Chiral N-Heterocyclic Carbene–Catalyzed Generation of Ester Enolate Equivalents from α,β-Unsaturated Aldehyde for Highly Enantioselective Inverse-Demand Diels-Alder Reactions

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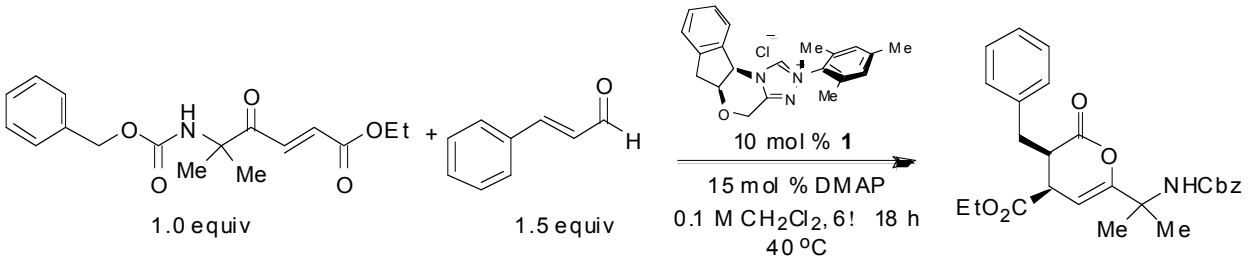
Supporting Information

General Methods. All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry Ar. Dichloromethane (CH_2Cl_2) was distilled over CaH_2; EtOH was distilled over Na. THF and toluene were dried by passage over activated alumina under an Ar atmosphere. Cinnamaldehyde, *trans*-2-hexene-1-al, *N*-methyl morpholine (NMM) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purified by vacuum distillation prior to use. *Trans*-3-(2-furyl)acrolein was purified by sublimation. Other reagents were used without further purification. Thin layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) and were visualized by fluorescence quenching under UV light or by staining with phosphomolybdic acid. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck Kieselgel 60 PF_{254} (Art 7747). Flash column chromatography was performed on E. Merck Silica Gel 60 (230–400 Mesh) using a forced flow of 0.5–1.0 bar. ^{1}H NMR and ^{13}C NMR were measured on Bruker Avance II 500 MHz, 125 MHz respectively. Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported as Hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; ad, approximate doublet; t, triplet; q, quartet; m, multiplet; asterisks (*) indicate peaks arising from the minor diastereomers. Infrared (IR) spectra were recorded on a JASCO FT:IR-4100 spectrophotometer and are reported as wavenumber (cm^{-1}). Optical rotations were measured on a JASCO P-1010 polarimeter operating at the sodium D line with a 100 mm path length cell, and were reported as follows: $[\alpha]_D^T$ (concentration (g:100 ml), solvent).

HPLC Conditions. Column, Diacel Chiralpak AD-H (4.6 × 250mm), Diacel Chiralpak AS-H (4.6 × 250 mm); eluent: hexanes:iPrOH; flow rate 1.0 mL/min; detection: 254 nm.

SFC Conditions. Column, Diacel Chiralpak AS-H (4.6 × 250 mm), Diacel Chiralpak AD-H (4.6 x 250 mm), Diacel Chiralpak OJ-H (4.6 x 250 mm); eluent: CO_2: *i*PrOH; oven temperature: 50 ^oC; pressure 100 bar; flow rate 2.0 mL/min; detection: 254 nm.

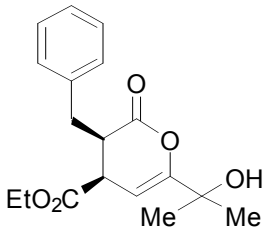
The general procedure for NHC catalyzed, Hetero Diels–Alder reactions of (*E*)-ethyl 5-(benzyloxycarbonylamino)-5-methyl-4-oxohex-2-enoate



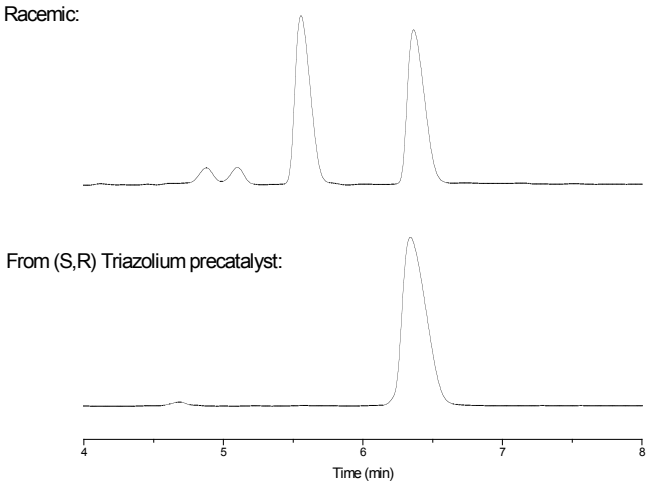
The reaction of (*E*)-ethyl-5-(benzyloxycarbonylamino)-5-methyl-4-oxohex-2-enoate and cinnamaldehyde is representative: Into an oven dried 10.0 mL round bottom flask was added enoate (57.5 mg, 0.18 mmol, 1.0 equiv) and triazolium precatalyst **1**[1] (6.9 mg, 0.02 mmol, 0.10 equiv). After that, 2.0 mL dichloromethane (0.1M) and cinnamaldehye (34 μL, 0.27 mmol, 1.5 equiv) were added via syringe. The solution was stirred for 5 min at room temperature before DMAP (0.5 M solution in CH_2Cl_2) was added (55 μL, 0.03 mmol, 0.15 equiv). The flask was sealed with yellow cap. The resulting solution was heated at 40 ^oC and stirred 8 h before it was diluted with 2.0 mL CH_2Cl_2 and poured into 5.0 ml H_2O. The mixture was extracted with 3 x 3 mL CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (5:1 hexanes: EtOAc) to give the product as a pale yellow oil (79 mg, 98%).

Racemic standards were prepared by the mixture of products from (*R,S*) triazolium and (*S,R*) triazolium precatalysts.

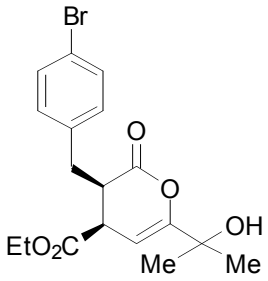
(1) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420



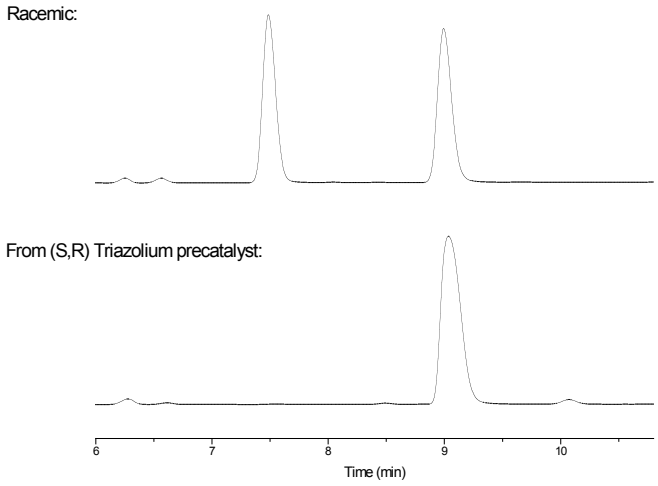
(*3R,4R*)-ethyl-3-benzyl-6-(2-hydroxypropan-2-yl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 2, entry 1,* **3a**). Prepared according to the general procedure from cinnamaldehyde and (*E*)-ethyl 5-hydroxy-5-methyl-4-oxohex-2-enoate[2] using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.1 M) in 93% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.00, $CHCl_3$): -166.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.30 (m, 2H), 7.26–7.23 (m, 1H), 7.16–7.14 (m, 2H), 5.40 (d, 1H, *J* = 7.0 Hz), 4.26–4.14 (m, 2H), 3.48 (dd, 1H, *J* = 14.0, 4.5 Hz), 3.10 (t, 1H, *J* = 7.0 Hz), 2.88–2.84 (m, 1H), 2.69 (dd, 1H, *J* = 14.0, 10.0Hz), 1.42 (s, 3H), 1.41 (s, 3H), 1.28 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 169.1, 160.0, 138.1, 129.1, 128.9, 127.0, 96.1, 70.5, 61.7, 42.8, 40.1, 33.3, 27.6, 27.5, 14.2; IR (thin film) ν 3469, 2980, 2934, 1773, 1732, 1190, 1093, 753, 700 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{18}H_{22}O_5$ 341.1365, found, 341.1362; 99% *ee* as determined by SFC (ADH, gradient 5%–50% *i*-PrOH in CO_2 rate 2%/min) *tr* = 5.6 and 6.3 min.

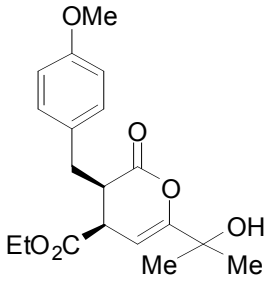


(2) Kaeobamrung, J.; Bode, W. J. *Org. Lett.*, **2009**, *11*, 677–680

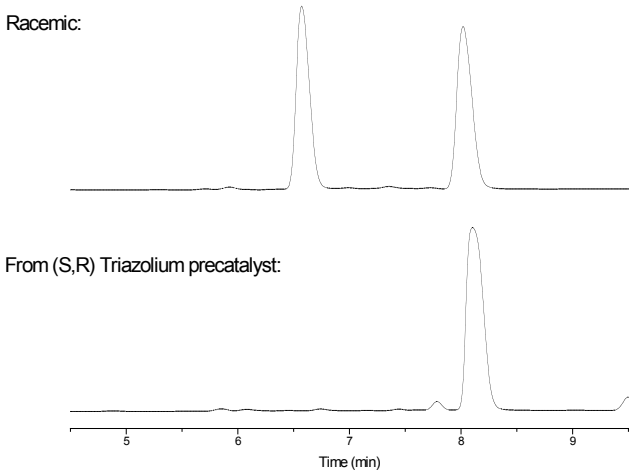


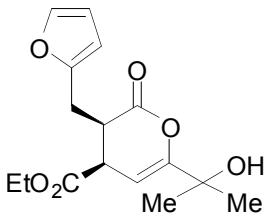
(*3R,4R*)-ethyl-3-(4-bromobenzyl)-6-(2-hydroxypropan-2-yl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 2, entry 2,* **3b**). Prepared according to the general procedure from 4-bromocinnamaldehyde and (*E*)-ethyl 5-hydroxy-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.1 M) in 93% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.02, $CHCl_3$): -182.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J* = 8.5 Hz), 7.04 (d, 2H, *J* = 8.5 Hz), 5.41 (d, 1H, *J* = 7.0 Hz), 4.24–4.14 (m, 2H), 3.41 (dd, 1H, *J* = 14.5, 5.0 Hz), 3.10 (t, 1H, *J* = 7.0 Hz), 2.84–2.80 (m, 1H), 2.66 (dd, 1H, *J* = 14.5, 10.0 Hz), 1.41 (s, 3H), 1.40 (s, 3H), 1.27 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ170.3, 168.6, 160.0, 137.1, 120.9, 96.0, 70.5, 61.7, 42.67, 40.2, 32.8, 27.6, 27.5, 14.2; IR (thin film) ν 3454, 2980, 2936, 1772, 1731, 1190, 1089, 1011, 844 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{18}H_{21}BrO_5$ 419.0470, found, 419.0464; 99% *ee* as determined by SFC (ADH, gradient 5%–50% *i*-PrOH in CO_2, rate 2%/min) *tr* = 7.5 and 9.1 min.



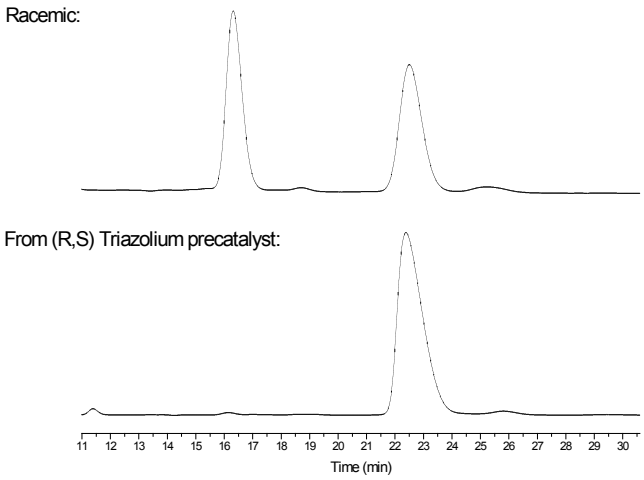


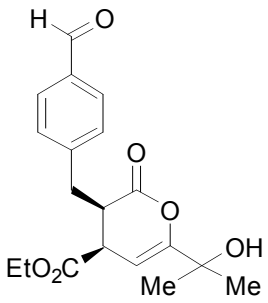
(*3R,4R*)-ethyl-6-(2-hydroxypropan-2-yl)-3-(4-methoxybenzyl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 2, entry 3,* **3c**). Prepared according to the general procedure from 4-methoxycinnamaldehyde and (*E*)-ethyl 5-hydroxy-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.1 M) in 92% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 0.54, $CHCl_3$): -183.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.5 Hz), 5.40 (d, 1H, J = 7.0 Hz), 4.24–4.15 (m, 2H), 3.80 (s, 3H), 3.40 (dd, 1H, J = 14.5, 4.5 Hz), 3.11 (t, 1H, J = 7.0 Hz), 2.83–2.80 (m, 1H), 2.63 (dd, 1H, J = 14.5, 10.0 Hz), 1.41 (s, 3H), 1.40 (s,3H), 1.26 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 169.1, 159.9, 158.6, 130.1, 130.0, 114.3, 96.1, 70.5, 61.7, 55.4, 43.0, 40.0, 32.4, 27.6, 27.5, 14.3; IR (thin film) ν 3470, 2979, 2932, 1773, 1731, 1513, 1248, 1180, 1089, 847 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{19}H_{24}O_6$ 371.1471, found, 371.1459; 99% *ee* as determined by SFC (ADH, gradient 5%–50% *i*-PrOH in CO_2 rate 2%/min) *tr* = 6.6 and 8.1 min.



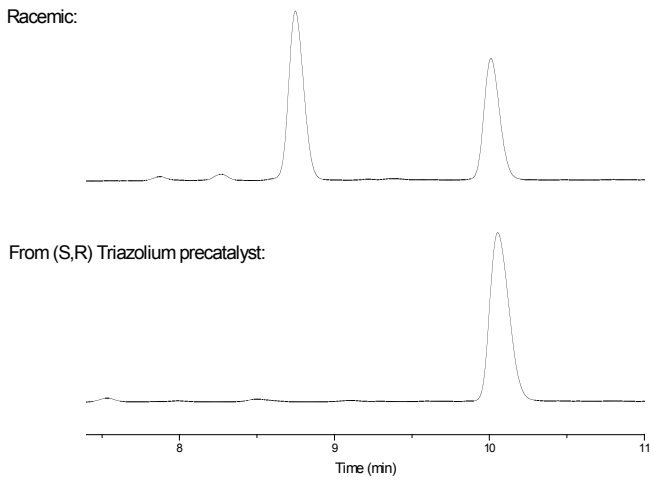


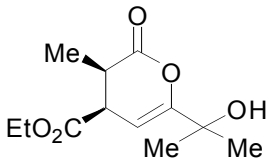
(*3R,4R*)-ethyl-3-(furan-2-ylmethyl)-6-(2-hydroxypropan-2-yl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 2, entry 4,* **3d**). Prepared according to the general procedure from *trans*-3-(2-furyl)acrolein and (*E*)-ethyl 5-hydroxy-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.1 M) in 85% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.26, $CHCl_3$): -225.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.30 (d, 1H, *J* = 1.5 Hz), 6.06 (d, 1H, *J* = 1.5 Hz), 5.44 (dd, 1H, *J* = 7.0 Hz), 4.21–4.12 (m, 2H), 3.44 (dd, 1H, *J* = 15.0, 4.5 Hz), 3.20 (t, 1H, *J* = 6.5 Hz), 3.02–3.00 (m, 1H), 2.85 (dd, 1H, *J* = 15.0, 10.0 Hz), 1.41 (s, 3H), 1.40 (s, 3H), 1.25 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 168.6, 160.0, 151.7, 142.0, 110.6, 107.7, 96.0, 70.5, 61.6, 40.2, 40.1, 27.6, 25.9, 14.2; IR (thin film) ν 3483, 2981, 2927, 1774, 1732, 1189, 1092, 1015, 969 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{16}H_{20}O_6$ 331.1158, found, 331.1151; 99% *ee* as determined by HPLC (ASH, 9:1, hexanes/*i*-PrOH) *tr* = 16.4 and 22.4 min.



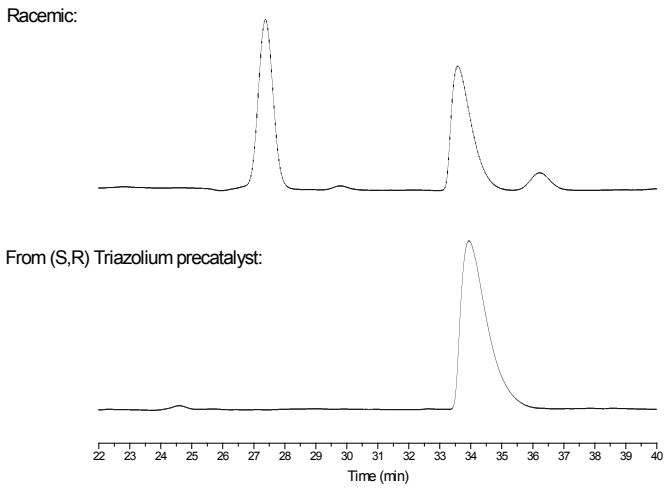


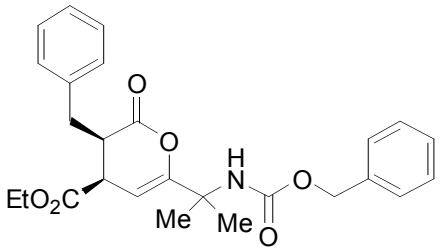
(*3R,4R*)-ethyl-3-(4-formylbenzyl)-6-(2-hydroxypropan-2-yl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 2, entry 5,* **3e**). Prepared according to the general procedure from 4-formylcinnamaldehyde and (*E*)-ethyl 5-hydroxy-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.1 M) in 96% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.75, $CHCl_3$): -137.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.84 (d, 2H, *J* = 8.0 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 5.42 (d, 1H, *J* = 7.0 Hz), 4.25–4.17 (m, 2H), 3.53 (dd, 1H, *J* = 14.0, 5.0 Hz), 3.10 (t, 1H, *J* = 6.5 Hz), 2.93–2.89 (m, 1H), 2.79 (dd, 1H, *J* = 14.0, 9.5 Hz), 1.42 (s, 3H), 1.41 (s, 3H), 1.29 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192, 170.2, 168.4, 160.13, 145.5, 135.4, 130.3, 129.9, 95.9, 70.5, 61.8, 42.5, 40.4, 33.6, 27.6, 27.5, 14.2; IR (thin film) ν 3471, 2980, 2937, 1772, 1730, 1698, 1606, 1190, 1089, 838, 785 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{19}H_{22}O_6$ 369.1314, found, 369.1313; 99% *ee* as determined by SFC (ADH, gradient 5%–50% *i*-PrOH in CO_2 rate 2%/min) *tr* = 8.5 and 10.0 min.



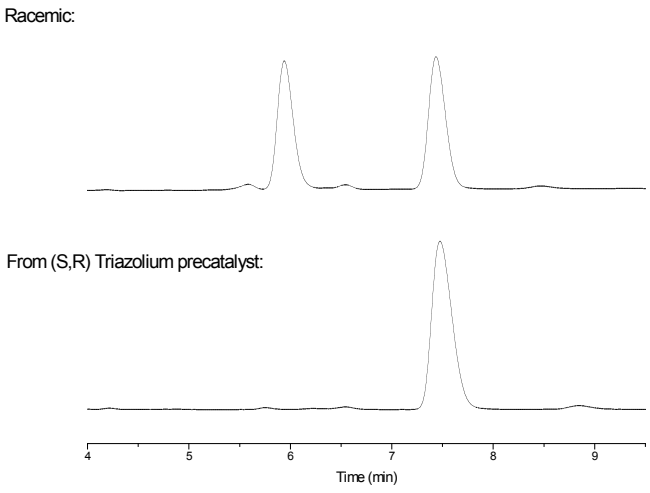


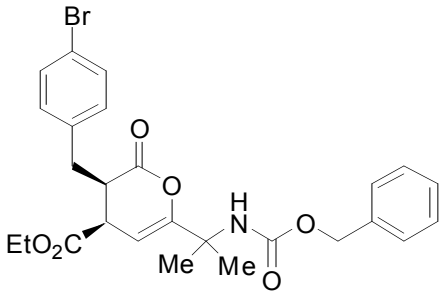
(*3R,4R*)-ethyl-6-(2-hydroxypropan-2-yl)-3-methyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 2, entry 6,* **3f**). Prepared according to the general procedure from acrolein and (*E*)-ethyl 5-hydroxy-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.1 M) in 89% yield as a colorless oil. $[\alpha]_D^{20}$ (c 0.96, $CHCl_3$): -137.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (d, 1H, *J* = 6.5 Hz), 4.20–4.13 (m, 2H), 3.28 (t, 1H, *J* = 6.5 Hz), 2.83–2.78 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.28 (d, 3H, *J* = 6.5 Hz), 1.25 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.0, 159.9, 95.8, 70.5, 61.6, 43.1, 35.6, 27.6, 27.5, 14.2, 12.6; IR (thin film) ν 3480, 2981, 2938, 1774, 1733, 1187, 1099 cm^{-1}; HRMS (ESI) $[M+CH_3CN+Na]^+$ calcd. for $C_{12}H_{18}O_5$ 265.1052, found, 265.1060; 99% *ee* as determined by HPLC (ADH, 20:1, hexanes: *i*-PrOH) *tr* = 26.2 and 33.9 min.



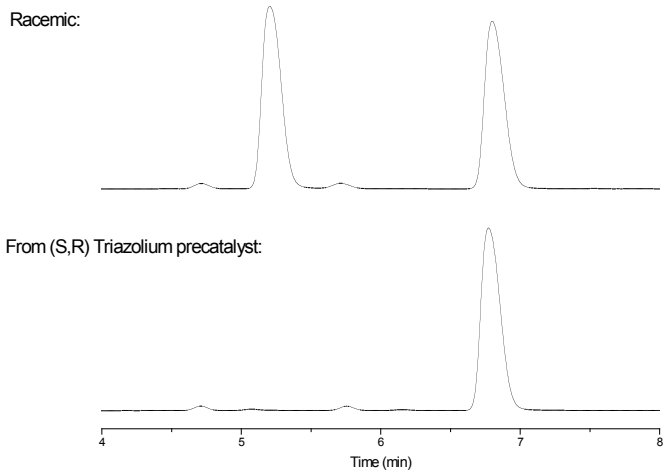


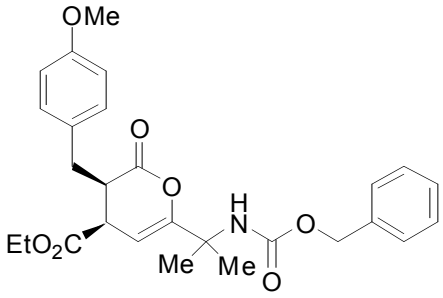
(*3R,4R*)-ethyl-3-benzyl-6-(2-(benzyloxycarbonylamino)propan-2-yl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 3, entry 1,* **6a**). Prepared according to the general procedure from cinnamaldehyde and (*E*)-ethyl-5-(benzyloxycarbonylamino)-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst in 98% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.42, $CHCl_3$): -120.8; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.28 (m, 7H), 7.26–7.22 (m, 1H), 7.12 (d, 2H, *J* = 7.5 Hz), 5.30 (d, 1H, *J* = 7.0 Hz), 5.03 (s, 2H), 4.92 (s, 1H), 4.26–4.40 (m, 2H), 3.44 (dd, 1H, *J* = 14.0, 4.5 Hz), 3.10 (t, 1H, *J* = 6.0 Hz), 2.82 (brs, 1H), 2.66 (dd, 1H, *J* = 14.0, 10.5 Hz), 1.49 (s, 3H), 1.46 (s, 3H), 1.26 (t, 3H, *J* = 7.5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 169.2, 154.5, 138.0, 136.6, 129.2, 128.8, 128.7, 128.2, 128.0, 126.9, 98.1, 66.5, 61.5, 53.6, 42.3, 40.2, 33.2, 26.4, 25.7, 14.2; IR (thin film) ν 3360, 2982, 2942, 1773, 1729, 1519, 1455, 1256, 1097, 740, 699 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{26}H_{29}NO_6$ 474.1893, found, 474.1872; 99% ee as determined by SFC (OJH, gradient 10%–80% *i*-PrOH in CO_2, rate 1%/min) *tr* = 6.1 and 7.5 min



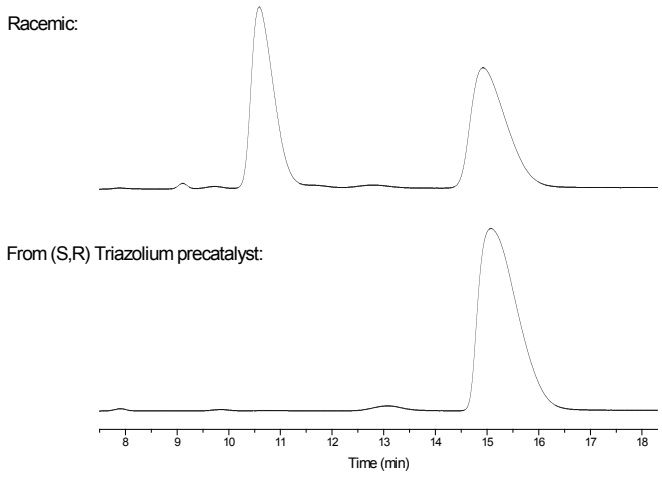


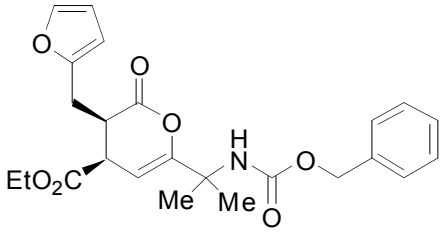
(*3R,4R*)-ethyl-6-(2-(benzyloxycarbonylamino)propan-2-yl)-3-(4-bromobenzyl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 3, entry 2,* **6b**). Prepared according to the general procedure from 4-bromocinnamaldehyde and (*E*)-ethyl-5-(benzyloxycarbonylamino)-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst in 98% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 0.94, $CHCl_3$): -112.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, 2H, *J* = 8.5 Hz), 7.34–7.26 (m, 5H), 7.00 (d, *J* = 8.0 Hz), 5.32 (d, 1H, *J* = 7.0 Hz), 5.02 (s, 2H), 4.53 (s, 1H), 4.21–4.13 (m, 2H), 3.36 (dd, 1H, *J* = 14.5, 5.0 Hz), 3.06 (t, 1H, *J* = 6.0 Hz), 2.78 (br, 1H), 2.63 (dd, 1H, *J* = 14.5, 10.0 Hz), 1.49 (s, 3H), 1.46 (s, 3H), 1.25 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 168.9, 157.0, 154.6, 137.1, 136.6, 131.9, 130.9, 128.7, 127.9, 120.9, 98.0, 66.5, 61.7, 53.6, 42.1, 40.3, 32.7, 26.4, 25.7, 14.2; IR (thin film) ν 3369, 2982, 1773, 1729, 1257, 1099, 1072, 736, 697 cm^{-1};HRMS (ESI) $[M+Na]^+$ calcd. for $C_{26}H_{28}BrNO_6$ 552.0998, found, 552.1010; 99% ee as determined by SFC (OJH, gradient 15%–80% *i*-PrOH in CO_2, rate 2%/min) *tr* = 5.2 and 6.8 min



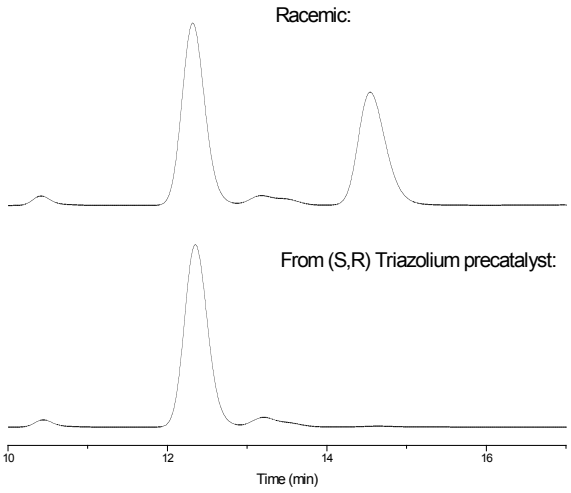


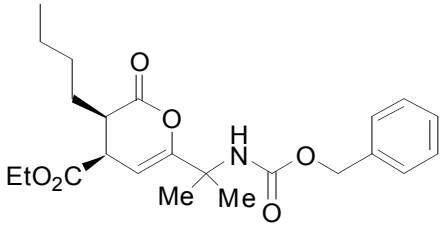
(*3R,4R*)-ethyl-6-(2-(benzyloxycarbonylamino)propan-2-yl)-3-(4-methoxybenzyl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 3, entry 3,* **6c**). Prepared according to the general procedure from 4-methoxycinnamaldehyde and (*E*)-ethyl-5-(benzyloxycarbonylamino)-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst in 79% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.00, $CHCl_3$): -125.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.30 (m, 6H), 7.30 (d, 2H, *J* = 8.0 Hz), 6.60 (d, 2H, *J* = 8.0H), 5.31 (d, 1H, *J* = 7.0 Hz), 5.02 (s, 2H), 4.93 (s, 1H), 4.23–4.05 (m, 2H), 3.79 (s, 3H), 3.36 (dd, 1H, *J* = 14.5, 5.0 Hz), 3.08 (t, 1H, *J* = 6.0 Hz), 2.77 (br, 1H), 2.61 (dd, 1H, *J* = 14.5, 10.5 Hz), 1.46 (s, 3H), 1.45 (s, 3H), 1.26 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 169.3, 158.6, 156.9, 154.6, 136.6, 130.2, 129.9, 128.7, 128.6, 128.2, 128.0, 114.2, 98.1, 66.5, 61.5, 55.4, 53.6, 42.4, 40.2, 32.3, 26.4, 25.7, 14.2; IR (thin film) ν 3361, 2982, 2936, 1774, 1730, 1513, 1249, 1178, 1096, 738, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{27}H_{31}NO_7$ 504.1998, found, 504.2007; 99% ee as determined by SFC (ADH, 10% *i*-PrOH in CO_2) *tr* = 10.7 and 15.1 min



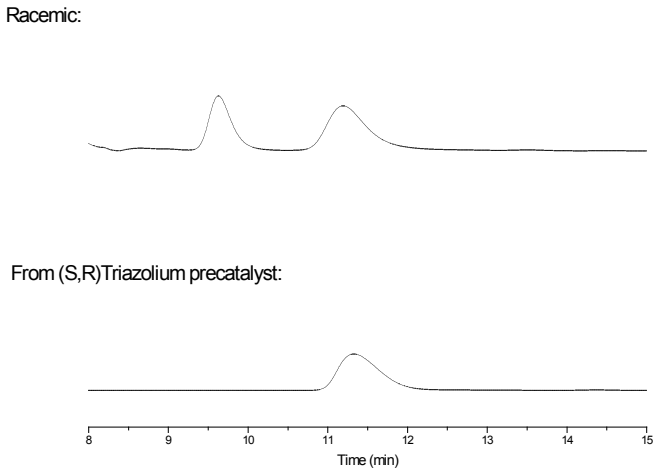


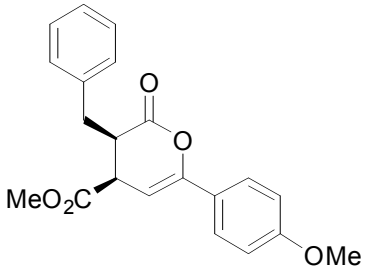
(*3R,4R*)-ethyl-6-(2-(benzyloxycarbonylamino)propan-2-yl)-3-(furan-2-ylmethyl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 3, entry 4,* **6d**). Prepared according to the general procedure from *trans*-3-(2-furyl)acrolein and (*E*)-ethyl-5-(benzyloxycarbonylamino)-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst in 98% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.50, $CHCl_3$): -143.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 6H), 6.29 (dd, 1H, *J* = 3.0, 2.0 Hz), 6.05 (d, 1H, *J* = 3.0 Hz), 5.35 (d, 1H, *J* = 7.0 Hz), 5.02 (s, 2H), 4.90 (s, 1H), 4.21–4.11 (m, 2H), 3.41 (dd, 1H, *J* = 15.5, 4.5 Hz), 3.15 (t, 1H, *J* = 6.0 Hz), 2.94 (br, 1H), 2.82 (dd, *J* = 15.5, 10.5 Hz), 1.50 (s, 3H), 1.46 (s, 3H), 1.24 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 168.8, 157.0, 154.6, 151.7, 141.9, 136.6, 128.7, 128.3, 128.1, 110.5, 107.7, 98.1, 66.6, 61.5, 53.6, 40.4, 39.7, 26.5, 25.8, 25.6, 14.2; IR (thin film) ν 3355, 2982, 1773, 1729, 1507, 1258, 1097, 743, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{24}H_{27}NO_7$ 464.1685, found, 464.1693; 99% ee as determined by HPLC (ASH, 9:1, hexanes/*i*-PrOH) *tr* = 12.4 and 14.6 min



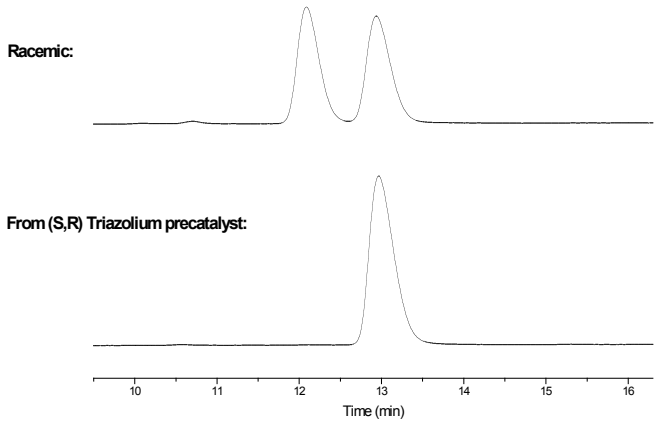


(*3R,4R*)-ethyl-6-(2-(benzyloxycarbonylamino)propan-2-yl)-3-butyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 3, entry 5,* **6e**). Prepared according to the general procedure from *trans*-2-hexenal and (*E*)-ethyl-5-(benzyloxycarbonylamino)-5-methyl-4-oxohex-2-enoate using 10 mol % **1** as the catalyst in 80% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.98, $CHCl_3$): -100.5; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.16 (m, 5H), 5.37 (d, J = 6.5 Hz), 5.17 (s, 2H), 4.92 (s, 1H), 4.20–4.10 (m, 2H), 3.33 (br, 1H), 2.56 (br, 1H), 1.96 (br, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.38 (br, 6H), 1.22 (t, 3H, J = 7.0 Hz), 0.90 (br, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 169.7, 156.7, 136.6, 128.7, 128.4, 128.3, 128.2, 128.0, 97.8, 66.5, 61.5, 53.6, 41.4, 40.3, 29.3, 26.8, 26.4, 25.7, 22.7, 14.1, 14.0; IR (thin film) ν 3362, 2958, 2872, 1772, 1731, 1259, 1096, 738, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{23}H_{31}NO_6$ 440.2049, found, 440.2018; 99% ee as determined by HPLC (ASH, 9:1, hexanes/*i*-PrOH) *tr* = 9.6 and 11.3 min

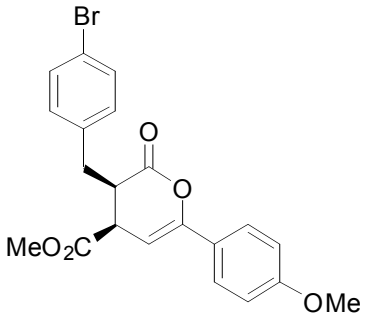




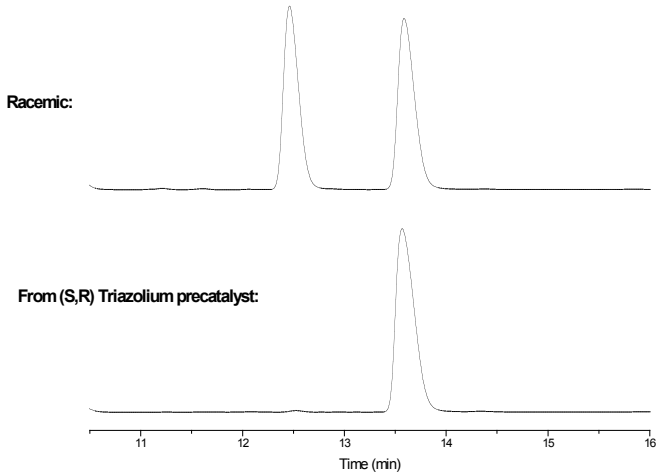
(*3R,4R*)-methyl-3-benzyl-6-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 4, entry 1,* **8a**). Prepared according to the general procedure from cinnamaldehyde and (*E*)-methyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate[3] using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in toluene (0.1 M) in 62% yield as a colorless oil. $[\alpha]_D^{20}$ (c 0.80, $CHCl_3$): -55.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 2H, *J* = 8.5 Hz), 7.34–7.31 (m, 2H), 7.28–7.25 (m, 1H), 7.17 (d, 2H, *J* = 7.5 Hz), 6.88 (d, 2H, J = 8.5 Hz), 5.66 (d, 1H, *J* = 7.0 Hz), 3.82 (s, 3H), 3.75 (s, 3H), 3.54 (dd, 1H, *J* = 4.5, 14.0 Hz), 3.26 (t, 1H, *J* = 6.0 Hz), 3.01–2.97 (m, 1H), 2.75 (dd, 1H, *J* = 10.5, 14.5Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 168.9, 160.8, 152.4, 138.2, 129.1, 128.9, 126.9, 126.4, 124.4, 114.0, 96.1, 55.5, 52.6, 42.9, 40.6, 33.4; IR (thin film) ν 2953, 2838, 1773, 1733, 1608, 1513, 1254, 1176, 1068, 837, 755, 700 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{21}H_{20}O_5$ 375.1208, found, 375.1209; 99% *ee* as determined by SFC (ADH, 10% *i*-PrOH in CO_2) *tr* = 12.1 and 13.0 min.

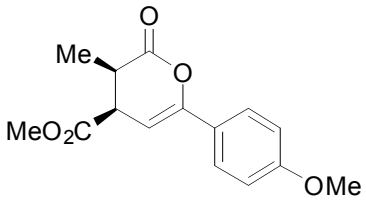


(3) Runcie, K. A.; Taylor, R. J. *Chem. Comm.* **2002**, 974–975.

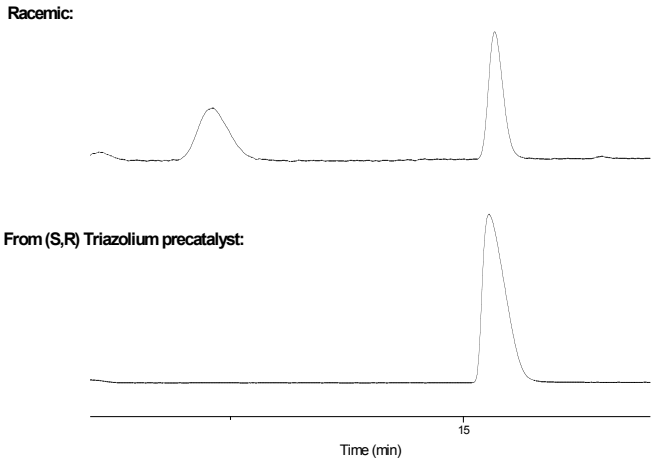


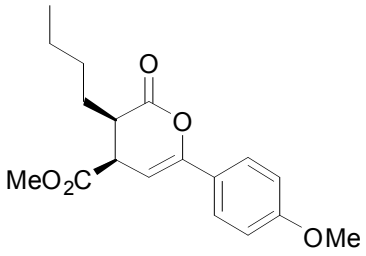
(*3R,4R*)-methyl-3-(4-bromobenzyl)-6-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 4, entry 2,* **8b**). Prepared according to the general procedure from 4-bromocinnamaldehyde and (*E*)-methyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in toluene (0.1 M) in 70% yield as pale yellow solid. $[\alpha]_D^{20}$ (c 0.77, $CHCl_3$): -125.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 2H, *J* = 10.0 Hz), 7.44 (d, 2H, *J* = 8.0 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 6.88 (d, 2H, *J* = 10.0 Hz), 5.68 (d, 1H, *J* = 7.0 Hz), 3.82 (s, 3H), 3.74 (s, 3H), 3.47 (dd, 1H, *J* = 14.5, 5.5 Hz), 3.26 (t, 1H, *J* = 7.0 Hz), 2.98–2.93 (m, 1H), 2.72 (dd, 1H, *J* = 14.5, 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 168.7, 152.5, 137.2, 132.0, 130.9, 126.5, 124.3, 120.9, 114.1, 95.9, 55.5, 52.7, 42.7, 40.7, 32.9; IR (thin film) ν 2956, 2357, 1773, 1733, 1512, 1254, 1175, 1134, 835, 668 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{21}H_{19}BrO_5$, 431.0494 found, 431.0481; 99% *ee* as determined by SFC (ADH, gradient 5%–50% *i*-PrOH in CO_2, rate 2%/min) *tr* = 12.5 and 13.6 min.



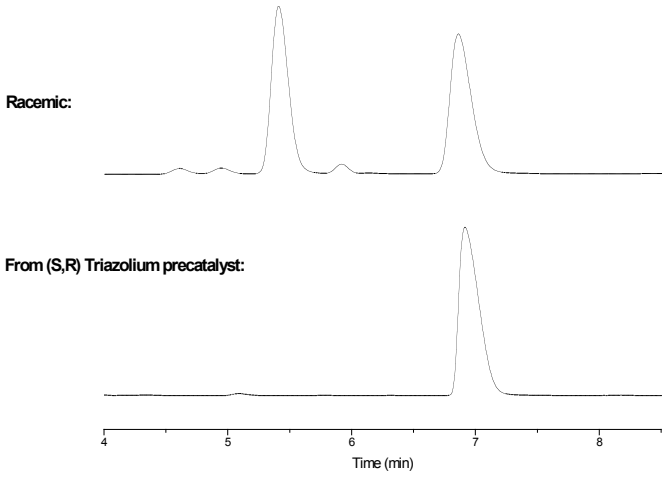


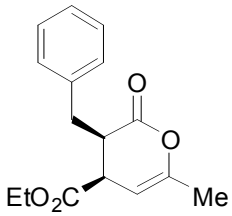
(*3R,4R*)-methyl-6-(4-methoxyphenyl)-3-methyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 4, entry 3,* **8c**). Prepared according to the general procedure from acrolein and (*E*)-methyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in toluene (0.1 M) in 54% yield as a white solid. $[\alpha]_D^{20}$ (c 1.25, $CHCl_3$): -121.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, 2H, *J* = 7.0 Hz), 6.89 (d, 2H, *J* = 7.0 Hz), 5.73 (d, 1H, *J* = 6.5 Hz), 3.83 (s, 3H), 3.73 (s, 3H), 3.45 (t, 1H, *J* = 6.5 Hz), 2.95–2.89 (m, 1H), 1.33 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 170.0, 160.8, 152.3, 126.5, 124.5, 114.0, 95.9, 55.5, 52.6, 43.6, 35.7, 12.7; IR (thin film) ν 2963, 2932, 1778, 1720, 1202, 1177, 1070, 1029, 836, 757 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{15}H_{16}O_5$ 277.1076, found, 277.1085; 99% *ee* as determined by SFC (ADH, gradient 5% (10 min.)–50% *i*-PrOH in CO_2, rate 2%/min) *tr* = 12.1 and 15.3 min.



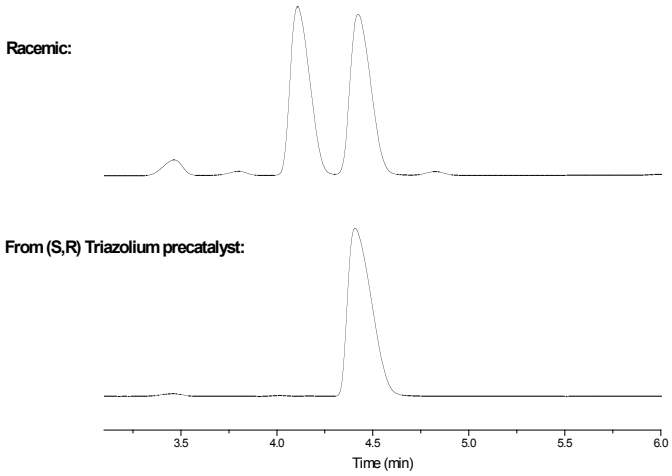


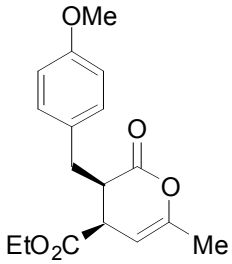
(*3R,4R*)-methyl-3-butyl-6-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 4, entry 4,* **8d**). Prepared according to the general procedure from *trans*-2-hexenal and (*E*)-methyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in toluene (0.1 M) in 60% yield as a white solid. $[\alpha]_D^{20}$ (c 0.97, $CHCl_3$): -91.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, 2H, J = 7.0, 2.5 Hz), 6.89 (dd, 2H, J = 7.0, 2.5 Hz), 5.74 (d, 1H, J = 6.5 Hz), 3.83 (s, 3H), 3.72 (s, 3H), 3.53 (t, 1H, J = 6.5 Hz), 2.74–2.71 (m, 1H), 2.06–2.04 (m, 1H), 1.45–1.35 (m, 5H), 0.91 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 169.5, 160.8, 152.2, 126.4, 124.5, 114.0, 95.9, 55.5, 52.6, 41.9, 40.8, 29.5, 27.0, 22.6, 14.0; IR (thin film) ν 2955, 2932, 1773, 1735, 1513, 1255, 1176, 1075, 837 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd. for $C_{18}H_{22}O_5$ 319.1545, found, 319.1537; 99% *ee* as determined by SFC (ADH, gradient 5%–50% *i*-PrOH in CO_2, rate 2%/min) *tr* = 5.8 and 6.9 min.



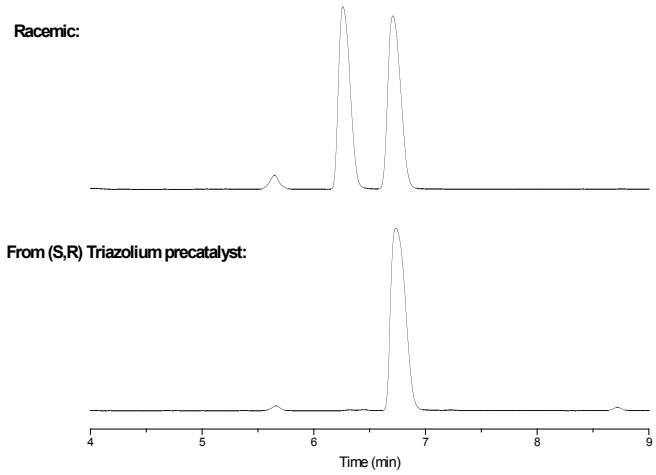


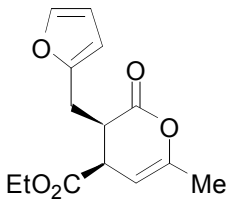
(*3R,4R*)-ethyl-3-benzyl-6-methyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 5, entry 1,* **10a**). Prepared according to the general procedure from cinnamaldehyde and (*E*)-ethyl 4-oxopent-2-enoate[3] using 10 mol % **1** as the catalyst, 15 mol % *N,N*-diisopropylethylamine as a base in CH_2Cl_2 (0.3 M) in 94% yield as a colorless oil. $[\alpha]_D^{20}$ (c 0.30, $CHCl_3$): -274.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.29 (m, 2H), 7.26–7.24 (m, 1H), 7.15–7.14 (m, 2H), 5.02 (d, 1H, *J* = 7.0 Hz), 4.20 (q, 2H, *J* = 7.5 Hz), 3.49 (dd, 1H, *J* = 14.5, 5.0 Hz), 3.00 (t, 1H, *J* = 7.0 Hz), 2.88–2.84 (m, 1H), 2.68 (dd, 1H, *J* = 14.5, 10.0 Hz), 1.90 (s, 3H), 1.27 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 169.3, 152.5, 138.3, 129.1, 128.9, 126.9, 98.7, 61.5, 42.8, 40.4, 33.3, 18.9, 14.3; IR (thin film) ν 2982, 1773, 1730, 1184, 1162, 754, 700 cm^{-1}; HRMS (ESI) $[M+CH_3CN+Na]^+$ calcd. for $C_{16}H_{18}O_4$ 338.1368, found, 338.1175; 99% *ee* as determined by SFC (ADH, gradient 5%–50% *i*-PrOH in CO_2, rate 2%/min) *tr* = 4.0 and 4.4 min.



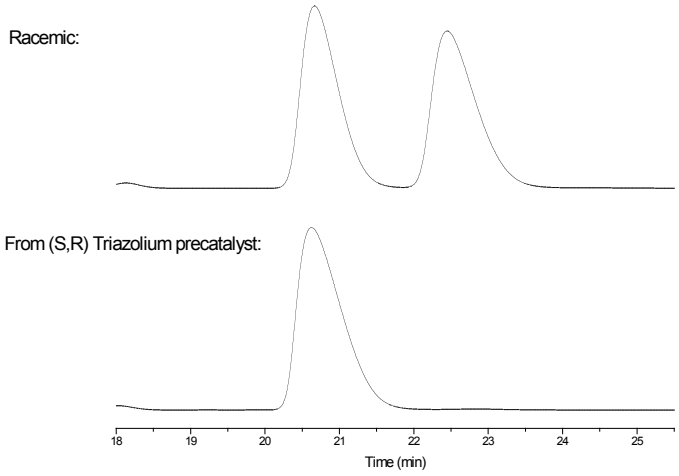


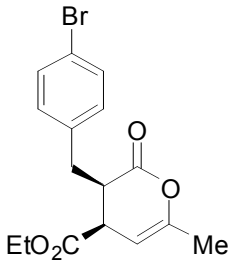
(*3R,4R*)-ethyl-3-(4-methoxybenzyl)-6-methyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 5, entry 2,* **10b**). Prepared according to the general procedure from 4-methoxycinnamaldehyde and (*E*)-ethyl 4-oxopent-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N,N*-diisopropylethylamine as a base in CH_2Cl_2 (0.3 M) in 70% yield as a colorless oil. $[\alpha]_D^{20}$ (c 1.56, $CHCl_3$): -247.0; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, 2H, *J* = 7.0 Hz), 6.83 (d, 2H, *J* = 7.0 Hz), 5.02 (d, 1H, *J* = 7.0 Hz), 4.19 (q, 2H, *J* = 7.5 Hz), 3.79 (s, 3H), 3.42 (dd, 1H, *J* = 14.5, 4.5 Hz), 3.00 (t, 1H, *J* = 7.0 Hz), 2.83–2.78 (m, 1H), 2.62 (dd, 1H, *J* = 14.5, 10.0 Hz), 1.90 (s, 3H), 1.28 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 169.4, 158.6, 152.4, 130.2, 130.1, 114.3, 98.7, 61.5, 55.4, 43.0, 40.4, 32.4, 18.9, 14.3; IR (thin film) ν 2957, 1773, 1730, 1513, 1247, 1181, 1160, 1036, 844 cm^{-1}; HRMS (ESI) $[M+CH_3CN+Na]^+$ calcd. for $C_{17}H_{20}O_5$ 327.1208, found, 327.1196; 99% *ee* as determined by SFC (ADH, gradient 0%–50% *i*-PrOH in CO_2, rate 3%/min) *tr* = 6.4 and 6.7 min.



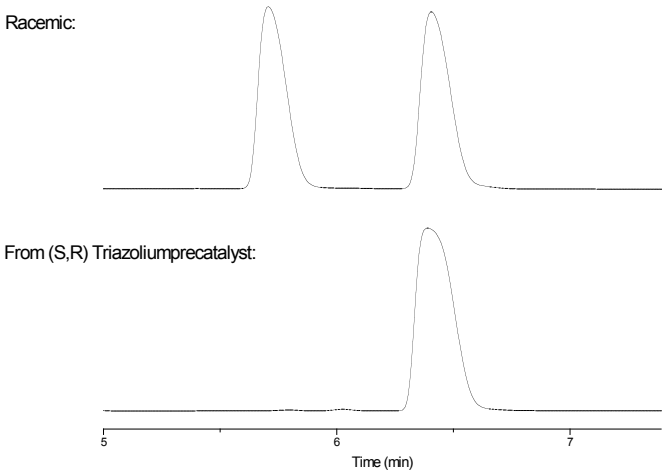


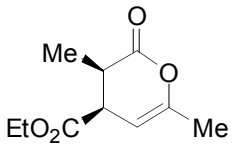
(*3R,4R*)-ethyl-3-(furan-2-ylmethyl)-6-methyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 5, entry 3,* **10c**). Prepared according to the general procedure from *trans*-3-(2-furyl)acrolein and (*E*)-ethyl 4-oxopent-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N,N*-diisopropylethylamine as a base in CH_2Cl_2 (0.3 M) in 54% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 0.70, $CHCl_3$): -321.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, 1H, *J* = 1.5 Hz), 6.29 (d, 1H, *J* = 3.0 Hz), 6.57 (d, 1H, *J* = 3.0 Hz), 5.06 (d, 1H, *J* = 7.0 Hz), 4.20–4.15 (m, 1H), 3.44 (dd, 2H, *J* = 15.5, 4.5 Hz), 3.08–3.05 (m, 1H), 2.85 (dd, 1H, *J* = 15.5, 10.5 Hz), 1.90 (s, 3H), 1.25 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 168.9, 152.4, 152.0, 141.9, 110.5, 107.6, 98.6, 61.5, 40.6, 40.0, 25.9, 18.9, 14.2; IR (thin film) ν 2982, 1773, 1730, 1186, 1158, 1058, 1012, 738 cm^{-1}; HRMS (ESI) [M+CH_3CN+Na]$^+$ calcd. for $C_{14}H_{16}O_5$ 328.1161, found, 328.1142; 99% *ee* as determined by HPLC (ASH, 40:1, hexanes/*i*-PrOH) *tr* = 20.6 and 22.9 min



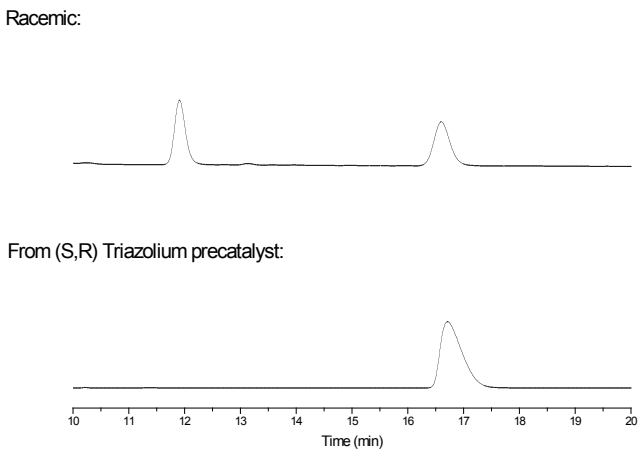


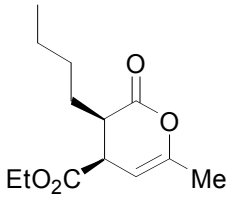
(*3R,4R*)-ethyl-3-(4-bromobenzyl)-6-methyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 5, entry 4,* **10d**). Prepared according to the general procedure from 4-bromocinnamaldehyde and (*E*)-ethyl 4-oxopent-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N,N*-diisopropylethylamine as a base in CH_2Cl_2 (0.3 M) in 88% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.30, $CHCl_3$): -212.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, 2H, *J* = 8.5 Hz), 7.03 (d, 2H, *J* = 8.5 Hz), 5.03 (d, 1H, *J* = 6.5 Hz), 4.19 (q, 2H, *J* = 7.5 Hz), 3.42 (dd, 1H, *J* = 10.0, 5.0 Hz), 2.99 (t, 1H, *J* = 6.5 Hz), 2.84–2.80 (m, 1H), 2.64 (dd, 1H, 14.0, 10.0 Hz), 1.90 (s, 3H), 1.28 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.0, 152.6, 137.4, 132.0, 130.9, 120.8, 98.6, 61.6, 42.6, 40.6, 32.9, 18.9, 14.2; IR (thin film) ν 2981, 1774, 1730, 1489, 1185, 1160, 1058, 1037, 843, 803 cm^{-1}; HRMS (ESI) $[M+CH_3CN+Na]^+$ calcd. for $C_{16}H_{17}BrO_4$ 416.0473, found, 416.0480; 99% *ee* as determined by SFC (ADH, gradient 5%–50% *i*-PrOH in CO_2 rate 2%/min) *tr* = 5.7 and 6.4 min.





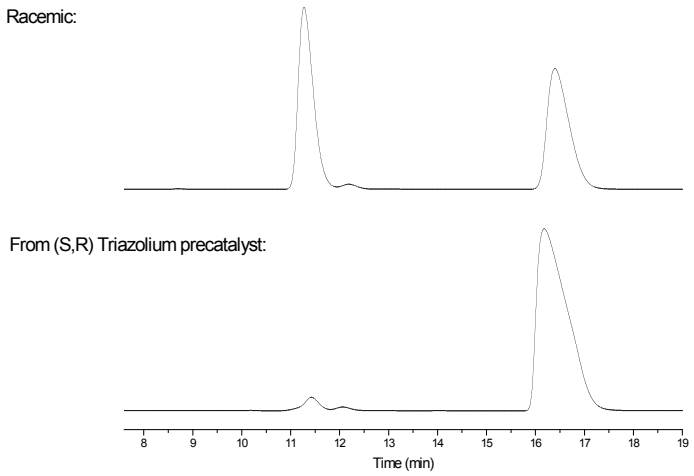
(*3R,4R*)-ethyl-3,6-dimethyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 5, entry 5,* **10e**). Prepared according to the general procedure from acrolein and (*E*)-ethyl 4-oxopent-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N,N*-diisopropylethylamine as a base in CH_2Cl_2 (0.3 M) in 63% yield as a colorless oil. $[\alpha]_D^{20}$ (c 1.24, $CHCl_3$): -308.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (d, 1H, *J* = 6.0 Hz), 4.17–4.10 (m, 2H), 3.17 (t, 1H, *J* = 6.0 Hz), 2.78–2.75 (m, 1H), 1.90 (s, 3H), 1.26–1.21 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.3, 152.4, 98.4, 61.5, 43.5, 35.6, 18.9, 14.2, 12.6; IR (thin film) ν 2983, 2899, 1774, 1720, 1369, 1189, 1165 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{10}H_{14}O_4$ 221.0790, found, 221.0792; 99% *ee* as determined by HPLC (ASH, 40:1, hexanes/*i*-PrOH) *tr* = 11.6 and 16.7 min.

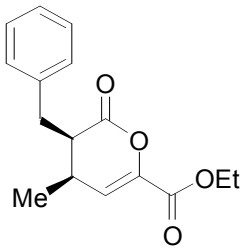




(*3R,4R*)-ethyl-3-butyl-6-methyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (*Table 5, entry 6,* **10f**). Prepared according to the general procedure from *trans*-2-hexenal and (*E*)-ethyl 4-oxopent-2-enoate using 10 mol % **1** as the catalyst, 15 mol % *N,N*-diisopropylethylamine as a base in CH_2Cl_2 (0.3 M) in 95% yield as a colorless oil. $[\alpha]_D^{20}$ (c 0.45, $CHCl_3$): -268.4; ^{1}H NMR (500

MHz, $CDCl_3$) δ 5.08 (d, 1H, *J* = 6.5 Hz), 4.17–4.13 (m, 2H), 3.27 (t, 1H, *J* = 6.5 Hz), 2.61–2.57 (m, 1H), 2.01–1.91 (m, 1H), 1.60 (s, 3H), 1.38–1.30 (m, 5H), 1.24 (t, 3H, *J* = 7.0 Hz), 0.90 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 169.8, 98.4, 61.4, 41.7, 40.6, 29.5, 26.9, 22.6, 18.9, 14.2, 14.0; IR (thin film) ν 2957, 2927, 1774, 1733, 1179, 1143 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{13}H_{20}O_4$ 263.1259, found, 263.1248; 94% *ee* as determined by HPLC (ASH, 50:1, hexanes/*i*-PrOH) *tr* = 11.0 and 15.7 min.

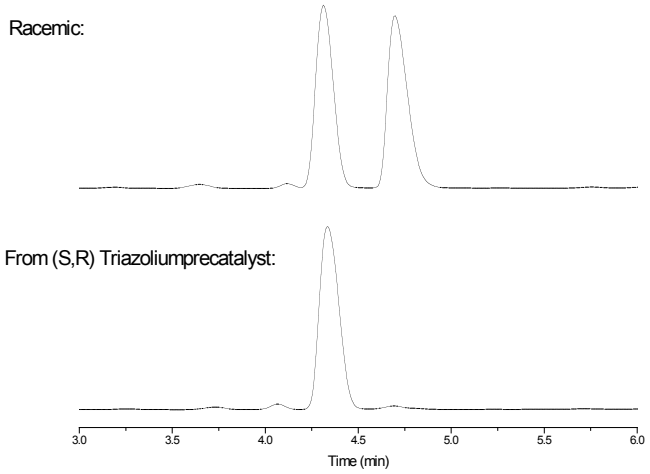


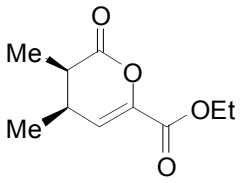


(*3R,4R*)-ethyl-3-benzyl-4-methyl-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate (*Table 6, entry 1,* **14a**). Prepared according to the general procedure from cinnamaldehyde and (*E*)-ethyl-2-oxopent-3-enoate[4] using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.2 M) in 85% yield as a pale yellow oil. $[\alpha]_D^{20}$ (c 1.37, $CHCl_3$): -65.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 2H), 7.26–7.20 (m, 3H), 6.55 (d, 1H, *J* = 6.5 Hz), 4.29 (q, 2H, *J* = 7.0 Hz), 3.40 (dd, 1H, *J* = 5.0, 14.5 Hz), 2.98–2.94 (m, 1H), 2.73 (dd, 1H, *J* = 10.0, 14.5 Hz), 2.51–2.44 (m, 1H), 1.33 (t, 3H, *J* = 7.0 Hz), 1.6 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz,

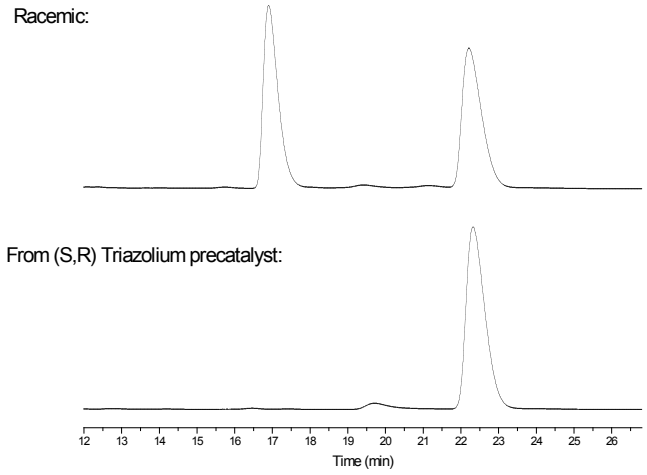
(4) Meijer, L. H. P.; Pandit, U. K. *Tetrahedron,* **1985**, *41*, 467–472.

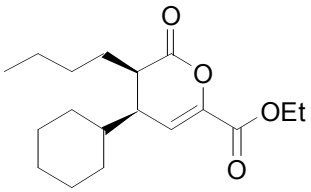
$CDCl_3$) δ 169.2, 160.6, 142.1, 138.3, 129.0, 128.8, 126.9, 121.1, 61.9, 44.8, 32.0, 28.3, 14.3, 13.4; IR (thin film) ν 2980, 2927, 1773, 1734, 1266, 1109, 701, 668 cm^{-1}; HRMS (ESI) $[M+CH_3CN+Na]^+$ calcd. for $C_{16}H_{18}O_4$ 338.1368, found, 338.1175; 98% ee as determined by SFC (ADH, gradient 5%–50% *i*-PrOH in CO_2, rate 2%/min) *tr* = 4.3 and 4.6 min.



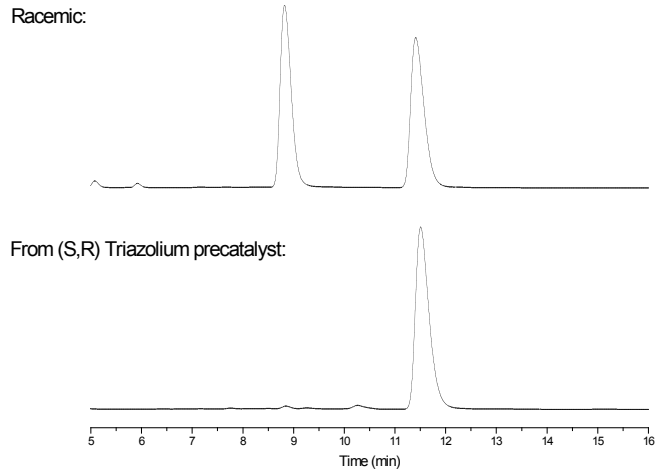


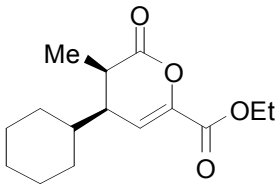
(*3R,4R*)-ethyl-3,4-dimethyl-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate (*Table 6, entry 2,* **14b**). Prepared according to the general procedure from acrolein and (*E*)-ethyl-2-oxopent-3-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.2 M) in 51% yield as a colorless oil. $[\alpha]_D^{20}$ (c 0.77, $CHCl_3$): -209.6; ^1H NMR (500 MHz, $CDCl_3$) δ 6.56 (d, 1H, *J* = 6.0 Hz), 4.29 (dq, 2H, *J* = 1.5, 7.5 Hz), 2.82–2.77 (m, 1H), 2.65–2.61 (m, 1H), 1.33 (dt, 3H, *J* = 1.5, 7.5 Hz), 1.25 (d, 3H, *J* = 7.0 Hz), 1.02 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 160.7, 142.0, 120.8, 61.9, 37.8, 31.2, 14.3, 13.6, 11.7; IR (thin film) ν 2981, 2937, 1775, 1736, 1311, 1251, 1022 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{10}H_{14}O_4$ 221.0790, found, 221.0788; 99% ee as determined by HPLC (ASH, 40:1, hexanes/*i*-PrOH) *tr* = 16.7 and 20.1 min.



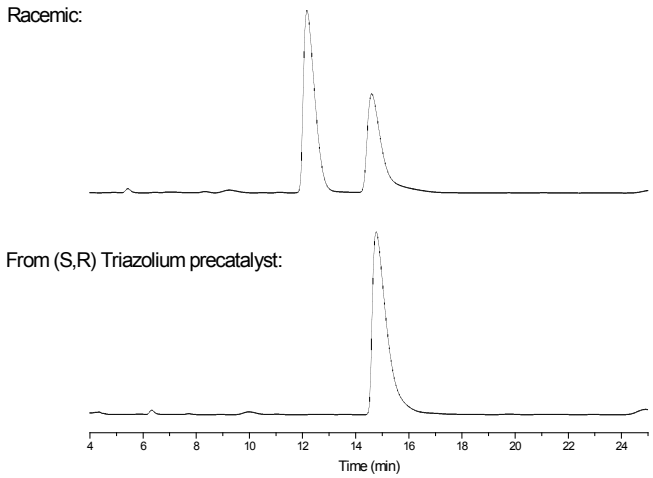


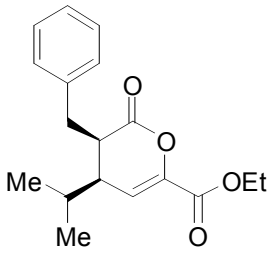
(*3R,4R*)-ethyl-3-butyl-4-cyclohexyl-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate (*Table 6, entry 3,* **14c**). Prepared according to the general procedure from *trans*-2-hexenal and (*E*)-ethyl-4-cyclohexyl-2-oxobut-3-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.2 M) in 79% yield as a colorless oil. $[\alpha]_D^{20}$ (c 1.70, $CHCl_3$): -126.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (d, 1H, *J* = 6.0 Hz), 4.30 (dq, 2H, *J* = 1.0, 7.0 Hz), 2.58–2.52 (m, 2H), 1.90–1.88 (m, 1H), 1.76–1.62 (m, 4H), 1.59–1.54 (m, 3H), 1.51–1.45 (m, 1H), 1.36–1.28 (m, 6H), 1.23–1.06 (m, 5H), 0.92 (t, 3H, *J* = 7.0 Hz), 0.88–0.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 160.7, 142.6, 117.4, 61.9, 40.9, 40.3, 37.5, 31.4, 29.7, 27.6, 26.6, 26.1, 26.0, 25.4, 22.7, 14.3, 14.0; IR (thin film) ν 2929, 2854, 1772, 1737, 1267, 1251, 1103, 766 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{18}H_{28}O_4$ 331.1885, found, 331.1891; 98% ee as determined by HPLC (ADH, 40:1, hexanes/*i*-PrOH) *tr* = 8.8 and 11.5 min.



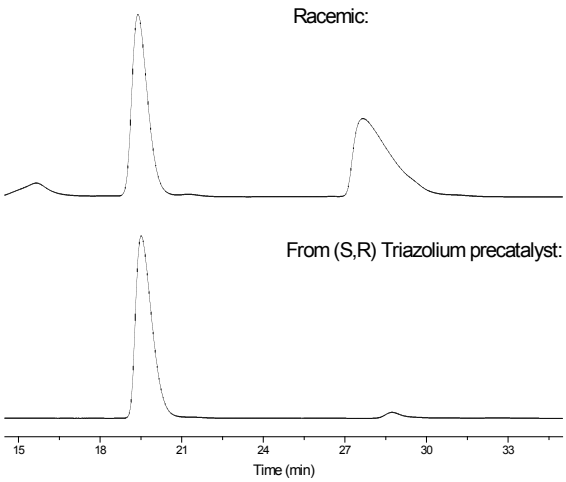


(*3R,4R*)-ethyl-4-cyclohexyl-3-methyl-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate (*Table 6, entry 4,* **14d**). Prepared according to the general procedure from acrolein and (*E*)-ethyl-4-cyclohexyl-2-oxobut-3-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.2 M) in 49% yield as a white solid. $[\alpha]_D^{20}$ (c 0.27, $CHCl_3$): -149.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (d, 1H, J = 6.0 Hz), 4.34–4.28 (m, 2H), 2.81–2.76 (m, 1H), 2.52–2.48 (m, 1H), 1.77–1.69 (m, 2H), 1.66–1.55 (m, 4H), 1.35 (t, 3H, J = 7.5 Hz), 1.27 (d, 3H, J = 7.0 Hz), 1.23–1.04 (m, 4H), 0.91–0.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 160.7, 142.7, 117.2, 62.0, 41.8, 37.5, 35.8, 31.2, 27.5, 26.6, 26.1, 26.0, 14.3, 11.5; IR (thin film) ν ; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{15}H_{22}O_4$ 289.1416, found, 289.1408; 99% ee as determined by HPLC (ASH, 40:1, hexanes/*i*-PrOH) *tr* = 12.3 and 14.4 min.

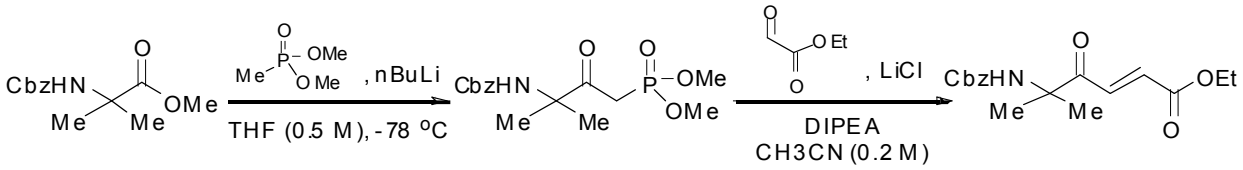




(*3R,4R*)-ethyl-3-benzyl-4-isopropyl-2-oxo-3,4-dihydro-2H-pyran-6-carboxylate (*Table 6, entry 5,* **14e**). Prepared according to the general procedure from cinnamaldehyde and (*E*)-ethyl-5-methyl-2-oxohex-3-enoate using 10 mol % **1** as the catalyst, 15 mol % *N*-methylmorpholine as a base in CH_2Cl_2 (0.2 M) in 91% yield as a colorless solid. $[\alpha]_D^{20}$ (c 0.80, $CHCl_3$): -95.4; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.32 (m, 2H), 7.28–7.26 (m, 3H), 6.46 (d, 1H, *J* = 6.5 Hz), 4.35–4.26 (m, 2H), 3.39 (dd, 1H, *J* = 6.0, 14.5 Hz), 3.00–2.90 (m, 1H), 2.78 (dd, 1H, *J* = 9.5, 14.5 Hz), 2.47–2.44 (m, 1H), 2.16–2.10 (m, 1H), 1.34 (t, 3H, *J* = 7.0 Hz), 0.92 (d, 3H, *J* = 6.5 Hz), 0.85 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 160.6, 143.2, 138.5, 128.8, 128.7, 126.8, 116.4, 62.0, 43.4, 39.7, 31.7, 27.5, 21.3, 16.7, 14.3; IR (thin film) ν 2964, 2873, 1774, 1735, 1313, 1271, 1096, 1024 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{18}H_{22}O_4$ 325.1416, found, 325.1432; 96% ee as determined by HPLC (ASH, 40:1, hexanes/*i*-PrOH) *tr* = 19.5 and 28.7 min.



Starting Material Preparation



Dimethyl methylphosphonate (4.3 mL, 39.7 mmol) was dissolved in THF (80.0 mL), and the solution mixture cooled to –78 °C, and *n*-BuLi (2.5 M solution in hexane, 16.0 mL, 40.0 mmol) added dropwise. After the addition, the mixture was allowed to stir at –78 °C for 45 min before adding the solution of methyl 2-(benzyloxycarbonylamino)-2-methylpropanoate (0.5 M in THF, 2.51 g, 10.0 mmol) at –78 °C. The mixture was stirred at –78 °C and the reaction was monitored by TLC (100% EtOAc). After 2–3 h, the reaction was quenched with sat. NH_4Cl and extracted with EtOAc. The organic extracts were combined, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (100% EtOAc) to give benzyl 4-(dimethoxyphosphoryl)-2-methyl-3-oxobutan-2-ylcarbamate as a colorless oil in 90% yield. To flame dried round bottom flask containing LiCl (183.0 mg, 4.32 mmol), a solution of benzyl 4-(dimethoxyphosphoryl)-2-methyl-3-oxobutan-2-ylcarbamate (0.2 M in CH_3CN, 1.2 g, 3.6 mmol) and ethyl glyoxalate (50% in toluene, 1.8 mL, 10.73 mmol) were added at room temperature. After addition, *N,N*-diisopropylethylamine (0.7 mL, 3.9 mmol) was added. The mixture was allowed to stirred at room temperature for 2 h before being quenched with sat. NH_4Cl and extracted with EtOAc. The organic extracts were combined, dried over Na_2SO_4 and

concentrated. The crude product was purified by flash chromatography (5:1 EtOAc:hexanes) to give (*E*)-ethyl-5-(benzyloxycarbonylamino)-5-methyl-4-oxohex-2-enoate in 65% yield as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, 1H, *J* = 15.5 Hz), 7.34–7.28 (m, 5H), 6.89 (d, 1H, *J* = 15.5 Hz), 5.45 (s, 1H), 5.10 (s, 2H), 4.26 (q, 2H, *J* = 7.0 Hz), 1.48 (s, 6H), 1.32 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ;IR (thin film) ν 3351, 2984, 2937, 1707, 1518, 1301, 1257, 1179, 1067, 741, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd. for $C_{17}H_{21}NO_5$ 342.1317, found, 342.1323.

Computational Enolate Structure Optimization

Calculations were performed on SGI workstations using an R-4000 or R-10,000 processor. Monte Carlo conformational searches were performed in MacroModel V. 6.0[5] using the Merck Molecular Force Field (MMFF) and 6 conformational isomers were identified. These conformational isomers were geometry optimized with a HF 6-32G* basis set using Spartan V. 5.1.2.[6]

Coordinates for the two lowest energy enolates are available as Supporting Information files.

(5) MacroModel V6.5; W. C. Still, Columbia Univ. b) Mohamdi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T., Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440-467

(6) SPARTAN v5.0 (Wavefunction, Inc.; 18401 Von Karman Avenue, Suite 370; Irvine, CA 92612 U.S.A.).