Catalytic Asymmetric Synthesis of Esters from Ketenes

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Supporting Information

I. General

Toluene and THF were passed through a neutral alumina column. *t*-Butylphenol (Aldrich) was distilled under reduced pressure. Me₂NEt (Alpha Aesar) was used without further purification. Catalyst **3**¹ and most of the ketenes (see Section II)² were prepared according to literature procedures.

II. Ketene Synthesis

Me₂NEt (6.00 mL, 55.4 mmol) was added over 5 min to a solution of 2-(3-thienyl)-3-methylbutyryl chloride (2.20 g, 12.0 mmol) in THF (15 mL) in an ice bath. The resulting mixture was stirred at room temperature for 4.5 h. Removal of the precipitate by filtration in a glovebox, followed by removal of the THF, furnished a bright-yellow oil. The oil was distilled under full vacuum (71-73 °C) to yield the desired ketene (0.77 g, 39%; unoptimized).

¹H NMR (CDCl₃, 300 MHz): δ 7.36-7.33 (m, 1H), 6.83-6.78 (m, 2H), 2.73 (septuplet, J=6.3, 1H), 1.24 (d, J=6.6, 6H).

¹³C NMR (CDCl₃, 125 MHz): δ 207.1, 131.1, 126.4, 125.6, 115.7, 44.9, 25.7, 22.4.

IR (neat): 2963, 2098, 1750, 1534, 765 cm⁻¹.

III. Catalytic Asymmetric Synthesis of Esters from Ketenes (Table 1)

General Procedure: In the air, catalyst (–)-3 (0.011 mmol; 0.030 equiv) was weighed into a flask, which was then purged with argon. Toluene (30 mL) and 2-*t*-butylphenol (0.390 mmol; 1.04 equiv) were added. A solution of ketene (0.375 mmol; 1.00 equiv) in toluene (1.0 mL) was added by syringe over 30 minutes to the solution of catalyst and 2-*t*-butylphenol. The reaction mixture was stirred at room temperature for 2 hours, and then *n*-propylamine (0.05 mL) was added. The resulting solution was passed through a plug of silica gel (a 1:1 mixture of Et₂O:hexanes was used to elute the ester, and then a 1:9 mixture of NEt₃:EtOAc was used to elute catalyst 3). The ester was then purified by flash chromatography.

Table 1, Entry 1. The General Procedure was followed: *t*-butylphenol (0.060 mL, 0.39 mmol), phenyl methyl ketene (0.050 mL 0.38 mmol), (–)-3 (0.0043 g, 0.011 mmol), toluene (30 mL). The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.094 g, 87%).

The ester was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 77% ee [Chiraldex G-TA column; flow rate = 0.9 mL/min; starting temperature = 65 °C, ramped at 2 °C/min to 85 °C, final time = 20 min; retention times: 6.4 min (major), 7.1 min (minor)]. $[\alpha]_{\text{D}}^{20} = +57.8^{\circ}$ (*l*=1.0, *c*=0.0018 g/mL, CH₂Cl₂).

A second run was performed on the same scale. The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.094 g, 87%; 81% ee).

¹H NMR (CDCl₃, 300 MHz): δ 7.46-7.28 (m, 6H), 7.20-7.10 (m, 2H), 6.85 (dd, *J*=2.1, 7.2, 1H), 4.00 (q, *J*=7.2, 1H), 1.68 (d, *J*=7.2, 3H), 1.21 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz): δ 173.2, 149.7, 141.2, 139.7, 129.0, 128.1, 127.7, 127.3, 127.0, 125.8, 123.8, 46.4, 34.5, 30.1, 18.4.

HRMS (ESI) calc. for C₁₉H₂₂O₂Na [*M*+Na]: 305.1512, found: 305.1511.

IR (neat): 2967, 1756, 1603, 1488, 1442, 1188, 1141 cm^{–1}.

Table 1, Entry 2. The General Procedure was followed: *t*-butylphenol (0.060 mL, 0.39 mmol), phenyl ethyl ketene (0.055 mL, 0.375 mmol), (–)-3 (0.0043 g, 0.011 mmol), toluene (30 mL). The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.101 g, 91%).

The ester was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 91% ee [Chiraldex G-TA column; flow rate = 0.9 mL/min; starting temperature = 65 °C, ramped at 2 °C/min to 85 °C, final time = 20 min; retention times: 8.2 min (major), 9.0 min (minor)]. $[\alpha]_{\text{D}}^{20} = +63.1^{\circ}$ (*l*=1.0, *c*=0.0020 g/mL, CH₂Cl₂).

A second run was performed on the same scale. The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.095 g, 86%; 90% ee).

¹H NMR (CDCl₃, 300 MHz): δ 7.45-7.28 (m, 6H), 7.21-7.10 (m, 2H), 6.87 (dd, *J*=2.1, 7.2, 1H), 3.74 (t, *J*=7.8, 1H), 2.38-2.24 (m, 1H), 2.05-1.90 (m, 1H), 1.21 (s, 9H), 1.03 (t, *J*=7.5, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 172.7, 149.7, 141.2, 138.2, 128.9, 128.5, 127.7, 127.3, 127.0, 125.7, 123.8, 54.3, 34.5, 30.1, 26.5, 12.4.

HRMS (ESI) calc. for $C_{20}H_{25}O_2$ [M+H]: 297.1849, found: 297.1844.
IR (neat): 2966, 1755, 1602, 1489, 1442, 1188, 1141 cm^{-1} .

Table 1, Entry 3. The General Procedure was followed: *t*-butylphenol (0.060 mL, 0.39 mmol), phenyl *i*-butyl ketene (0.067 mL, 0.375 mmol), (–)-3 (0.0043 g, 0.011 mmol), toluene (30 mL). The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.095 g, 78%).

The ester was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 83% ee [Chirasil Dex CB column; flow rate = 1.0 mL/min; starting temperature = 100 °C, hold 5 min, ramped at 3 °C/min to 140 °C, final time = 18.3 min; retention times: 12.2 min (major), 12.6 min (minor)]. $[\alpha]_D^{20} = +56.5^\circ$ (*l*=1.0, *c*=0.0020 g/mL, CH₂Cl₂).

A second run was performed on the same scale. The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.098 g, 80%; 85% ee).

¹H NMR (CDCl₃, 300 MHz): δ 7.44–7.26 (m, 6H), 7.19–7.09 (m, 2H), 6.83 (dd, *J*=1.2, 7.2, 1H), 3.93 (t, *J*=7.8, 1H), 2.18–2.08 (m, 1H), 1.90–1.80 (m, 1H), 1.67–1.54 (m, 1H), 1.18 (s, 9H), 0.98 (d, *J*=6.6, 6H).

¹³C NMR (CDCl₃, 125 MHz): δ 172.9, 149.7, 141.2, 138.4, 128.9, 128.6, 127.7, 127.3, 127.0, 125.7, 123.8, 50.4, 42.2, 34.5, 30.1, 25.9, 22.9, 22.5.

HRMS (ESI) calc. for $C_{22}H_{29}O_2$ [M+H]: 325.2162, found: 325.2153.

IR (neat): 2957, 1755, 1602, 1488, 1443, 1187, 1140, 1114 cm^{-1} .

Table 1, Entry 4. The General Procedure was followed: *t*-butylphenol (0.060 mL, 0.39 mmol), phenyl cyclopentyl ketene (0.069 mL, 0.375 mmol), (–)-3 (0.0043 g, 0.011 mmol), toluene (30 mL). The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.111 g, 88%).

The ester was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 87% ee [Chirasil Dex CB column; flow rate = 1.0 mL/min; starting temperature = 140 °C, hold 2 min, ramped at 0.5 °C/min to 150 °C, final time = 27 min; retention times: 7.8 min (major), 8.0 min (minor)]. $[\alpha]_D^{20} = +59.4^\circ$ (*l*=1.0, *c*=0.0030 g/mL, CH₂Cl₂).

A second run was performed on the same scale. The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.100 g, 87%; 87% ee).

¹H NMR (CDCl₃, 300 MHz): δ 7.44–7.26 (m, 6H), 7.18–7.08 (m, 2H), 6.81 (dd, *J*=2.1, 7.5, 1H), 3.56 (d, *J*=11.1, 1H), 2.82–2.68 (m, 1H), 2.17–2.07 (m, 1H), 1.78–1.36 (m, 6H), 1.17 (s, 9H), 1.20–1.04 (m, 1H).

¹³C NMR (CDCl₃, 125 MHz): δ 173.2, 150.2, 141.8, 138.7, 129.3, 129.3, 128.1, 127.8, 127.4, 126.2, 124.3, 59.3, 43.7, 35.0, 32.5, 31.5, 30.6, 26.0, 25.6.

HRMS (ESI) calc. for $C_{23}H_{28}O_2Na$ [M+Na]: 359.1982, found: 359.1976.

IR (neat): 2956, 1755, 1602, 1488, 1442, 1188, 1117, 1086 cm^{-1} .

Table 1, Entry 5. The General Procedure was followed: *t*-butylphenol (0.060 mL, 0.39 mmol), phenyl *i*-propyl ketene (0.059 mL, 0.375 mmol), (–)-3 (0.0043 g, 0.011 mmol), toluene (30 mL). The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.078 g, 67%).

The ester was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 91% ee [Chiraldex G-TA column; flow rate = 1.5 mL/min; starting temperature = 65 °C, ramped at 2 °C/min to 85 °C, final time = 20 min; retention times: 9.7 min (minor), 10.7 min (major)]. [α]_D²⁰ = +70.2° (l=1.0, c=0.0029 g/mL, CH₂Cl₂).

A second run was performed on the same scale. The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.074 g, 64%; 91% ee).

¹H NMR (CDCl₃, 300 MHz): δ 7.42-7.26 (m, 6H), 7.19-7.08 (m, 2H), 6.83 (dd, J=1.8, 7.8, 1H), 3.43 (d, J=5.4, 1H), 2.59-2.51 (m, 1H), 1.22 (d, J=6.6, 3H), 1.17 (s, 9H), 0.80 (d, J=6.6, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 172.6, 149.7, 141.2, 137.6, 129.0, 128.8, 127.7, 127.3, 126.9, 125.7, 123.8, 60.7, 34.5, 31.7, 30.1, 22.0, 20.4.

HRMS (ESI) calc. for C₂₁H₂₆O₂Na [M+Na]: 333.1825, found: 333.1826.

IR (neat): 2961, 1755, 1601, 1489, 1443, 1191, 1143, 1105 cm⁻¹.

Table 1, Entry 6. The General Procedure was followed: *t*-butylphenol (0.060 mL, 0.39 mmol), *o*-tolyl ethyl ketene (0.060 mL, 0.38 mmol), (–)-3 (0.0043 g, 0.011 mmol), toluene (30 mL). The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.099 g, 84%).

The ester was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 90% ee [Chiraldex G-TA column; flow rate = 0.9 mL/min; starting temperature = 65 °C, ramped at 1.5 °C/min to 85 °C, hold 10 min, final time = 23.3 min; retention times: 12.3 min (major), 13.1 min (minor)]. [α]_D²⁰ = +105.7° (l=1.0, c=0.0029 g/mL, CH₂Cl₂).

A second run was performed on a similar scale. The General Procedure was followed: *t*-butylphenol (0.052 mL, 0.34 mmol), *o*-tolyl ethyl ketene (0.052 mL, 0.33 mmol), (–)-3 (0.0037 g, 0.010 mmol), toluene (30 mL). The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.085 g, 83%; 93% ee).

¹H NMR (CDCl₃, 300 MHz): δ 7.42-7.39 (m, 1H), 7.33 (dd, J=1.8, 7.5, 1H), 7.26-7.08 (m, 5H), 6.82 (dd, J=1.8, 6.9, 1H), 4.03 (t, J=7.8, 1H), 2.48 (s, 3H), 2.36-2.22 (m, 1H), 1.99-1.84 (m, 1H), 1.19 (s, 9H), 1.01 (t, J=7.5, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 172.8, 149.6, 141.2, 136.8, 136.5, 130.8, 127.4, 127.3, 127.1, 126.9, 126.7, 125.7, 123.8, 49.2, 34.4, 30.1, 26.4, 20.2, 12.4.

HRMS (ESI) calc. for C₂₁H₂₇O₂ [M+H]: 311.2006, found: 311.1999.

IR (neat): 2966, 1756, 1604, 1488, 1443, 1185, 1148, 1111 cm⁻¹.

Table 1, Entry 7. The General Procedure was followed: *t*-butylphenol (0.060 mL, 0.39 mmol), *o*-anisyl methyl ketene (0.056 mL, 0.375 mmol), (–)-3 (0.0043 g, 0.011 mmol), toluene (30 mL). The product was isolated by HPLC (5% EtOAc in hexanes at 5 mL/min) as a colorless oil (0.091 g, 78%).

The ester was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 92% ee [Chiraldex CB column; flow rate = 1.5 mL/min; starting temperature = 100 °C, hold 5 min, ramped at 1 °C/min to 120 °C, final time = 25 min; retention times: 16.8 min (major), 17.2 min (minor)]. [α]_D²⁰ = +78.3° (l=1.0, c=0.0030 g/mL, CH₂Cl₂).

A second run was performed on the same scale. The product was isolated by HPLC (5% EtOAc in hexanes at 5 mL/min) (0.092 g, 78%; 96% ee).

¹H NMR (CDCl₃, 300 MHz): δ 7.36-7.08 (m, 5H), 7.00-6.89 (m, 3H), 4.31 (q, J=7.2, 1H), 3.87 (s, 3H), 1.64 (d, J=7.5, 3H), 1.22 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz): δ 174.0, 157.5, 150.5, 141.6, 129.2, 129.1, 129.0, 127.7, 127.4, 126.0, 124.2, 121.5, 111.2, 56.0, 40.7, 35.0, 30.6, 17.5.

HRMS (ESI) calc. for C₂₀H₂₄O₃Na [M+Na]: 335.1618, found: 335.1614.

IR (neat): 2959, 1754, 1601, 1494, 1442, 1246, 1187, 1089 cm⁻¹.

Table 1, Entry 8. The General Procedure was followed: *t*-butylphenol (0.060 mL, 0.39 mmol), *p*-chlorophenyl *i*-propyl ketene (0.067 mL, 0.375 mmol), (+)-**3** (0.0043 g, 0.011 mmol), toluene (30 mL). The product was isolated by flash chromatography (5% Et₂O in hexanes) as a white solid (0.127 g, 98%).

The ester was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 89% ee [Chirasil Dex CB column; flow rate = 0.6 mL/min; starting temperature = 100 °C, hold 2 min, ramped at 0.2 °C/min to 111 °C, hold 2 min, ramped at 0.2 °C/min to 112 °C, hold 2 min, ramped at 0.1 °C/min to 113 °C, hold 5 min, ramped at 0.1 °C/min to 114 °C, hold 5 min, final time = 46 min; retention times: 38.1 min (major), 38.7 min (minor)]. [α]_D²⁰ = -59.1° (l=1.0, c=0.0030 g/mL, CH₂Cl₂).

A second run was performed on the same scale. The product was isolated by flash chromatography (5% Et₂O in hexanes) as a white solid (0.124 g, 96%; 89% ee).

¹H NMR (CDCl₃, 500 MHz): δ 7.37-7.31 (m, 5H), 7.20-7.09 (m, 2H), 6.83 (dd, J=1.8, 7.5, 1H), 3.41 (d, J=10.5, 1H), 2.54-2.42 (m, 1H), 1.21 (d, J=6.6, 3H), 1.17 (s, 9H), 0.79 (d, J=6.6, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 172.4, 149.5, 141.2, 136.1, 133.6, 130.3, 129.0, 127.4, 127.0, 125.9, 123.7, 60.0, 34.5, 31.9, 30.1, 21.9, 20.3.

HRMS (ESI) calc. for C₂₁H₂₅ClO₂Na [M+Na]: 367.1435, found: 367.1448.

IR (neat): 2968, 2254, 1749, 1490, 908 cm⁻¹.

Table 1, Entry 9. The General Procedure was followed: *t*-butylphenol (0.060 mL, 0.39 mmol), 3-thienyl *i*-propyl ketene (0.058 mL, 0.375 mmol), (-)-**3** (0.0043 g, 0.011 mmol), toluene (30 mL). The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.109 g, 92%).

The ester was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 80% ee [Chiraldex G-TA column; flow rate = 1.5 mL/min; starting temperature = 65 °C, ramped at 2 °C/min to 85 °C, final time = 20 min; retention times: 12.2 min (major), 13.3 min (minor)]. [α]_D²⁰ = +54.5° (l=1.0, c=0.0031 g/mL, CH₂Cl₂).

A second run was performed on the same scale. The product was isolated by flash chromatography (5% Et₂O in hexanes) as a colorless oil (0.113 g, 95%; 78% ee).

¹H NMR (CDCl₃, 500 MHz): δ 7.36-7.09 (m, 6H), 6.87 (dd, J=1.5, 7.8, 1H), 3.62 (d, J=10.2, 1H), 2.57-2.40 (m, 1H), 1.18 (d, J=6.3, 3H), 1.18 (s, 9H), 1.35 (d, J=6.6, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 172.3, 149.7, 141.3, 137.7, 127.8, 127.4, 127.0, 126.0, 125.8, 123.8, 123.2, 55.8, 34.5, 32.0, 30.1, 21.8, 20.5.

HRMS (ESI) calc. for C₁₉H₂₄O₂SNa [M+Na]: 339.1389, found: 339.1397.

IR (neat): 2962, 1755, 1576, 1488, 1442, 1187, 1136, 1104 cm^{-1} .

The absolute configuration of the products was assigned by comparison of the GC elution times of the trifluoroacetates (*vide supra*) with the products generated in: Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006-10007.

IV. Functionalizations (Eq 6)

Eq 6/Hydrolysis: 2-Phenylbutyric acid [90-27-7]. H₂O₂ (30% in water; 0.195 mL) and LiOH (2.0 M; 0.5 mL) were added to a 0 °C solution of the ester (0.100 g, 0.34 mmol; 91% ee) in THF (2 mL) and water (0.3 mL). The mixture was stirred at 0 °C for 6.5 h. Then, the reaction was quenched with Na₂S₂O₃ (0.7 M; 2 mL) and NaHCO₃ (0.5 M; 4 mL), and the resulting mixture was allowed to stir for 15 minutes. HCl (20%) was added until the mixture was acidic. The aqueous layer was extracted with Et₂O and then EtOAc. The combined organic layers were evaporated, and the product was isolated by flash chromatography (10% EtOAc in hexanes, then 25% EtOAc in hexanes), which furnished a colorless oil (0.053 g, 96%).

To determine if any racemization had occurred, the acid was reduced to the alcohol (excess LAH in Et₂O at room temperature), trifluoroacetylated (trifluoroacetic anhydride), and then analyzed by GC: 90% ee [ChiralDEX G-TA column, flow rate = 0.9 mL/min; starting temperature = 65 °C, ramped at 2 °C/min to 85 °C, final time = 20 min; retention time: 8.2 min (minor), 9.0 min (major)].

A second run was performed on the same scale (0.050 g, 90%).

¹H NMR (CDCl₃, 300 MHz): δ 7.34-7.26 (m, 5H), 3.47 (t, J=7.5, 1H), 2.19-2.05 (m, 1H), 1.90-1.75 (m, 1H), 0.92 (t, J=7.2, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 180.7, 138.5, 128.8, 128.3, 127.6, 53.5, 26.5, 12.3.

Eq 6/Reduction: 2-phenylbutan-1-ol [2035-94-1]. LiAlH₄ (1.0 M in Et₂O; 0.32 mL, 0.32 mmol) was added to a solution of the ester (0.100 g, 0.34 mmol; 85% ee) in Et₂O (2 mL) under argon. The mixture was allowed to stir for 30 minutes at room temperature, and then it was quenched by the addition of water (0.012 mL), 15% NaOH (0.012 mL), and then water (0.036 mL). The reaction mixture was passed through a plug of silica gel to remove the solids, and then the product was isolated by flash chromatography (10% Et₂O in hexanes followed by 50% Et₂O in hexanes), which furnished a colorless oil (0.045 g, 89%).

To determine if any racemization had occurred, the alcohol was trifluoroacetylated (trifluoroacetic anhydride) and then analyzed by GC: 85% ee [ChiralDEX G-TA column, flow rate = 0.9 mL/min; starting temperature = 65 °C, ramped at 2 °C/min to 85 °C, final time = 20 min; retention time: 8.2 min (minor), 9.0 min (major)].

A second run was performed on the same scale (0.047 g, 93%).

¹H NMR (CDCl₃, 300 MHz): δ 7.36-7.20 (m, 5H), 3.81-3.69 (m, 2H), 2.74-2.64 (m, 1H), 1.83-1.69 (m, 1H), 1.66-1.51 (m, 1H), 1.36 (s, 1H), 0.84 (t, J=7.2, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 142.4, 128.8, 128.3, 126.9, 67.5, 50.7, 25.2, 12.2.

References

- (1) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532-11533.
- (2) (a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006-10007. (b) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578-1579. (c) Allen, A. D.; Baigrie, L. M.; Gong, L.; Tidwell, T. T. *Can. J. Chem.* **1991**, *69*, 138-145.