Chiral NHC-Catalyzed Oxodiene Diels-Alder Reactions with α-Chloroaldehye Bisulfite Salts

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Supporting Information

General Methods. Toluene was dried by passage over activated alumina under Ar atmosphere. All aldehydes were purified by distillation or sublimation prior to use. Triazolium salt **1** and ***ent*-1** are commercially available from Sigma-Aldrich or BioBlocks. Inc. 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 (400 MHz) and ^{13}C NMR (100 MHz) were measured on a Varian Unity 400 spectrometer. 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; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a JASCO FT/IR-430 spectrophotometer and are reported as wavenumber (cm^{-1}). Optical rotations were measured on a Jasco DIP-1000 polarimeter operating at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]^{T}$ (concentration (g/100 ml), solvent).

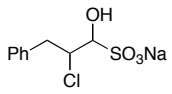
HPLC Conditions. Column, Daicel Chiralpak IA, (4.6 x 250mm) Eluent: hexanes/i-PrOH. Flow Rate 1.0 mL/min. Detection: 220 nm and 254 nm. Column, Daicel Chiralpak IB, (4.6

x250mm) Eluent: hexanes/iPrOH. Flow Rate 1.0 mL/min. Detection: 220 nm and 254 nm. Column, Daicel Chiralcel OJ–H, (4.6 x250mm) Eluent: hexanes/iPrOH. Flow Rate 1.0 mL/min. Detection: 220 nm and 254 nm.

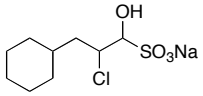
SFC (Supercritical Fluid Chromatography) Conditions. Columns: Daicel Chiralpak AS-H (4.6 x 250 mm), Daicel Chiralpak AD-H (4.6 x 250 mm), Regis (*R*,*R*)-WHELK-O1 (4.6 x 250 mm). Eluents: gradient 5%–80% *i*-PrOH in CO_2, rate 3%/min or 5%/min, Flow rate 2.0 ml/min; isocratic 15% *i*-PrOH in CO_2, Flow rate 2.0 ml/min. Detection: 254 nm.

General procedure for the preparation of sodium bisulfite adducts of α-chloroaldehydes.

The corresponding α-chloroaldehydes were prepared according to a previous literature procedure.[1] L-proline (10 mol %) was added to a stirred ice-cooled solution of aldehyde in CH_2Cl_2 (0.5 M), followed by the addition of NCS (1.3 equiv). After 1 h, the reaction mixture was warmed to rt and stirred until the aldehyde was completely consumed as determined by ^{1}H NMR spectroscopy of the reaction mixture. Pentane was added to the reaction mixture and the precipitated NCS, succinimide and catalyst were filtered off. The solution was concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography (hexanes/EtOAc). To the resulting α-chloroaldehyde in EtOAc (0.2 M) was slowly added the aqueous solution of sodium bisulfite (1.1 equiv, 3.3 M) at rt and the mixture stirred 14 hr. The white precipitate was filtered, washed with EtOAc and dried under vacuum.



Sodium 2-chloro-1-hydroxy-3-phenylpropane-1-sulfonate (9) was obtained in 95% yield as a white solid. IR (KBr pellet) ν 3446, 3154, 1631, 1497, 1454, 1434, 1185, 1050 cm^{-1}.



Sodium 2-chloro-3-cyclohexyl-1-hydroxypropane-1-sulfonate (10) was obtained in 87% yield as a white solid. IR (KBr pellet) ν 3536, 2982, 1641, 1490, 1440, 1424, 1196, 1040 cm^{-1}.

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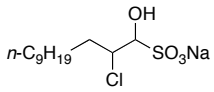
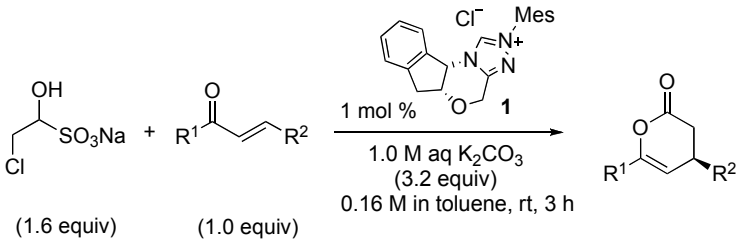
(1) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jøgensen, K. A. *J. Am. Chem. Soc.* **2004,** *126*, 4790–4791.



Sodium 2-chloro-1-hydroxydodecane-1-sulfonate (11) was obtained in 93% yield as a white solid. IR (KBr pellet) ν 3539, 2956, 2923, 2852, 1655, 1469, 1400, 1379, 1200, 1042 cm^{-1}.

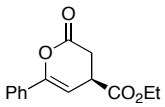
General Procedure for Enantioselective Diels–Alder Reaction with Sodium Bisulfite Salts.



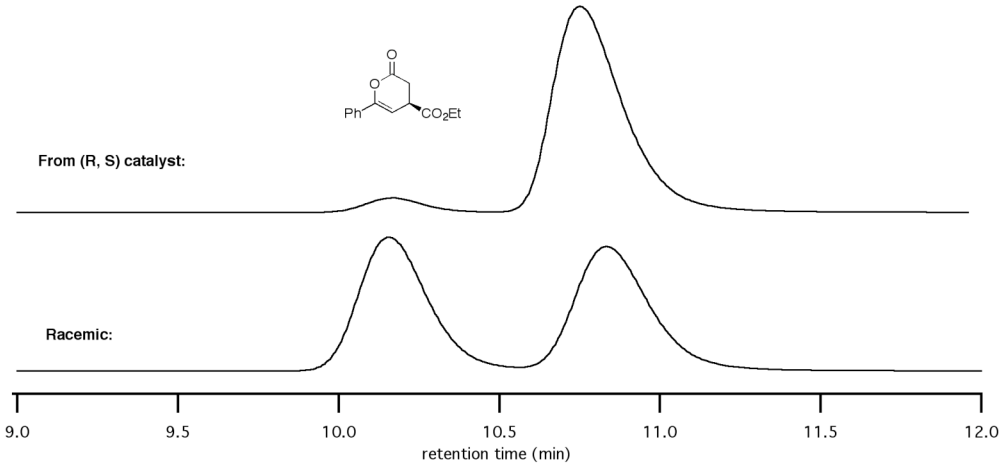
α-Chloroacetaldehyde sodium bisulfite (80.2 mg, 0.44 mmol, 1.6 equiv) was dissolved in 0.88 ml aq. 1.0 M K_2CO_3, followed by the addition of 1.76 ml toluene. The biphasic mixture was stirred vigorously for 5 min before the chiral triazolium precatalyst (1.0 mg, 0.003 mmol, 1 mol %) and methyl 4-oxo-4-phenylbut-2-enoate (56.1 mg, 0.28 mmol, 1.0 equiv) were added. The resulting mixture was stirred at rt for 6.5 h. The organic layer was separated, and the aqueous layer extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes/EtOAc) to afford a colorless oil (52.7 mg, 84%).

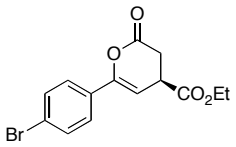
Racemic standards of the chiral products were prepared by the use of 2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium chloride[2] as the catalyst. In most cases, this catalyst was slightly less efficient in terms of chemical yield than the chiral triazolium salts.

(2) (a) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873–3876. (b) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420.

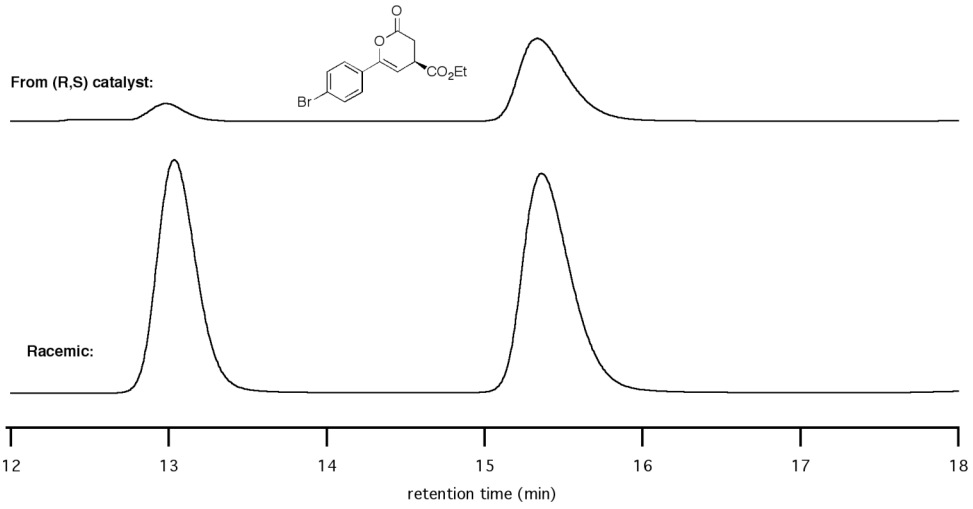


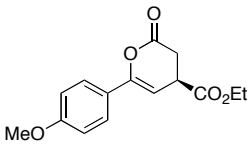
(*R*)-Ethyl 2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-4-carboxylate (**5b**). Prepared according to the general procedure from α-chloroacetaldehyde sodium bisulfite **2** and (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate **3b** using 1% chiral catalyst **1** in 84% yield a colorless oil. $[\alpha]_D^{20}$ (c 1.34, $CHCl_3$) = +68.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (m, 2H), 7.41–7.38 (m, 3H), 5.92 (d, 1H, *J* = 4.9 Hz), 4.23 (q, 2H, *J* = 7.1 Hz), 3.65–3.60 (m, 1H), 3.00 (dd, 1H, *J* = 16.4, 7.5 Hz), 2.89 (dd, 1H, *J* = 16.4, 6.8 Hz), 1.31 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 166.8, 151.7, 132.0, 129.7, 128.7, 125.0, 98.0, 62.0, 37.4, 30.7, 14.3; IR (thin film) ν 3089, 2996, 2963, 1767, 1717, 1486, 1369, 1237, 1157, 1089 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}O_4$ $[M+Na]^+$ 269.0784, found 269.0789; 90% ee (*R*)-isomer as determined by HPLC (IA, 9:1 hexanes/*i*-PrOH), t_r(*R*) = 10.8 min, t_r(*S*) = 10.2 min.



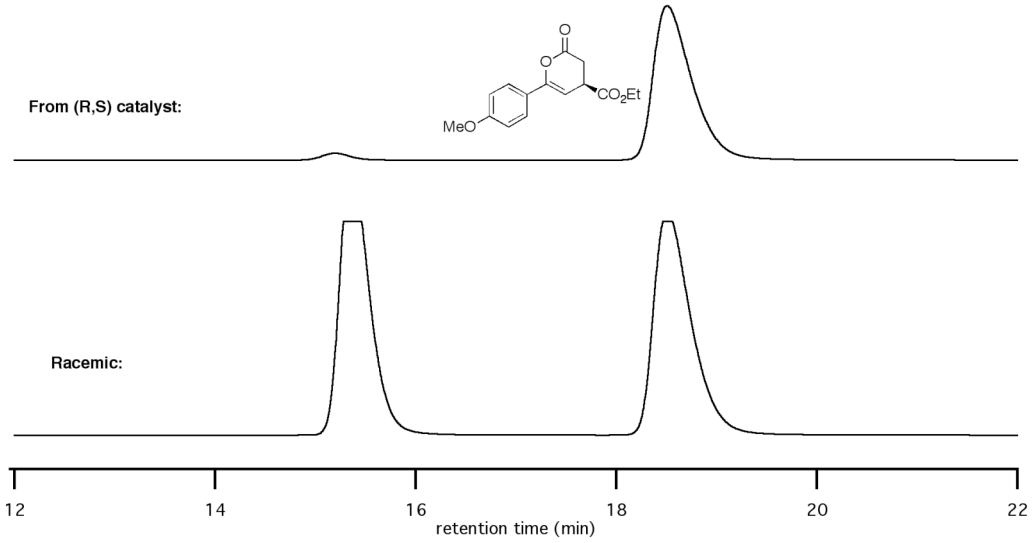


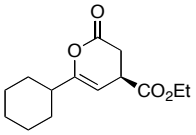
(*R*)-Ethyl 6-(4-bromophenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate (**5c**). Prepared according to the general procedure from α-chloroacetaldehyde sodium bisulfite **2** and (*E*)-ethyl 4-(4-bromophenyl)-4-oxo-but-2-enoate **3c** using 1% chiral catalyst **1** in 71% yield as a white solid. $[\alpha]_D^{20}$ (c 1.21, $CHCl_3$) = +53.2; mp = 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2H), 7.63–7.60 (m, 2H), 5.91 (d, 1H, J = 4.8 Hz), 4.20 (q, 2H, J = 7.1 Hz), 3.62–3.57 (m, 1H), 2.97 (dd, 1H, J = 16.3, 7.4 Hz), 2.87 (dd, 1H, J = 16.3, 6.8 Hz), 1.28 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 168.0, 132.1, 131.9, 129.7, 126.5, 98.5, 61.4, 39.3, 36.5, 14.2; IR (thin film) ν 3089, 2925, 2849, 1768, 1717, 1332, 1237, 1178, 1081 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{13}BrO_4$ $[M+H]^+$ 325.0070, found 325.0057; 73% ee (*R*)-isomer as determined by HPLC (IA, 9:1 hexanes/*i*-PrOH), t_r(*R*) = 15.3 min, t_r(*S*) = 13.0 min.



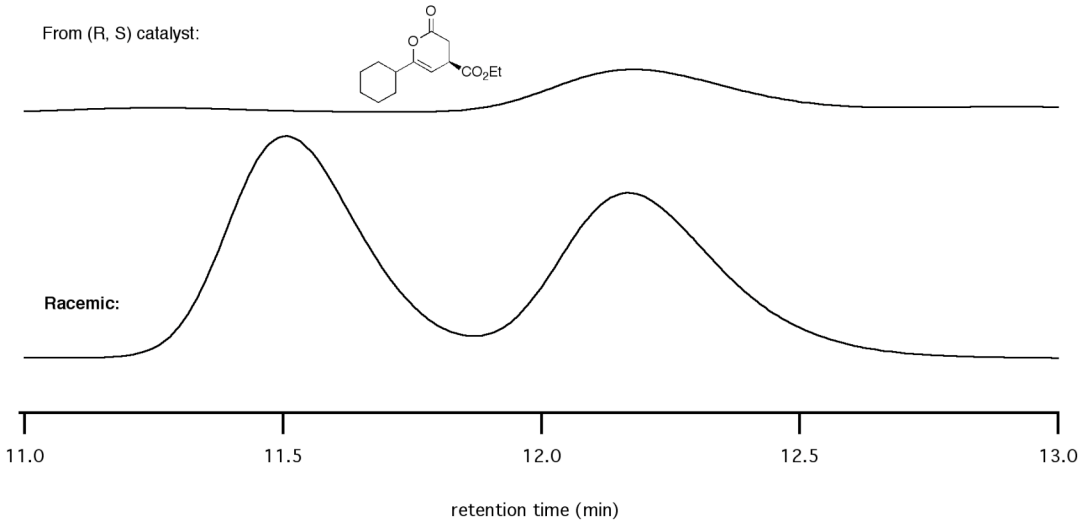


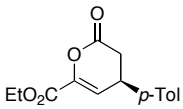
(*R*)-Ethyl 6-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate (**5d**). Prepared according to the general procedure from α-chloroacetaldehyde sodium bisulfite **2** and (*E*)-ethyl 4-(4-methoxyphenyl)-4-oxo-but-2-enoate **3d** using 1% chiral catalyst **1** in 90% yield as a colorless oil. $[\alpha]_D^{20}$ (c 1.33, $CHCl_3$) = +31.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.57 (m, 2H), 6.96–6.90 (m, 2H), 5.78 (d, 1H, *J* = 4.9 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 3.84 (s, 3H), 3.62–3.59 (m, 1H), 2.98 (dd, 1H, *J* = 16.3, 7.4 Hz), 2.87 (dd, 1H, *J* = 16.3, 6.8 Hz), 1.29 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 168.6, 160.2, 130.5, 126.4, 114.0, 114.0, 96.0, 62.0, 55.7, 37.3, 30.7, 14.2; IR (thin film) ν 3082, 2983, 2842, 1777, 1730, 1600, 1514, 1332, 1258, 1237, 1177, 1026 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}O_5$ $[M+H]^+$ 299.0890, found 299.0900; 99% ee (*R*)-isomer as determined by HPLC (IA, 9:1 hexanes/*i*-PrOH), t_r(*R*) = 18.8 min, t_r(*S*) = 15.5 min.



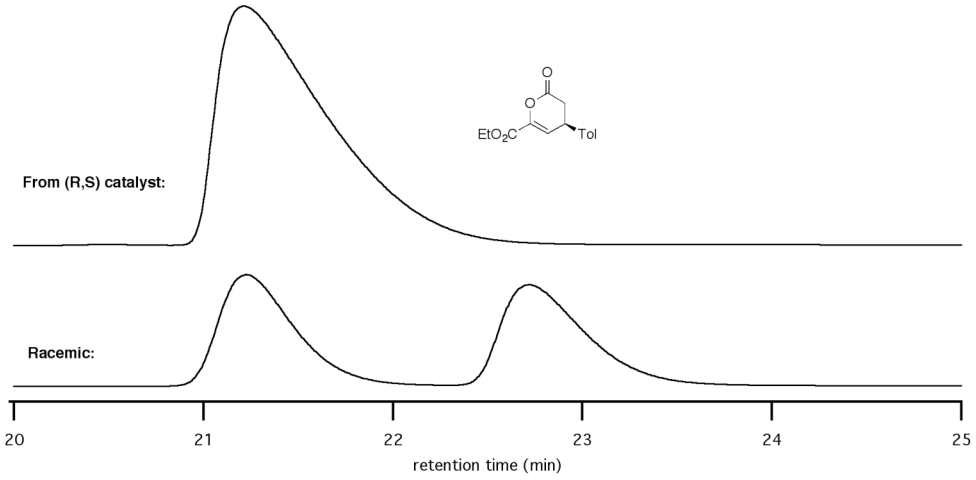


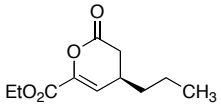
(*R*)-Ethyl 6-cyclohexyl-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate (**5e**). Prepared according to the general procedure from α-chloroacetaldehyde sodium bisulfite **2** and (*E*)-ethyl 4-cyclohexyl-2-oxo-but-3-enoate **3e** using 1% chiral catalyst **1** in 52% yield as a colorless oil. $[\alpha]_D^{20}$ (c 0.96, $CHCl_3$) = +108.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (d, 1H, *J* = 4.2 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 3.39–3.37 (m, 1H), 2.84 (dd, 1H, *J* = 16.3, 7.4 Hz), 2.74 (dd, 1H, *J* = 16.3, 6.8 Hz), 2.16–2.02 (m, 1H), 1.87–1.60 (m, 4H), 1.29–1.18 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 167.6, 159.3, 95.8, 61.8, 41.2, 36.8, 30.9, 30.2, 26.1, 26.0, 14.3; IR (thin film) ν 2930, 2855, 1774, 1737, 1451, 1267, 1221, 1186, 1148, 1007 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}O_4$ $[M]^+$ 252.1362, found 252.1363; 91% ee (*R*)-isomer as determined by HPLC (OJ–H, 30:1 hexanes/*i*-PrOH), t_r(*R*) = 12.2 min, t_r(*S*) = 11.5 min.



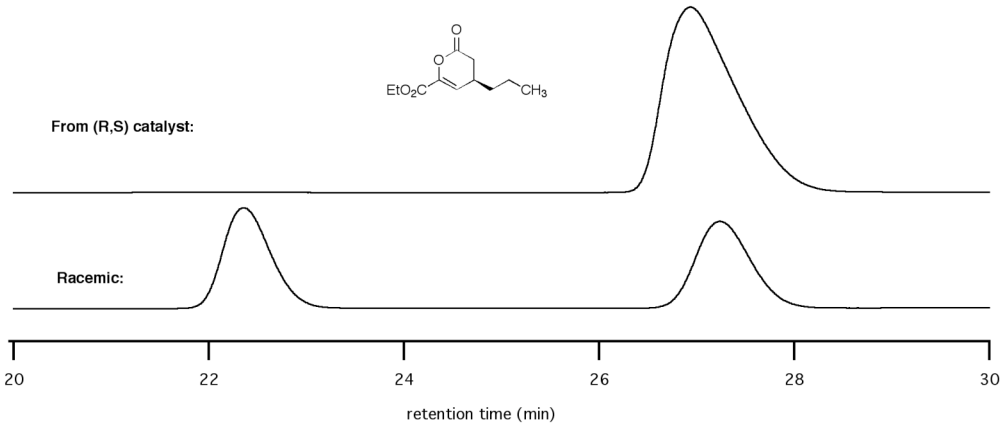


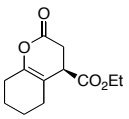
(*R*)-Ethyl 2-oxo-4-*p*-tolyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**6a**). Prepared according to the general procedure from α-chloroacetaldehyde sodium bisulfite **2** and (*E*)-ethyl 2-oxo-4-*p*-tolylbut-3-enoate **4a** using 1% chiral catalyst **1** in 74% yield as a colorless oil. $[\alpha]_D^{20}$ (c 0.92, $CHCl_3$) = –4.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.07 (m, 4H), 6.63 (d, 1H, *J* = 4.4 Hz), 4.35–4.29 (m, 2H), 3.93–3.88 (m, 1H), 2.98 (dd, 1H, *J* = 17.0, 0.6 Hz), 2.94 (dd, 1H, *J* = 17.0, 0.6 Hz), 2.34 (s, 3H), 1.35 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 160.6, 142.9, 138.0, 136.8, 130.2, 127.0, 118.3, 62.2, 37.0, 36.1, 21.3, 14.4; IR (thin film) ν 3028, 2924, 1778, 1740, 1659, 1464, 1370, 1316, 1262, 1108 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}O_4$ $[M+H]^+$ 261.1121, found 261.1134; 99% ee (*R*)-isomer as determined by HPLC (IB, 30:1 hexanes/*i*-PrOH), t_r(*R*) = 21.2 min, t_r(*S*) = 22.8 min.



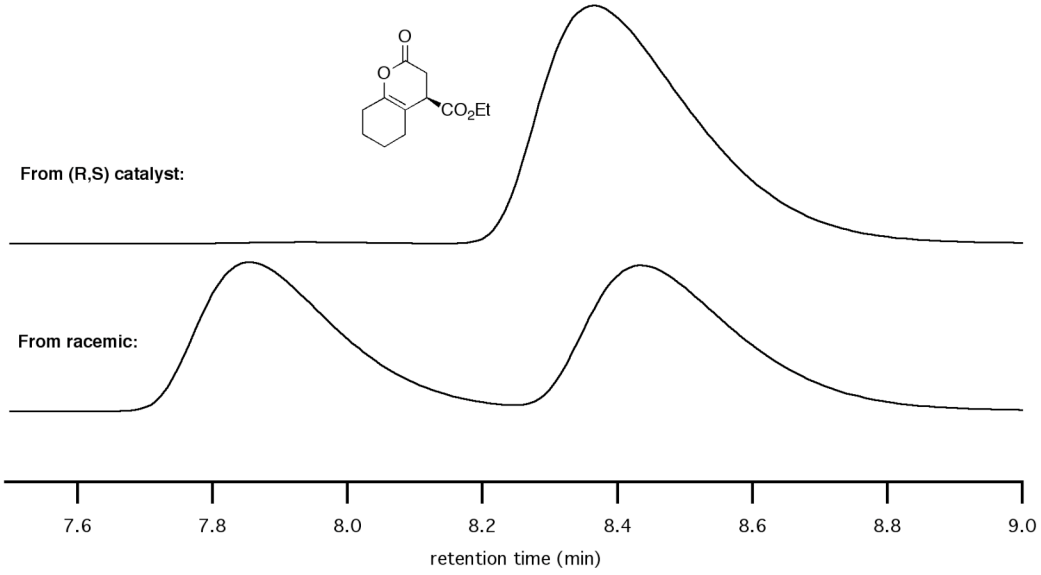


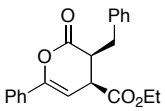
(*R*)-Ethyl 2-oxo-4-propyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**6b**). Prepared according to the general procedure from α-chloroacetaldehyde sodium bisulfite **2** and (*E*)-ethyl 2-oxohept-3-enoate (**4b**) using 1% chiral catalyst **1** in 80% yield as a colorless oil. $[\alpha]_D^{20}$ (c 1.32, $CHCl_3$) = –11.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, 1H, *J* = 2.3 Hz), 4.29 (q, 2H, *J* = 7.2 Hz), 2.74–2.64 (m, 2H), 2.46–2.38 (m, 1H), 1.42–1.38 (m, 4H), 1.33 (t, 3H, *J* = 7.2 Hz), 0.93 (t, 3H, *J* = 7.1 Hz); ^{13}X NMR (100 MHz, $CDCl_3$) δ 167.1, 160.5, 142.1, 119.3, 61.8, 36.0, 33.6, 30.9, 19.7, 14.2, 13.9; IR (thin film) ν 3027, 2959, 2924, 1776, 1736, 1450, 1365, 1274, 1208, 1109 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{16}O_4$ $[M+H]^+$ 213.1121, found 213.1130; >99% ee (*R*)-isomer as determined by HPLC (IA, 30:1 hexanes/EtOH), t_r(*R*) = 27.6 min, t_r(*S*) = 22.2 min.



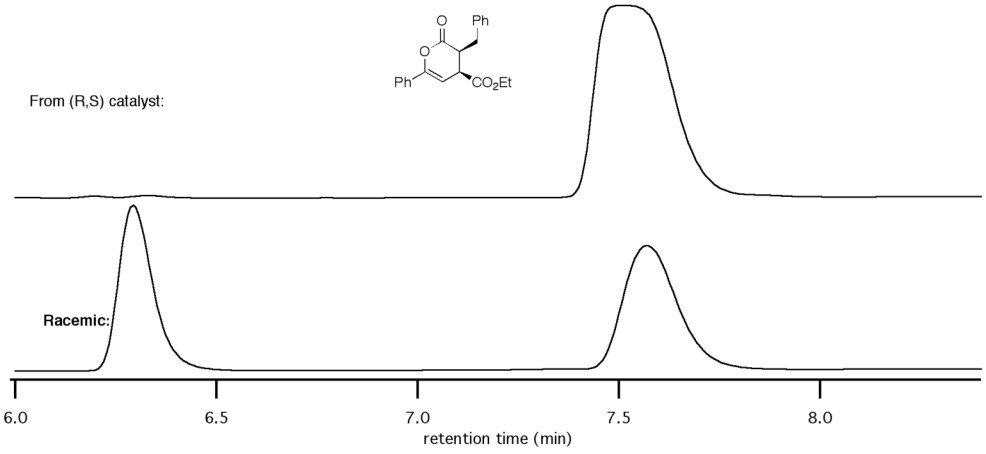


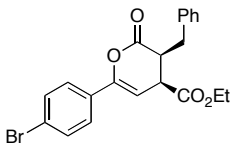
(*R*)-Methyl 2-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromene-4-carboxylate (**8**). Prepared according to the general procedure from α-chloroacetaldehyde sodium bisulfite **2** and (*E*)-ethyl 2-(2-oxocyclohexylidene)acetate **7** using 5% chiral catalyst **1** in 40% yield as a white solid. $[\alpha]_D^{20}$ (c 1.00, $CHCl_3$) = +161.5; mp = 56–60°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22–4.13 (m, 2H), 3.08–3.06 (m, 1H), 2.93 (dd, 1H, *J* = 16.1, 3.1 Hz), 2.68 (dd, 1H, *J* = 16.1, 6.9 Hz), 2.30–2.04 (m, 4H), 1.74–1.57 (m, 4H), 1.28–1.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 167.3, 148.5, 107.4, 61.7, 41.8, 31.6, 26.8, 26.6, 22.4, 22.2, 14.3; IR (thin film) ν 3437, 2949, 2938, 2861, 1767, 1732, 1437, 1348, 1237, 1155, 1120 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{16}O_4$ $[M]^+$ 224.1049, found 224.1045; >99% ee (*R*)-isomer as determined by HPLC (IB-H, 9:1 hexanes/*i*-PrOH), t_r(*R*) = 8.4 min, t_r(*S*) = 7.8 min.



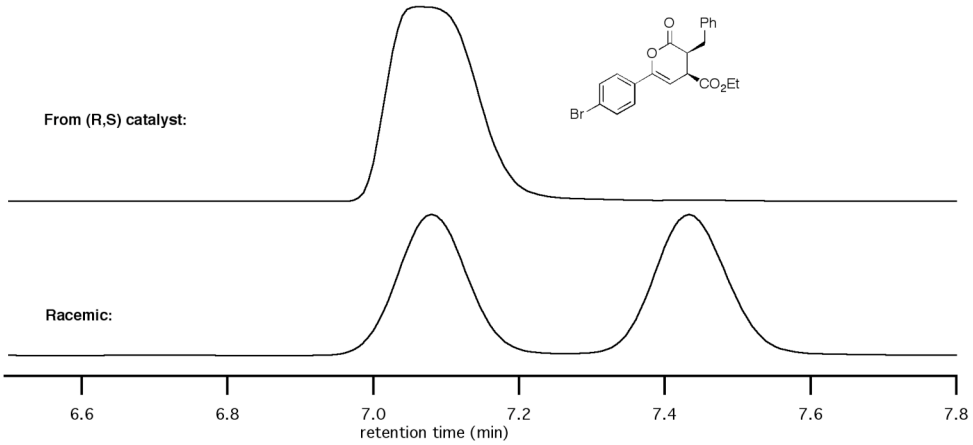


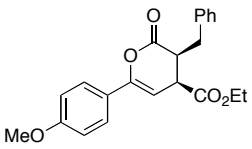
(3*S*,4*S*)-Ethyl 3-benzyl-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-4-carboxylate (*R*)-Ethyl 2-oxo-4-*p*-tolyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**12b**). Prepared according to the general procedure from sodium 2-chloro-1-hydroxy-3-phenylpropane-1-sulfonate **9** and (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate **3b** using 1% chiral catalyst **1** in 98% yield as a colorless oil. $[\alpha]_D^{20}$ (c 0.82, $CHCl_3$) = +107.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.18 (m, 10H), 5.81 (d, 1H, *J* = 7.0 Hz), 4.22 (q, 2H, *J* = 7.2 Hz), 3.56 (dd, 1H, *J* = 14.2, 4.6 Hz), 3.27–3.24 (m, 1H), 3.03–2.98 (m, 1H), 2.78 (dd, 1H, *J* = 14.2, 10.1 Hz), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.0, 152.5, 138.2, 131.9, 129.7, 129.2, 129.0, 128.7, 127.0, 125.0, 98.2, 61.8, 42.8, 40.7, 33.4, 14.3; IR (thin film) ν 2927, 2854, 1731, 1449, 1371, 1259, 1157, 1071 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{20}O_4$ $[M+Na]^+$ 359.1254, found 359.1247; 99% ee (3*S,* 4*S*)-isomer as determined by SFC (WHELK, gradient 5%–80% *i*-PrOH in CO_2, 5% per min), t_r(3*S,* 4*S*) = 7.6 min, t_r(3*R,* 4*R*) = 6.3 min.



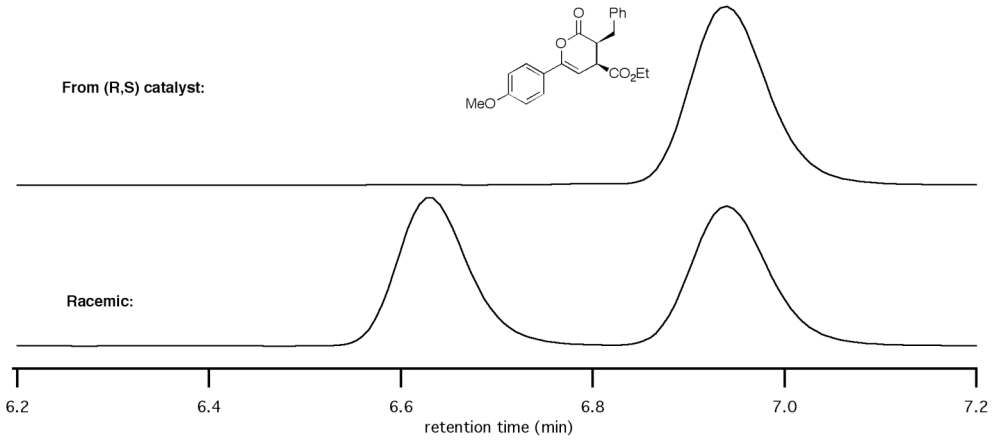


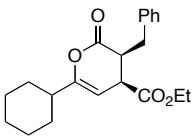
(3*S*,4*S*)-Ethyl 3-benzyl-6-(4-bromophenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate (**12c**). Prepared according to the general procedure from sodium 2-chloro-1-hydroxy-3-phenylpropane-1-sulfonate **9** and (*E*)-ethyl 4-(4-bromophenyl)-4-oxo-but-2-enoate **3c** using 1% chiral catalyst **1** in 84% yield as a white solid. $[\alpha]_D^{20}$ (c 1.39, $CHCl_3$) = +122.7; mp = 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.17 (m, 9H), 5.81 (d, 1H, *J* = 7.0 Hz), 4.22 (q, 2H, *J* = 7.2 Hz), 3.54 (dd, 1H, *J* = 14.2, 4.0 Hz), 3.27–3.24 (m, 1H), 3.01–2.97 (m, 1H), 2.77 (dd, 1H, *J* = 14.3, 10.1 Hz), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 168.7, 151.7, 138.1, 131.9, 130.8, 129.2, 129.0, 127.1, 126.5, 124.0, 98.7, 61.9, 42.8, 40.7, 33.3, 14.3; IR (thin film) ν 2989, 2930, 1778, 1730, 1590, 1490, 1454, 1371, 1263, 1176, 1069 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{19}BrO_4$ $[M+Na]^+$ 437.0359, found 437.0375; >99% ee (3*S,* 4*S*)-isomer as determined by SFC (OJ-H, gradient 5%–80% *i*-PrOH in CO_2, 5% per min), t_r(3*S,* 4*S*) = 7.12 min, t_r(3*R,* 4*R*) = 7.47 min.



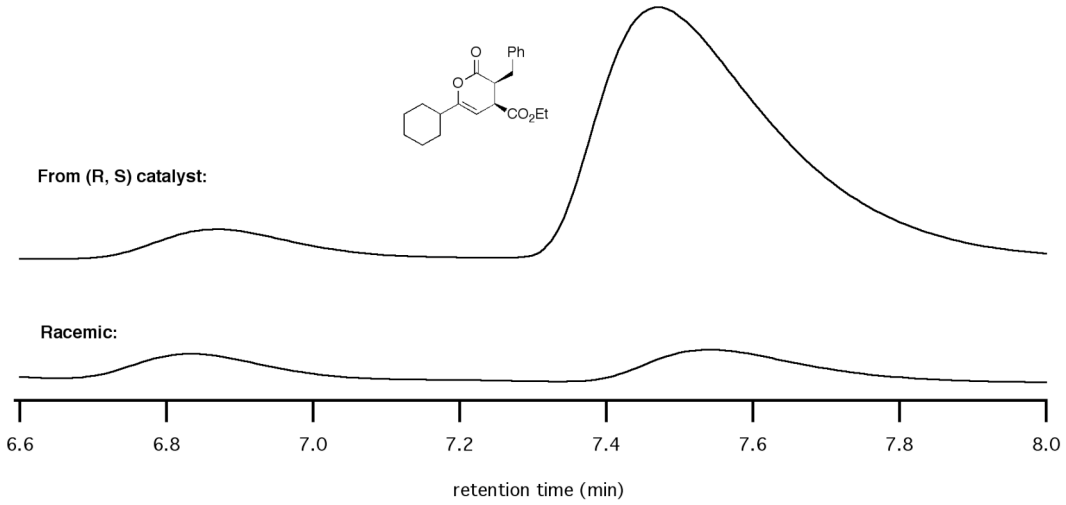


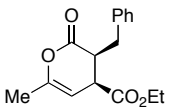
(3*S*,4*S*)-Ethyl 3-benzyl-6-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate (**12d**). Prepared according to the general procedure from sodium 2-chloro-1-hydroxy-3-phenylpropane-1-sulfonate **9** and (*E*)-ethyl 4-(4-methoxyphenyl)-4-oxo-but-2-enoate **3d** using 1% chiral catalyst **1** in 55% yield as a colorless oil. $[\alpha]_D^{20}$ (c 1.06, $CHCl_3$) = +79.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.55 (m, 2H), 7.33–7.19 (m, 5H), 6.90–6.88 (m, 2H), 5.67 (d, 1H, *J* = 6.9 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 3.55 (dd, 1H, *J* = 14.3, 4.8 Hz), 3.23 (dd, 1H, *J* = 6.9, 5.8 Hz), 3.02–2.97 (m, 1H), 2.77 (dd, 1H, *J* = 14.3, 10.1 Hz), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.2, 160.8, 151.7, 138.3, 132.1, 130.6, 129.2, 128.9, 127.0, 126.5, 124.5, 114.3, 96.3, 61.9, 55.5, 42.9, 40.7, 33.4, 14.3; IR (thin film) ν 2990, 2933, 1734, 1720, 1601, 1512, 1456, 1372, 1258, 1173, 1027 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{22}O_5$ $[M+Na]^+$ 389.1359, found 389.1356; >99% ee (3*S,* 4*S*)-isomer as determined by SFC (AS-H, gradient 5%–80% *i*-PrOH in CO_2, 5% per min), t_r(3*S,* 4*S*) = 6.9 min, t_r(3*R,* 4*R*) = 6.6 min.



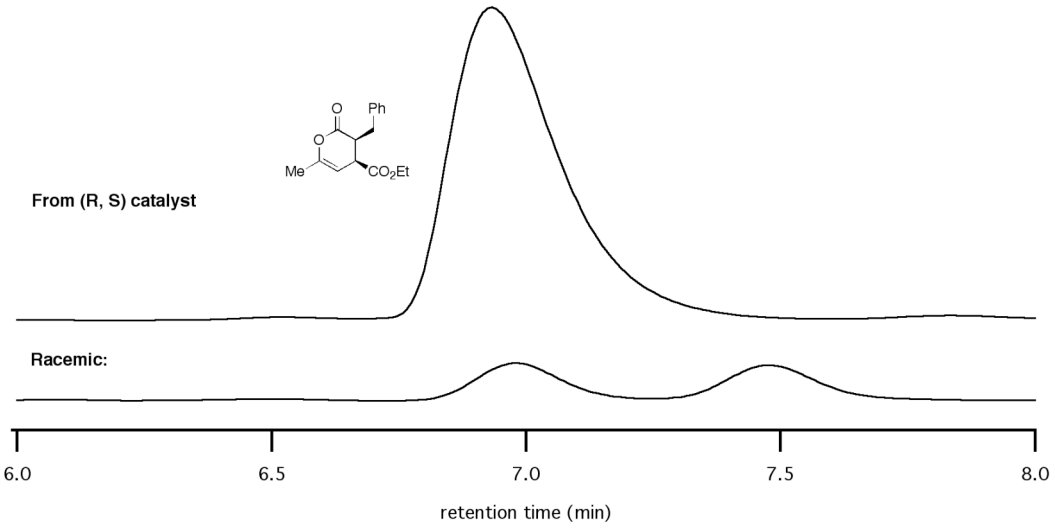


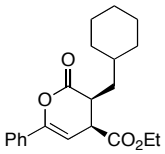
(3*S*,4*S*)-ethyl 3-benzyl-6-cyclohexyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (**12e**). Prepared according to the general procedure from sodium 2-chloro-1-hydroxy-3-phenylpropane-1-sulfonate **9** and (*E*)-ethyl 4-cyclohexyl-2-oxo-but-3-enoate **3e** using 1% chiral catalyst **1** in 70% yield as a white solid. $[\alpha]_D^{20}$ (c 1.25, $CHCl_3$) = +144.0; mp = 49–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.22 (m, 3H), 7.16–7.14 (m, 2H), 4.99 (d, 1H, *J* = 6.8 Hz), 4. 26–4.18 (m, 2H), 3.48 (dd, 1H, *J* = 14.1, 4.8 Hz), 3.04–3.01 (m, 1H), 2.85–2.80 (m, 1H), 2.67 (dd, 1H, *J* = 14.1, 10.1 Hz), 2.06–2.03 (m, 1H), 1.86–1.75 (m, 4H), 1.34–1.17 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.7, 160.3, 138.4, 129.2, 128.9, 127.0, 96.3, 61.5, 43.1, 41.1, 40.2, 33.4, 33.1, 30.3, 26.9, 26.1, 26.0, 26.0, 14.3; IR (thin film) ν 3029, 2929, 2854, 1773, 1733, 1452, 1371, 1275, 1183, 1154, 1056 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{26}O_4$ $[M+Na]^+$ 365.1723, found 365.1723; 91% ee (3*S,* 4*S*)-isomer as determined by HPLC (IB, 30:1 hexanes/*i*-PrOH), t_r(3*S,* 4*S*) = 7.5 min, t_r(3*R,* 4*R*) = 6.8 min.



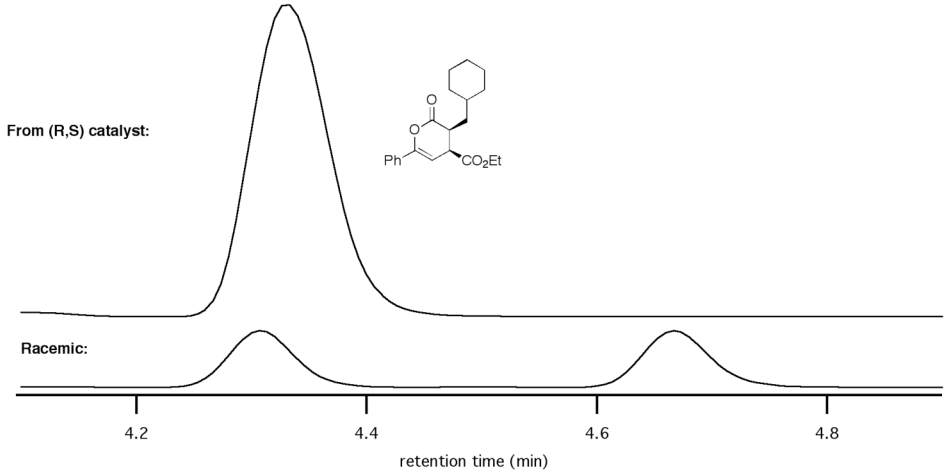


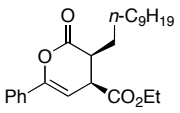
(3*S*,4*S*)-ethyl 3-benzyl-6-methyl-2-oxo-3,4-dihydro-2H-pyran-4-carboxylate (12f). Prepared according to the general procedure from sodium 2-chloro-1-hydroxy-3-phenylpropane-1-sulfonate **9** and (*E*)-ethyl 4-methyl-2-oxo-but-3-enoate **3f** using 1% chiral catalyst **1** in 65% yield as a colorless oil. $[\alpha]_D^{20}$ (c 0.93, $CHCl_3$) = +250.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 3H), 7.22–7.13 (m, 2H), 5.02 (dd, 1H, *J* = 6.8, 0.9 Hz), 4. 23–4.18 (m, 2H), 3.49 (dd, 1H, *J* = 14.3, 4.6 Hz), 3.01–2.98 (m, 1H), 2.88–2.83 (m, 1H), 2.68 (dd, 1H, *J* = 14.3, 10.1 Hz), 1.90 (t, 1H, *J* = 0.9 Hz), 1.29 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.4, 152.6, 138.4, 129.2, 128.9, 127.0, 98.8, 61.6, 42.8, 40.4, 33.4, 19.0, 14.3; IR (thin film) ν 3029, 2959, 2925, 1773, 1731, 1455, 1372, 1185, 1163, 1135 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}O_4$ $[M+Na]^+$ 297.1097, found 297.1097; 99% ee (3*S,* 4*S*)-isomer as determined by HPLC (IA, 9:1 hexanes/*i*-PrOH), t_r(3*S,* 4*S*) = 7.0 min, t_r(3*R,* 4*R*) = 7.5 min.



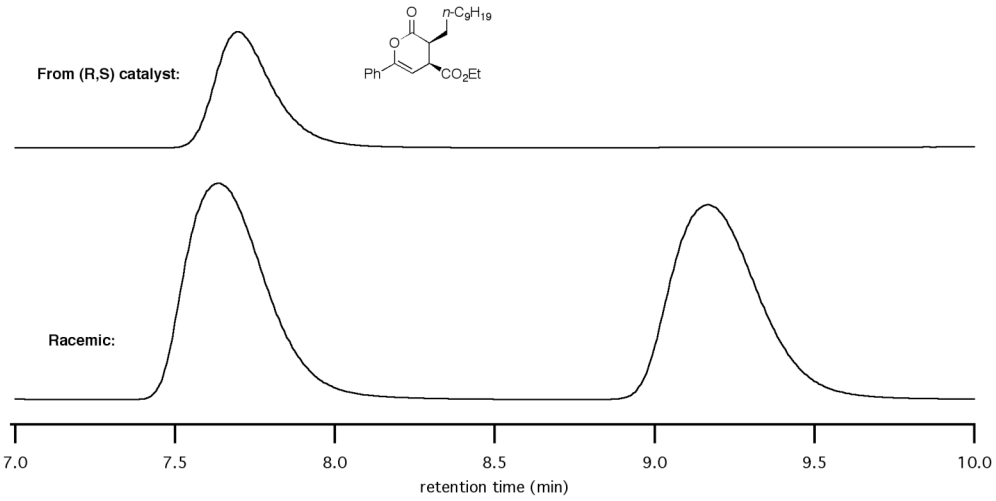


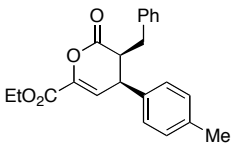
(3*S*,4*S*)-ethyl 3-(cyclohexylmethyl)-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-4-carboxylate (**13**). Prepared according to the general procedure from sodium 2-chloro-3-cyclohexyl-1-hydroxypropane-1-sulfonate **10** and (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate **3b** using 1% chiral catalyst **1** in 59% yield as a white solid. $[\alpha]_D^{20}$ (c 1.23, $CHCl_3$) = +161.5; mp = 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.63 (m, 2H), 7.40–7.36 (m, 3H), 5.91 (d, 1H, *J* = 6.9 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 3.57 (dd, 1H, *J* = 6.8, 5.8 Hz), 2.54 (dd, 1H, *J* = 8.3, 5.7 Hz), 2.23–2.20 (m, 1H), 2.01–1.98 (m, 1H), 1.77–1.66 (m, 4H), 1.39–0.99 (m, 5H), 1.26 (t, 3H, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.8, 152.4, 132.0, 129.6, 128.7, 125.0, 98.6, 61.7, 46.3, 40.2, 35.8, 33.2, 30.1, 26.4, 26.3, 26.1, 14.2; IR (thin film) ν 3090, 2990, 2924, 2850, 1768, 1716, 1664, 1447, 1332, 1191, 1146, 1081 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}O_4$ $[M+Na]^+$ 351.1567, found 351.1583; >99% ee (3*S,* 4*S*)-isomer as determined by SFC (WHELK, gradient 5%–80% *i*-PrOH in CO_2, 5% per min), t_r(3*S,* 4*S*) = 4.3 min, t_r(3*R,* 4*R*) = 4.7 min.



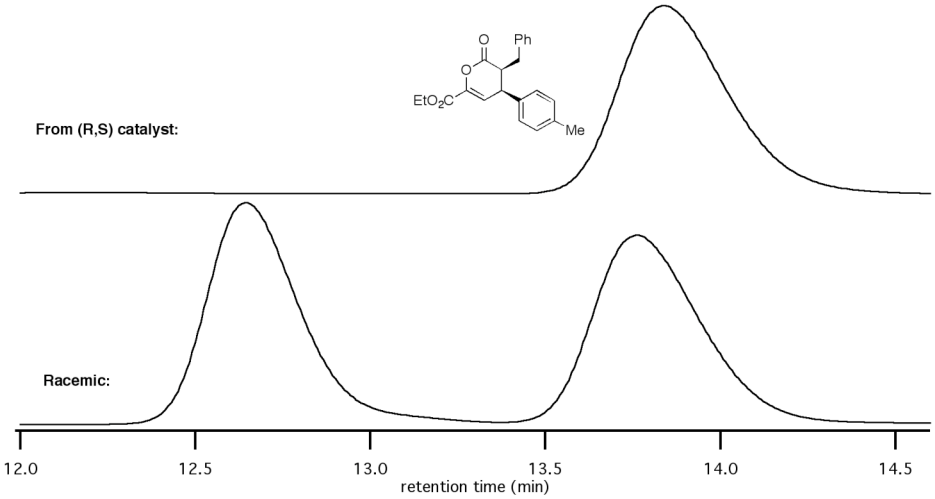


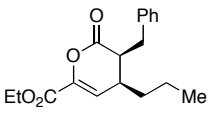
(3*S*,4*S*)-Ethyl 3-decyl-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-4-carboxylate (**14**). Prepared according to the general procedure from sodium 2-chloro-1-hydroxydodecane-1-sulfonate **11** and (*E*)-ethyl 4-oxo-4-phenylbut-2-enoate **3b** using 1% chiral catalyst **1** in 74% yield as a white solid. $[\alpha]_D^{20}$ (c 1.44, $CHCl_3$) = +153.7; mp = 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.64 (m, 2H), 7.40–7.37 (m, 3H), 5.89 (d, 1H, *J* = 6.5 Hz), 4.22–4.16 (m, 2H), 3.55–3.52 (m, 1H), 3.27–3.24 (m, 1H), 2.77–2.74 (m, 1H), 2.08–2.02 (m, 1H), 1.48–1.25 (m, 20H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.5, 152.3, 132.1, 129.7, 128.7, 125.0, 98.0, 61.7, 42.0, 40.7, 32.1, 29.8, 29.7, 29.6, 29.5, 27.3, 27.2, 22.9, 14.3, 14.3; IR (thin film) ν 3026, 2919, 2845, 1767, 1717, 1465, 1185, 1158, 1076 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{34}O_4$ $[M+Na]^+$ 409.2349, found 409.2348; >99% ee (3*S,* 4*S*)-isomer as determined by HPLC (IB, 30:1 hexanes/*i*-PrOH), t_r(3*S,* 4*S*) = 7.7 min, t_r(3*R,* 4*R*) = 9.3 min.



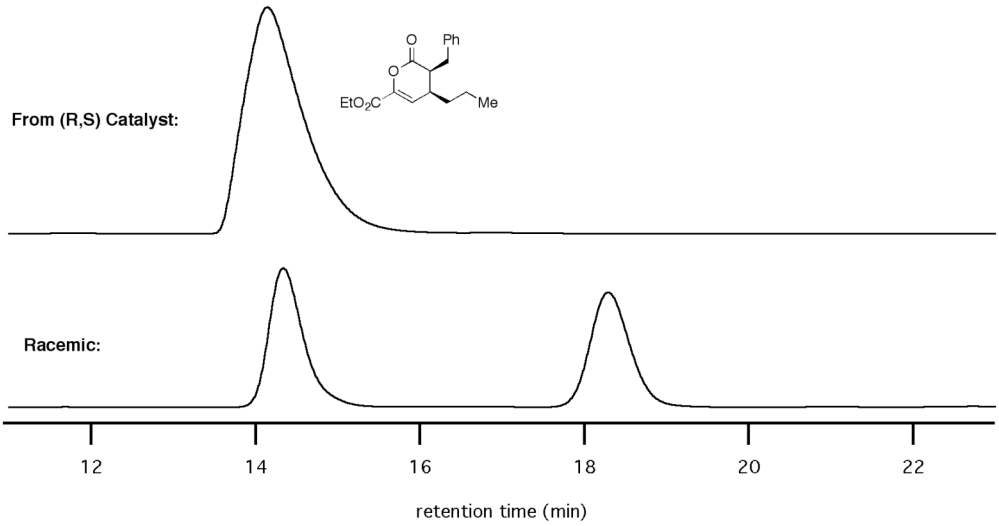


(3*S*,4*S*)-Ethyl 3-benzyl-2-oxo-4-*p*-tolyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**15a**). Prepared according to the general procedure from sodium 2-chloro-1-hydroxy-3-phenylpropane-1-sulfonate **9** and (*E*)-ethyl 2-oxo-4-*p*-tolylbut-3-enoate **4a** using 1% chiral catalyst **1** in 73% yield as a colorless oil. $[\alpha]_D^{20}$ (c 1.02, $CHCl_3$) = +310.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 3H), 7.16–7.07 (m, 4H), 6.93–6.91 (m, 2H), 6.65 (d, 1H, *J* = 6.8 Hz), 4.30 (q, 1H, *J* = 7.1 Hz), 3.58 (t, 1H, J = 6.7 Hz), 3.29–3.23 (m, 2H), 2.41 (dd, 1H, *J* = 15.8, 10.9 Hz), 2.35 (s, 3H), 1.33 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 160.7, 142.1, 138.3, 132.8, 130.0, 129.1, 128.8, 128.4, 126.9, 118.9, 62.1, 45.0, 40.3, 32.1, 21.3, 14.3; IR (thin film) ν 3062, 3027, 2982, 2925, 1776, 1732, 1316, 1267, 1106 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{22}O_4$ $[M+Na]^+$ 373.1410, found 373.1409; >99% ee (3*S,* 4*S*)-isomer as determined by HPLC (IA, 30:1 hexanes/EtOH), t_r(3*S,* 4*S*) = 13.8 min, t_r(3*R,* 4*R*) = 12.6 min.





(3*S*,4*S*)-Ethyl 3-benzyl-2-oxo-4-*p*-tolyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**15b**). Prepared according to the general procedure from sodium 2-chloro-1-hydroxy-3-phenylpropane-1-sulfonate **9** and (*E*)-ethyl 2-oxo-4-*p*-tolylbut-3-enoate **4b** using 1% chiral catalyst **1** in 78% yield as a colorless oil. $[\alpha]_D^{20}$ (c 1.27, $CHCl_3$) = +85.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 5H), 6.58 (d, 1H, *J* = 6.6 Hz), 4.30 (q, 1H, *J* = 6.8 Hz), 3.35 (dd, 1H, *J* = 14.4, 5.5 Hz), 2.97–2.92 (m, 1H), 2.79–2.73 (m, 1H), 2.45–2.41 (m, 1H), 1.63–1.60 (m, 1H), 1.42–1.23 (m, 6H), 0.89 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 160.6, 142.2, 138.4, 129.3, 128.9, 126.9, 120.4, 62.0, 44.4, 33.2, 31.9, 31.1, 20.0, 14.3, 14.3; IR (thin film) ν 3029, 2959, 2932, 2872, 1774, 1734, 1655, 1455, 1370, 1312, 1262,1111; HRMS (ESI) calcd for $C_{18}H_{22}O_4$ $[M]^+$ 302.1518, found 302.1528; >99% ee (3*S,* 4*S*)-isomer as determined by HPLC (OJ–H, 30:1 hexanes/EtOH), t_r(3*S,* 4*S*) = 14.3 min, t_r(3*R,* 4*R*) = 18.2 min.



Determination of the relative and absolute stereochemistry. Single crystal X-ray analysis of (*R*)-Ethyl 6-(4-bromophenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate **5c** (93% ee)[3]: A crystal of approximate dimensions 0.25*0.05*0.05 mm was mounted on a glass fiber and transferred to a Bruker CCD platform diffractometer. The SMART[4] program was used to determine the unit cell parameters and data collection (20 sec / frame, 0.3 deg. /frame for a sphere of diffraction data). The data were collected at room temperature. The raw frame data were processed using SAINT[5] program. The absorption correction was applied using program SADABS.[6] The structure was solved by direct methods and refined on F2 by full-matrix least-squares techniques. Hydrogen atoms were theoretically added. At convergence, GOF = 0.745 for 176 variables refined to R1= 0.0544 for 805 reflections with $I>2\sigma(I)$. The absolute structure was determined from the Flack parameters,[7] which are -0.02 (3) and 0.99 (3), respectively. See the corresponding CIF file for further information.

(3) CCDC 689207 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(4) SMART Software Users Guide, Version 5.1, Bruker Analytical X-ray Systems, Inc., Madison, WI 1999.
(5) SAINT Software Users Guide, Version 5.1, Bruker Analytical X-ray Systems, Inc., Madison, WI 1999.
(6) G. M. Sheldrick, SADABS, Version 2.05, Bruker Analytical X-ray Systerms, Inc.; Madison, WI 2001.
(7) Flack, H. D. *Acta Cryst.* A39(1983) 876–881.

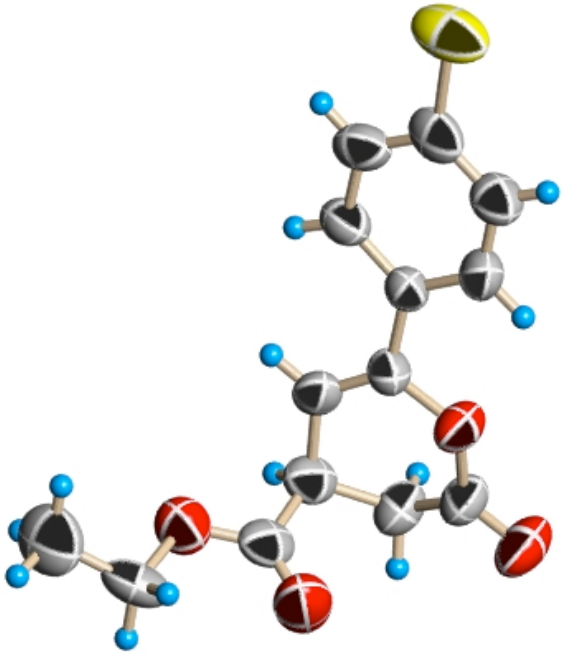


Figure 1. ORTEP representation of (*R*)-Ethyl 6-(4-bromophenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate

Single crystal X-ray analysis of (3*S*,4*S*)-Ethyl 3-benzyl-6-(4-bromophenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate **12c** [8]: A crystal of approximate dimensions 0.25*0.06*0.06 mm was mounted on a glass fiber and transferred to a Bruker CCD platform diffractometer. The structure was solved by direct methods and refined on F2 by full-matrix least-squares techniques. Hydrogen atoms were theoretically added. At convergence, GOF = 0.669 for 242 variables refined to R1= 0.0521 for 878 reflections with I>2σ(I). The absolute structure was determined from the Flack parameters, which are -0.03 (3) and 1.02 (3), respectively. See the corresponding CIF file for further information.

(8) CCDC 689208 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

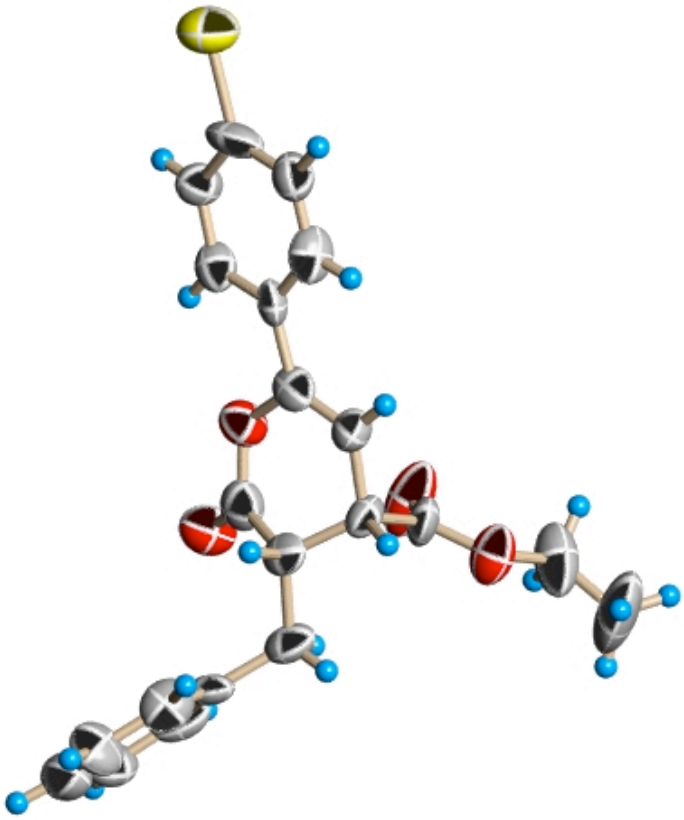


Figure 2. ORTEP representation of (3*S*,4*S*)-Ethyl 3-benzyl-6-(4-bromophenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate