 211.6, 171.4, 76.0, 61.2, 48.9, 45.8, 32.5, 30.2, 19.2, 18.8, 13.0, 9.2; Anal. Calcd for C₁₂H₂₃NO₄: C, 58.75; H, 9.45; N, 5.71. Found: C,

58.58; H, 9.43; N, 5.63. Capillary GC analysis (CP-Chirasil-Dex CB, 25 m, 15.5 psi, 140°C isothermal) of the purified *syn,syn* diastereomer showed a >99.5:0.5 mixture of enantiomers ($R_{t\ 2S,4S,5R} = 30.8$ min; $R_{t\ 2R,4R,5S} = 31.8$ min).

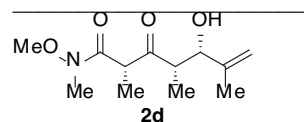
The relative stereochemistry of **2a** was proven as shown in the following scheme. Reduction of **2a** with $Zn(BH_4)_2$, followed by acetonide formation, yielded an internal acetonide. The ^{13}C shift of the acetonide carbon in this compound,² combined with the small coupling constants around the ring in this compound, indicated that the $Zn(BH_4)_2$ reduction had occurred to form the *syn* diastereomer shown, and that the C_2 -methyl group was in an axial position relative to the acetonide ring. Further reduction of the $Zn(BH_4)_2$ product, followed by acetonide formation, yielded an external acetonide. The small coupling constants in the ring in this compound indicated that the C_2 -methyl group was in an axial position, leading to the stereochemical assignment shown.



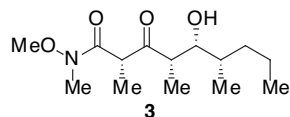
[2S,4S,5R]-5-Hydroxy-N-methoxy-3-oxo-2,4-trimethyloctanamide (2b). Capillary GC analysis (AT1701, 30 m, 7.2 psi, 150°C isothermal) of the unpurified reaction mixture showed a 89:11 mixture of *syn,syn:syn,anti*-diastereomers ($R_{t\ syn,syn} = 50.4$ min; $R_{t\ anti,syn} = 51.9$ min), data for *syn,syn*-diastereomer: $[\alpha]_D^{23} = -17.0^\circ (c\ 1.045, CH_2Cl_2)$; IR (neat film) 3460, 2960, 2940, 2875, 1710, 1660, 1460, 1380, 990; 1H NMR ($CDCl_3$, 400 MHz) δ 3.99-3.95 (m, 2H), 3.73 (s, 3H), 3.24 (m, 3H), 2.76 (d, 1H, $J=2.6$ Hz), 2.73 (qd, 1H, $J=7.2, 2.4$ Hz), 1.59-1.49 (m, 2H), 1.39-1.31 (m, 2H), 1.37 (d, 3H, $J=7.1$ Hz), 1.15 (d, 3H, $J=7.2$ Hz), 0.95 (t, 3H, $J=7.0$ Hz); ^{13}C ($CDCl_3$, 100.7 MHz) δ 211.6, 171.6, 70.5, 61.4, 49.0, 48.4, 35.8, 32.5, 19.2, 13.9, 13.0, 9.8; Anal Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 59.03; H, 9.68; N, 5.74.



[2S,4S,5S]-5-Hydroxy-N-methoxy-3-oxo-5-phenyl-N,2,4-trimethylpentanamide (2c). $[\alpha]_D^{23} = -9.0^\circ (c\ 1.02, CH_2Cl_2)$; IR (neat film) 3455, 3030, 2980, 2940, 2820, 1710, 1660, 1455, 1380, 1245, 990; 1H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.25 (m, 5H), 5.20 (apt. t, 1H, $J=2.3$ Hz), 3.96 (q, 1H, $J=7.0$ Hz), 3.73 (s, 3H), 3.25 (s, 3H), 2.98 (qd, 1H, $J=7.1, 2.6$ Hz), 1.37 (d, 3H, $J=7.0$ Hz), 1.06 (d, 3H, $J=7.1$ Hz); ^{13}C ($CDCl_3$, 100.7 MHz) δ 211.4, 171.5, 141.5, 128.1, 127.2, 125.9, 72.5, 61.4, 50.9, 49.1, 32.5, 12.9, 9.9; Anal Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.24; H, 7.58; N, 4.94.



[2S,4S,5S]-5-Hydroxy-N-methoxy-3-oxo-N,2,4,6-tetramethyl-6-heptenamide (2d). Capillary GC analysis (AT1701, 30 m, 7.2 psi, 150°C isothermal) of the unpurified reaction mixture showed a 84:16 mixture of *syn,syn:syn,anti*-diastereomers ($R_{t\ syn,syn} = 45.4$ min; $R_{t\ anti,syn} = 49.0$ min), data for *syn,syn*-diastereomer: $[\alpha]_D^{23} = -23.2^\circ (c\ 1.01, CH_2Cl_2)$; IR (neat film) 3475, 2980, 2940, 1710, 1660, 1455, 1380, 990; 1H NMR ($CDCl_3$, 400 MHz) δ 5.09 (br. s, 1H), 4.94 (br. s, 1H), 4.42 (br. s, 1H), 3.98 (q, 1H, $J=7.0$ Hz), 3.71 (s, 3H), 3.21 (s, 3H), 3.05 (d, 1H, $J=2.4$ Hz), 2.85 (qd, 1H, $J=7.2, 2.4$ Hz), 1.67 (br. s, 3H), 1.35 (d, 3H, $J=7.0$ Hz), 1.05 (d, 3H, $J=7.2$ Hz); ^{13}C ($CDCl_3$, 100.7 MHz) δ 211.2, 171.5, 143.1, 111.6, 73.2, 61.4, 49.0, 48.3, 32.5, 19.6, 13.0, 9.3; Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.20; H, 8.63; N, 5.52.



[2*S*,4*S*,5*R*,6*S*]-5-Hydroxy-*N*-methoxy-3-oxo-*N*,2,4,6-tetramethylnonanamide (3). $[\alpha]_{\text{D}}^{23} = -0.23^{\circ}$ (c 0.15, CHCl_3); IR (neat film) 3470, 2930, 2870, 1710, 1660, 1455, 1380, 990 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.95 (q, 1 H, $J = 7.06$ Hz), 3.68 (s, 3 H), 3.60 (dd, 1 H, $J = 7.6, 3.4$ Hz), 3.18 (s, 3 H), 2.88 (qd, 1 H, 7.2, 2.4 Hz), 1.57–1.43 (m, 1 H), 1.31 (d, 3 H, $J = 7.2$ Hz), 1.28–1.17 (m, 2 H), 1.09 (d, 3 H, $J = 7.1$ Hz), 1.06–0.97 (m, 2 H), 0.92 (d, 3 H, $J = 6.6$ Hz), 0.86 (t, 3 H, $J = 7.3$ Hz); ^{13}C NMR (100.7 MHz, CDCl_3) δ 211.2, 171.4, 74.6, 61.3, 48.9, 46.1, 35.1, 34.8, 32.5, 19.5, 15.1, 14.2, 13.0, 10.4. Anal. Calcd for $\text{C}_{14}\text{H}_{27}\text{NO}_4$: C, 61.51; H, 9.95; N, 5.12. Found: C, 61.44; H, 9.92; N, 5.08.

¹ Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308-5309.

² (a) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100.