A New Catalytic Enantioselective Approach to Optically Active Lactones by Addition Reactions to α-Dicarbonyl Compounds

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Supplementary Material:

Experimental Section

General Methods. All reactions were carried out under an atmosphere of N_2 using anhydrous solvents and flame-dried glassware. Solvents were dried according to standard procedures. Purification of the products was carried out by flash-chromatography (FC) using Merck silica gel 60 (230-400 mesh). ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as the solvent and are reported in ppm downfield from TMS (δ = 0) for ^1H NMR and relative to the central $CDCl_3$ resonance (δ = 77.00) for ^{13}C NMR. Mass spectra and high resolution mass spectra were obtained on a LC-TOF spectrometer (Micromass). The enantiomeric excess (ee) of the products were determined by chiral GC-MS using a Chrompack Chiralsil-Dex CB column, or by HPLC using a Daicel Chiralpak AD column, a Chiralcel OD column, or Chiralcel OJ and AS columns.

Materials. 2,2'-Isopropylidenebis[(4*S*)-4-tert-butyl-2-oxazoline], (*R*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline), $CuBr_2$, $Cu(OTf)_2$, and $AgPF_6$ from Aldrich were stored under an inert atmosphere and used without further purification. Ketene diethylacetal was purchased from Fluka. Ethyl

benzoylformate, methyl pyruvate, 2,3-butanedione, 2,3-pentanedione, 1-phenyl-1,2-propanedione were purchased from Aldrich. 3-Methyl-2-oxo-butyric acid ethyl ester and ethyl bromopyruvate were purchased from Acros Organics. 2-Oxo-butyric acid methyl ester and (*E*)-2-oxo-4-phenylbut-3-enoic acid methyl ester were prepared according to the literature procedure.[1,2]

General Procedure for the Formation of Optically Active δ-Lactones by Reaction of α-Dicarbonyl Compounds with Ketene Diethylacetal Catalyzed by (*S*)-5a-Cu(OTf)$_2$: Preparation of 4,4,6,6-tetraethoxy-2-phenyl-tetrahydro-pyran-2-carboxylic acid ethyl ester 3a: Catalyst (*S*)-**5a**-Cu(OTf)$_2$ was prepared by the addition of Cu(OTf)$_2$ (36 mg, 0.1 mmol) to 2,2'-isopropylidenebis[(4*S*)-4-tert-butyl-2-oxazoline] (30.9 mg, 0.105 mmol) under N_2. The mixture was dried under vacuum for 1-2 h, then anhydrous Et_2O (2.0 mL) was added, and the resulting suspension was stirred vigorously for 1-5 h. To the catalyst in solution at -78 °C were added the ethyl benzoylformate **1a** (81 μL, 0.5 mmol) followed by 3 equiv. of ketene diethylacetal **2** (190 μL, 1.5 mmol), and the reaction was stirred at -78 °C overnight. Purification by FC on silica gel (pentane:EtOAc 45:1 + 0.5% TEA) gave 2 products:

The cyclised compound **3a** (166 mg) isolated in 80% yield and with 93% ee detected by HPLC using a Chiralpak AD column (hexane:*i*-PrOH 99.5:0.5). $[\alpha]^{rt}_D$ = +12.18° (c = 0.033 g/mL; CH_2Cl_2); ^{1}H NMR δ 7.58-7.52 (m, 2H), 7.34-7.20 (m, 3H), 4.07 (dq, 2H, *J* = 7.1, 2.7 Hz), 3.80-3.70 (m, 2H), 3.64 (q, 2H, *J* = 7.1 Hz), 3.60-3.50 (m, 1H), 3.50-3.40 (m, 2H), 3.40-3.29 (m, 1H), 3.14 (d, 1H, *J* = 13.7 Hz), 2.38 (d, 1H, *J* = 14.3 Hz), 2.16 (d, 1H, *J* = 14.3 Hz), 2.05 (d, 1H, *J* = 13.7 Hz), 1.18 (t, 3H, *J* = 7.1 Hz), 1.17 (t, 3H, *J* = 7.1 Hz), 1.13 (t, 3H, *J* = 7.1 Hz), 1.12 (t, 3H, *J* = 7.1 Hz), 1.07 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 172.36, 142.38, 128.01, 127.43, 124.99, 113.46, 98.24, 79.28, 60.95, 57.72, 56.98, 55.57, 55.28, 39.27, 38.74, 15.17, 15.14, 15.00, 13.85; mass (TOF ES$^+$): *m/z* 433; HRMS calcd for $C_{22}H_{34}O_7Na$ 433.2203, found 433.2207.

Compound **6a** was also isolated in 10% yield and with 85% ee detected by HPLC using a Chiralpak AD column (hexane:*i*-PrOH 96:4). $[\alpha]^{rt}_D$ = +25.45° (c = 0.0055 g/mL; CH_2Cl_2); This compound was identical in all respects (^1H NMR, ^{13}C NMR, mass spectra) to that previously reported.[3]

Preparation of 4,4,6,6-tetraethoxy-2-methyl-tetrahydro-pyran-2-carboxylic acid methyl ester 3b: Prepared according to the general procedure using methyl pyruvate **1b** (51 mg, 0.5 mmol) to provide **3b** in 74% yield (123 mg, 0.37 mmol). $[\alpha]^{rt}_D$ = +14.70° (c = 0.051 g/mL; CH_2Cl_2); ^1H NMR δ 3.68 (s, 3H), 3.67-3.36 (m, 8H), 2.48 (d, 1H, *J* = 13.7 Hz), 2.20 (d, 1H, *J* = 14.3 Hz), 2.07 (d, 1H, *J* = 14.3 Hz), 1.98 (d, 1H, *J* = 13.7 Hz), 1.49 (s, 3H), 1.16 (t, 3H, *J* = 7.1 Hz), 1.15 (t, 3H, *J* = 7.1 Hz), 1.14 (t, 3H, *J* = 7.1 Hz), 1.08 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 174.48, 113.17, 98.06, 76.75, 57.39, 56.56, 55.48, 55.43, 51.90, 40.40, 38.30, 27.20, 15.16, 15.03; mass (TOF ES+): *m/z* 357; HRMS calcd for $C_{16}H_{30}O_7Na$ 357.1890, found 357.1889.

Preparation of 4,4,6,6-tetraethoxy-2-ethyl-tetrahydro-pyran-2-carboxylic acid methyl ester 3c: Prepared according to the general procedure using 2-oxo-butyric acid methyl ester **1c** (58 mg, 0.5 mmol) to provide **3c** in 70% yield (121 mg, 0.35 mmol). $[\alpha]^{rt}_D$ = +18.52° (c = 0.021 g/mL; CH_2Cl_2); ^1H NMR δ 3.78-3.65 (m, 2H), 3.64 (s, 3H), 3.59-3.31 (m, 6H), 2,44 (d, 1H, *J* = 13.3 Hz), 2.20 (d, 1H, *J* = 14.0 Hz), 2.10 (d, 1H, *J* = 14.1 Hz), 1.97 (d, 1H, *J* = 13.5 Hz), 1.87-1.75 (m, 1H), 1.75-1.62 (m, 1H), 1.13 (t, 3H, *J* = 7.1 Hz), 1.12 (t, 3H, *J* = 7.1 Hz), 1.11 (t, 3H, *J* = 7.1 Hz), 1.04 (t, 3H, *J* = 7.1 Hz), 0.85 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 173.84, 113.22, 98.11, 79.58, 57.24, 56.71, 55.43, 55.34, 51.56, 39.31, 38.45, 33.91, 15.23, 15.07, 14.93, 7.73; mass (TOF ES+): *m/z* 371; HRMS calcd for $C_{17}H_{32}O_7Na$ 371.2046, found 371.2049.

Preparation of 4,4,6,6-tetraethoxy-2-isopropyl-tetrahydro-pyran-2-carboxylic acid ethyl ester 3d: Prepared according to the general procedure using 3-methyl-2-oxo-butyric acid ethyl ester **1d** (77 μL, 0.5 mmol) to provide **3d** in 58% yield (109 mg, 0.29 mmol). $[\alpha]^{rt}_D$ = +29.27° (c = 0.0218 g/mL; CH_2Cl_2); ^{1}H NMR δ 4.22-4.04 (m, 2H), 3.84-3.70 (m, 2H), 3.64-3.53 (m, 2H), 3.53-3.32 (m, 4H), 2.44 (d, 1H, *J* = 13.7 Hz), 2.25 (d, 1H, *J* = 14.0 Hz), 2.09 (d, 1H, *J* = 13.8 Hz), 2.05 (d, 1H, *J* = 13.7 Hz), 2.06-1.96 (m, 1H), 1.28 (t, 3H, *J* = 7.2 Hz), 1.17 (t, 3H, *J* = 7.1 Hz), 1.16 (t, 3H, *J* = 7.1 Hz), 1.15 (t, 3H, *J* = 7.1 Hz), 1.08 (t, 3H, *J* = 7.2 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 0.92 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 173.38, 113.03, 98.47, 81.48, 60.39, 57.18, 56.90, 55.42, 55.23, 38.08, 36.91, 36.72, 17.17, 16.43, 15.32, 15.20, 15.16, 14.94, 14.12.

Preparation of 2-bromomethyl-4,4,6,6-tetraethoxy-tetrahydro-pyran-2-carboxylic acid ethyl ester 3e: Prepared according to the general procedure using ethyl bromopyruvate **1e** (97.5 mg, 0.5 mmol) to provide **3e** in 55% yield (118 mg, 0.29 mmol). $[\alpha]^{rt}_D$ = +4.64° (c = 0.0125 g/mL; CH_2Cl_2); ^{1}H NMR δ 4.26-4.18 (dq, 2H, *J* = 7.0, 1.95 Hz), 3.80 (s, 2H), 3.75-3.62 (m, 4H), 3.59-3.38 (m, 4H), 2.35 (d, 1H, *J* = 13.7 Hz), 2.28 (d, 1H, *J* = 13.7 Hz), 2.24 (d, 1H, *J* = 14.0 Hz), 2.08 (d, 1H, *J* = 14.0 Hz), 1.31 (t, 3H, *J* = 7.1 Hz), 1.19 (t, 3H, *J* = 7.1 Hz), 1.17 (t, 3H, *J* = 7.1 Hz), 1.16 (t, 3H, *J* = 7.1 Hz), 1.13 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 170.60, 113.38, 98.00, 78.88, 61.56, 57.92, 57.06, 55.85, 55.40, 37.98, 37.79, 37.35, 15.12, 15.07, 14.95, 14.08.

Preparation of 4,4,6,6-tetraethoxy-2-((E)-styryl)-tetrahydro-pyran-2-carboxylic acid methyl ester 3f: Prepared according to the general procedure using (*E*)-2-oxo-4-phenylbut-3-enoic acid methyl ester **1f** (95 mg, 0.5 mmol) to provide **3f** in 80% yield (170 mg, 0.4 mmol) and with 85% ee detected by HPLC using a Chiralpak OD column (hexane:*i*-PrOH 99.5:0.5). ^{1}H NMR δ 7.40-7.20 (m, 5H), 6.78 (d, 1H, *J* = 15.9 Hz), 6.33 (d, 1H, *J* = 15.9 Hz), 3.83 (m,

2H), 3.71 (s, 3H), 3.67 (q, 2H, J = 7.1 Hz), 3.56-3.40 (m, 4H), 2.73 (d, 1H, J = 13.7 Hz), 2.33 (d, 1H, J = 14.3 Hz), 2.19 (d, 1H, J = 13.8 Hz), 2.13 (d, 1H, J = 13.7 Hz), 1.21 (t, 3H, J = 7.1 Hz), 1.17 (t, 3H, J = 7.1 Hz), 1.16 (t, 3H, J = 7.1 Hz), 1.12 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 172.50, 136.45, 130.23, 129.62, 128.49, 127.73, 126.64, 113.54, 98.06, 78.92, 57.61, 57.00, 55.62, 55.58, 52.17, 39.99, 38.81, 15.33, 15.12, 15.07; mass (TOF ES$^+$): m/z 445.3; HRMS calcd for $C_{23}H_{34}O_7Na$ 445.2202 found 445.2192.

Preparation of 1-(4,4,6,6-tetraethoxy-2-methyl-tetrahydro-pyran-2-yl)-ethan-one 3g: Prepared according to the general procedure using 2,3-butanedione **1g** (43 mg, 0.5 mmol) to provide **3g** in 71% yield (113 mg, 0.35 mmol) and with 95% ee detected by GC-MS. ^{1}H NMR δ 3.80-3.34 (m, 8H), 2.54 (d, 1H, J = 14.0 Hz), 2.25 (s, 3H), 2.20 (d, 1H, J = 14.0 Hz), 1.97 (d, 1H, J = 14.0 Hz), 1.73 (d, 1H, J = 14.0 Hz), 1.34 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz), 1.16 (t, 3H, J = 7.0 Hz), 1.15 (t, 3H, J = 7.0 Hz), 1.1(t, 3H, J = 7.0 Hz); ^{13}C NMR δ 211.13, 112.99, 98.30, 81.51, 58.03, 55.89, 55.39, 55.24, 38.34, 36.86, 25.89, 24.69, 15.15, 14.95, 14.61; mass (TOF ES$^+$): m/z 341; HRMS calcd for $C_{16}H_{30}O_6Na$ 341.1940 found 341.1939.

Preparation of 1-(4,4,6,6-tetraethoxy-2-methyl-tetrahydro-pyran-2-yl)-propan-1-one 3h: Prepared according to the general procedure using 2,3-pentanedione **1h** (52 μL, 0.5 mmol) to provide **3h** in 70% yield (117 mg, 0.35 mmol) and with 90% ee detected by GC-MS. $[\alpha]^{rt}_D$ = +3.91° (c = 0.011 g/mL; CH_2Cl_2); ^{1}H NMR δ 3.74-3.57 (m, 3H), 3.56-3.34 (m, 5H), 2.80 (dq, 1H, J = 18.3, 7.4 Hz), 2.64 (dq, 1H, J = 18.3, 7.0 Hz), 2.42 (d, 1H, J = 14.0 Hz), 2.12 (d, 1H, J = 14.0 Hz), 2.06 (d, 1H, J = 14.0 Hz), 1.85 (d, 1H, J = 13.7 Hz), 1.35 (s, 3H), 1.19 (t, 3H, J = 7.0 Hz), 1.16 (t, 6H, J = 7.0 Hz), 1.08 (t, 3H, J = 7.0 Hz), 1.02 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ 214.15, 113.14, 98.40, 81.80, 57.87, 56.10, 55.41, 55.35, 38.57,

37.63, 29.57, 16.13, 15.17, 15.04, 14.95, 7.81; mass (TOF ES+): *m/z* 355; HRMS calcd for $C_{17}H_{32}O_6Na$ 355.2097 found 355.2094.

Preparation of 1-phenyl-1-(4,4,6,6-tetraethoxy-2-methyl-tetrahydro-pyran-2-yl)-methanone 3i: Prepared according to the general procedure using 1-phenyl-1,2-propanedione **1i** (74 mg, 0.5 mmol) to provide **3i** in 58% yield (109 mg, 0.29 mmol) and with 90% ee detected by HPLC using a Chiralpak AD column (hexane:*i*-PrOH 99.8:0.2). ^{1}H NMR δ 8.14 (m, 2H), 7.48-7.32 (m, 3H), 3.76-3.64 (m, 2H), 3.54-3.32 (m, 5H), 3.12 (m, 1H), 2.89 (d, 1H, *J* = 14.4 Hz), 2.19 (d, 1H, *J* = 13.7 Hz), 1.91 (d, 1H, *J* = 14.0 Hz), 1.75 (d, 1H, *J* = 14.0 Hz), 1.64 (s, 3H), 1.16 (t, 6H, *J* = 7.0 Hz), 1.10 (t, 3H, *J* = 7.0 Hz), 0.68 (t, 3H, *J* = 7.0 Hz); mass (TOF ES+): *m/z* 403; HRMS calcd for $C_{21}H_{32}O_6Na$ 403.2097 found 403.2099.

General procedure for the hydrolysis of the ketal groups: Preparation of 4-ethoxy-2-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylic acid methyl ester 4b: To compound **3b** (100 mg, 0.3 mmol) in a mixture of 4 mL of CH_2Cl_2 and 2 mL of pentane at 0 °C was added 2.5 mL of HCOOH. The mixture was then stirred for 3 h at 0 °C. The reaction was quenched by careful addition of a saturated solution of $NaHCO_3$, which was followed by an extraction with CH_2Cl_2. The organic phase was further washed with a saturated solution of $NaHCO_3$ (3x), dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by FC on silica gel (pentane:EtOAc 3:1) to afford 40 mg of compound **4b** (0.19 mmol, 63%) with 83% ee detected by HPLC using a Chiralpak AS column (hexane:*i*-PrOH 90:10). ^{1}H NMR δ 5.06 (d, 1H, *J* = 1.9 Hz), 3.88 (m, 2H), 3.74 (s, 3H), 2.91 (d, 1H, *J* = 16.8 Hz), 2.64 (dd, 1H, *J* = 17.2, 1.6 Hz), 1.62 (s, 3H), 1.33 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR δ 172.43, 170.23, 165.78, 90.37, 79.55, 64.92, 53.13, 36.49, 24.77, 13.82; mass (TOF ES+): *m/z* 237; HRMS calcd for $C_{10}H_{14}O_5Na$ 237.0739 found 237.0736.

Preparation of 4-ethoxy-2-ethyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylic acid methyl ester 4c: Prepared according to the general procedure using compound **3c** (105 mg, 0.3 mmol) to provide **4c** in 72% yield (50 mg, 0.22 mmol) and with 77% ee detected by HPLC using a Chiralpak OD column (hexane:*i*-PrOH 90:10). $[\alpha]^{rt}_D$ = +39.14° (c = 0.007 g/mL; CH_2Cl_2); ^{1}H NMR δ 5.09 (d, 1H, *J* = 1.6 Hz), 3.92 (m, 2H), 3.77 (s, 3H), 2.86 (d, 1H, *J* = 16.8 Hz), 2.70 (dd, 1H, *J* = 17.2, 1.6 Hz), 1.97 (m, 2H), 1.37 (t, 3H, *J* = 7.0 Hz), 1.01 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR δ 172.19, 170.28, 165.97, 90.57, 82.86, 64.92, 52.95, 34.85, 31.31, 13.87, 7.65; mass (TOF ES$^+$): *m/z* 251; HRMS calcd for $C_{11}H_{16}O_5Na$ 251.0896 found 251.0894.

Preparation of 4-ethoxy-2-isopropyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylic acid ethyl ester 4d: Prepared according to the general procedure using compound **3d** (109 mg, 0.29 mmol) to provide **4d** in 67% yield (50 mg, 0.19 mmol) and with 80% ee detected by HPLC using a Chiralpak OD column (hexane:*i*-PrOH 95:5). $[\alpha]^{rt}_D$ = +61.62° (c = 0.0076 g/mL; CH_2Cl_2); ^{1}H NMR δ 5.07 (d, 1H, *J* = 1.6 Hz), 4.22 (m, 2H), 3.92 (m, 2H), 2.82 (d, 1H, *J* = 16.8 Hz), 2.74 (dd, 1H, *J* = 16.8, 1.6 Hz), 2.18 (m, 1H), 1.37 (t, 3H, *J* = 7.0 Hz), 1.26 (t, 3H, *J* = 7.4 Hz), 1.04 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR δ 171.40, 170.72, 166.19, 90.55, 85.21, 64.87, 61.91, 34.74, 32.78, 16.81, 16.62, 14.08, 13.89; mass (TOF ES$^+$): *m/z* 278.9; HRMS calcd for $C_{13}H_{20}O_5Na$ 279.1209 found 279.1215.

Preparation of 2-bromomethyl-4-ethoxy-6-oxo-3,6-dihydro-2*H*-pyran-2-carboxylic acid ethyl ester 4d: Prepared according to the general procedure using compound **3e** (102 mg, 0.24 mmol) to provide **4e** in 50% yield (38 mg, 0.12 mmol) and with 53% ee detected by HPLC using a Chiralpak AD column (hexane:*i*-PrOH 96:4). $[\alpha]^{rt}_D$ = +21.36° (c = 0.0041 g/mL; CH_2Cl_2); ^{1}H NMR δ 5.11 (s, 1H), 4.28 (q, 2H, *J* = 7.4 Hz), 3.95 (m, 2H), 3.73 (d, 1H, *J* = 11.3 Hz), 3.68

(d, 1H, J = 10.9 Hz), 2.95 (s, 2H), 1.38 (t, 3H, J = 7.0 Hz), 1.29 (t, 3H, J = 7.0 Hz); ^{13}C NMR δ 169.53, 168.76, 164.53, 90.31, 80.82, 65.22, 63.02, 34.38, 33.82, 14.02, 13.89; mass (TOF ES$^+$): m/z 328.8; HRMS calcd for $C_{11}H_{15}BrO_5Na$ 329.0001 found 329.0002.

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