Supporting Information

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Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones. Preparation of Air Stable and Catalytically Active Cu•Peptide Complexes

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General. Infared (IR) spectra were recorded on a Nicolet 210 spectrophotometer, $\nu_{\text{max}}$ in cm$^{-1}$. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). $^1$H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl$_3$: $\delta$ 7.26 ppm). Data are reported as follows: chemical shift, intergration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). $^{13}$C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl$_3$: $\delta$ 77.0 ppm). $^{31}$P NMR spectra were recorded on a Varian Unity INOVA 400 (162 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from H$_3$PO$_4$ (δ 0.00). High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College and by the University of Illinois Mass Spectrometry Laboratories (Urbana, Illinois). Elemental microanalysis were performed by Robertson Microlit Laboratories (Madison, NJ). Enantiomer ratios were determined by chiral GLC analysis (Alltech Associated ChiralDEX GTA column (30m x 0.25mm), Betadex 120 column (30m x 0.25mm), Alphadex (30m x 0.25mm) or chiral HPLC analysis (Chiral Technologies Chiralpak AS column (25 cm x 0.46 cm) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N$_2$ in oven- (135 °C) and flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry Ar by a modified Innovative Technologies purification system: toluene and benzene were purified through a copper oxide and alumina column; CH$_2$Cl$_2$ and Et$_2$O were purged with argon and purified by passing them through two alumina columns. THF was purified by distillation from sodium benzophenone ketal.
immediately prior to use. All work-up and purification procedures were carried out with reagent solvents in air. All reagent solvents were purchased from Doe and Ingalls. Diethylzinc (neat), dimethylzinc (2N toluene solution) and diisopropylzinc (1N in toluene) were purchase from Aldrich. Dimethylzinc (neat) was purchased from Strem, Inc. 2(5H)-Furanone (4), 5,6-Dihydro-2H-pyran-2-one (7), 2,2-Dimethyl-3(2H)-furanone (20) and benzaldehyde were purchased from Aldrich and distilled under N₂ prior to use. Chromone (22) was purchased from Aldrich and used without further purification. (Z)-benzo[b]oxepin-2(5H)-one (12)¹ and copper (I) triflate benzene complex (2:1)² were prepared by known methods. Copper (I) iodide and copper (I) chloride were purchased from Strem and used as received. Chiral ligands 1-3 were prepared as previously described.³ Pyridinium chlorochromate (PCC) (Acros), Sodium acetate (Alrich), 4Å MS (Aldrich), Potassium carbonate (Aldrich), Celite 545 (Fisher), 3,4-dihydroxy-1-butene (Aldrich), Dibutyltin oxide (Aldrich), Allylbromide (Lancaster), Ruthenium catalyst C (Scheme S1) (Materia), Tetrapropylammonium perruthenate (TPAP) (Aldrich), 4-methylmorpholine N-oxide (NMO) (Aldrich), Sodium triacetoxyborohydride (Aldrich), Acetic Acid (Fisher), and 2,2-dimethoxypropane (Aldrich) were used as received. p-TsOH was purchased from Aldrich and azotroped with benzene prior to use.

Representative experimental procedure for three-component Cu-catalyzed conjugate addition of dialkylzinc reagents to unsaturated lactones (4, 7, 12) with benzaldehyde: (CAUTION: Et₂Zn IS PYROPHORIC! USE EXTREME CAUTION!) An oven-dried 13x100 mm test tube charged with 2 (10.1 mg, 0.0150 mmol) and (CuOTf)₂•C₆H₆ (3.0 mg, 0.0060 mmol), weighed out under a N₂ atmosphere in a glove box, was sealed with a septum and parafilm and removed from the glove box. Toluene (1.0 mL) was added followed by 2(5H)-furanone (4) (11.0 µL, 0.150 mmol) and benzaldehyde (29.0 µL, 0.300 mmol) to give an orange solution. The mixture was cooled to -30 °C and Et₂Zn (46.0 µL, 0.450 mmol) was added. The mixture was allowed to stir at -30 °C for 6 h at which time the reaction was quenched by addition of saturated aqueous NH₄Cl (1 mL) then H₂O (1 mL). The aqueous layer was washed with EtOAc (2 x 2 mL). The combined organic layers were passed through a short plug of silica gel with EtOAc and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (30% diethyl ether/hexanes) yielded 5a a clear oil (23.7 mg, 0.101 mmol, 67%).
(5a) 4-ethyl-3-hydroxy(phenyl)methyl)-dihydrofuran-2(3H)-one. 4:1 mixture of trans-erythro and trans-threo diastereomers, relative configuration not determined. IR (neat): 3461 (br m), 2969 (m), 2925 (w), 1764 (s), 1455 (m), 1394 (m), 1327 (w), 1178 (m), 1012 (s), 769 (w), 703 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz): \(\delta\) 7.37-7.26 (10H, m, major + minor), 5.36 (1H, br s, minor), 4.81 (1H, d, \(J = 8.4\) Hz, major), 4.38 (1H, t, \(J = 8.4\) Hz, minor), 4.28 (1H, t, \(J = 8.4\) Hz, major), 4.20 (1H, br s, major), 3.82 (1H, dd, \(J = 6.8, 8.8\) Hz, minor), 3.79 (1H, t, \(J = 8.8\) Hz, major), 2.77 (1H, br s, minor), 2.59 (1H, dd, \(J = 3.2, 7.6\) Hz, minor), 2.56-2.47 (2H, m, major + minor), 2.16 (1H, m, major), 1.16-0.97 (2H, m, minor), 0.98-0.77 (2H, m, major), 0.63 (3H, t, \(J = 7.2\) Hz, major), 0.59 (3H, t, \(J = 7.6\) Hz, minor); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 179.6 (major), 178.7 (minor), 141.3 (minor), 140.4 (major), 128.8 (major), 128.8 (major), 128.7 (minor), 128.0 (minor), 126.9 (major), 125.6 (minor), 74.9 (major), 72.8 (minor), 72.3 (major), 72.0 (minor), 53.2 (minor), 51.7 (major), 39.5 (major), 36.3 (minor), 26.5 (major), 25.2 (major), 11.0 (major + minor); HRMS Anal. Calcd for C\(_{13}\)H\(_{16}\)O\(_3\): 220.1099 Found: 220.1097.

(6a) Hydroxy(phenyl)methyl)-4-isopropyl-dihydrofuran-2(3H)-one. 4:1 mixture of trans-erythro and trans-threo diastereomers, relative configuration not determined. IR (neat): 3463 (br), 2958 (m), 2924 (w), 2872 (w), 1766 (s), 1490 (w), 1456 (w), 1393 (w), 1187 (m), 1049 (m), 992 (w), 911 (w), 768 (w), 705 (m), 676 (w) cm\(^{-1}\); \(^1\)H NMR (400 MHz): \(\delta\) 7.39-7.26 (10H, m, major + minor), 5.36 (1H, d, \(J = 2.8\) Hz, minor), 4.88 (1H, d, \(J = 7.6\) Hz, major), 4.27 (1H, t, \(J = 9.2\) Hz, minor), 4.07-3.94 (3H, m, major + minor), 3.73 (1H, br s, major), 2.71 (1H, t, \(J = 7.2\) Hz, major), 2.67 (1H, dd, \(J = 3.2, 5.2\) Hz, minor), 2.39-2.33 (1H, m, minor), 2.26-2.19 (1H, m, major), 1.43-1.34 (1H, m, minor), 1.26-1.14 (1H, m major), 0.71 (3H, d, \(J = 6.8\) Hz, major), 0.68 (3H, d, \(J = 6.8\) Hz, minor), 0.63 (3H, d, \(J = 6.8\) Hz, minor), 0.56 (3H, d, \(J = 6.8\) Hz, minor); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 179.2 (major), 179.1 (minor), 141.2 (major), 140.3 (major), 128.8 (major), 128.7 (minor), 128.7 (major), 128.0 (minor), 126.7 (major), 125.7 (minor), 74.6 (major), 73.3 (minor), 70.9 (minor), 69.1 (major), 50.7 (minor), 49.5 (major), 43.1 (major), 40.5 (minor), 30.2 (minor), 28.6 (major), 19.9 (major), 19.1 (minor), 18.2 (minor), 17.1 (major); HRMS Anal. Calcd for C\(_{14}\)H\(_{18}\)O\(_3\): 234.1256 Found: 234.1258.

(8a) 3-(hydroxy(phenyl)methyl)-4-methyl-tetrahydropyran-2-one. 1:1 mixture of trans-erythro and trans-threo diastereomers. IR (neat): 3427 (br s), 3072 (w), 3034 (w), 2957 (m), 2924 (m), 2875 (w),
2859 (w), 1717 (s), 1466 (m), 1400 (m), 1269 (m), 1231 (m), 1203 (m), 1089 (m), 1061 (m), 914 (w), 876 (w), 761 (w), 706 (s), 657 (w) cm⁻¹; ¹H NMR (400 MHz): δ 7.39-7.26 (10H, m), 5.25 (1H, dd, J = 3.6, 6.8 Hz), 4.94 (1H, t, J = 5.2 Hz), 4.31-4.25 (2H, m), 4.18-4.13 (1H, m), 4.04 (1H, td, J = 2.0, 10.4 Hz), 3.92 (1H, d, J = 4.8 Hz), 3.83 (1H, d, J = 6.4 Hz), 2.65 (1H, dd, J = 3.6, 8.4 Hz), 2.52 (1H, t, J = 6.4 Hz), 2.04-1.88 (3H, m), 1.83-1.76 (1H, m), 1.58-1.47 (2H, m), 0.82 (3H, d, J = 6.8 Hz), 0.76 (3H, d, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 174.1, 141.4, 141.3, 128.7, 128.6, 128.2, 128.1, 126.8, 126.5, 74.4, 73.7, 68.2, 66.8, 55.2, 54.6, 31.6, 31.1, 27.9, 27.2, 21.5, 21.3; HRMS Anal. Calcd for C₁₃H₁₆O₃: 220.1099 Found: 220.1099.

(9a) 4-ethyl-3-(hydroxy(phenyl)methyl)-tetrahydropyran-2-one. 1.6:1 mixture of trans-erythro and trans-threo diastereomers, relative configuration not determined. IR (neat): 3427 (br, s), 3056 (w), 3024 (w), 2968 (s), 2905 (m), 2855 (m), 1703 (s), 1451 (m), 1432 (m), 1269 (s), 1237 (m), 1203 (m), 1089 (m), 1061 (m), 765 (w), 702 (s) cm⁻¹; ¹H NMR (400 MHz): δ 7.39-7.27 (10H, major + minor), 5.24 (1H, dd, J = 3.6, 6.8 Hz, major), 4.93 (1H, dd, J = 4.8, 6.0 Hz, minor), 4.30-4.24 (2H, m, major + minor), 4.16 (1H, ddd, J = 4.0, 6.4, 11.2 Hz, minor), 3.99 (1H, ddd, J = 2.4, 10.0, 11.2 Hz, major), 3.80 (1H, d, J = 4.8 Hz, minor), 3.71 (1H, d, J = 6.8 Hz, major), 2.71 (1H, dd, J = 3.6, 7.2 Hz, major), 2.61 (1H, t, J = 6.4 Hz, minor), 1.95-1.75 (4H, m, major + minor), 1.61-1.40 (2H, m, minor), 1.27-1.15 (2H, m, minor), 1.14-1.03 (2H, m, major), 0.75 (3H, t, J = 7.2 Hz, minor), 0.74 (3H, d, J = 7.2 Hz, major); ¹³C NMR (100 MHz, CDCl₃) δ 174.0 (major), 174.0 (minor), 141.2 (major), 141.1 (minor), 128.5 (major), 128.4 (major), 128.0 (minor), 127.9 (minor), 126.3 (major), 74.3 (minor), 74.1 (major), 67.9 (major), 66.7 (minor), 53.3 (major), 52.8 (minor), 34.1 (minor), 33.3 (major), 27.7 (major), 27.7 (major), 27.4 (minor), 27.1 (minor), 11.0 (minor), 10.8 (major); HRMS Anal. Calcd for C₁₄H₁₈O₃Na (M+Na⁺): 257.1154 Found: 257.1152.

(11a) 3-(hydroxy(phenyl)methyl)-4-(4-methylpentyl)-tetrahydropyran-2-one. 1:1 mixture of trans-erythro and trans-threo diastereomers, relative configuration not determined. IR (neat): 3427 (br, m), 3056 (w), 3031 (w), 2962 (s), 2911 (s), 2861 (m), 1703 (s), 1470 (s), 1406 (s), 1269 (s), 1231 (m), 1212 (m), 1092 (m), 1055 (m), 765 (w), 708 (s), 664 (m), 564 (w) cm⁻¹; ¹H NMR (400 MHz): δ 7.37-7.24 (10H, m), 5.25 (1H, dd, J = 3.6, 6.0 Hz). 4.90 (1H, dd, J = 4.0, 6.0 Hz), 4.26-4.21 (2H, m), 4.14-4.08 (1H, m), 4.03 (1H, t, J = 9.6 Hz), 3.95-3.94 (1H, m), 3.80-3.77 (1H, m), 2.64 (1H, t, J =
3.2 Hz), 2.57 (1H, t, J = 6.4 Hz), 1.95-1.72 (4H, m), 1.54-1.29 (5H, m), 1.20-1.04 (4H, m), 1.02-0.82 (7H, m), 0.78-0.75 (12H m); ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 174.0, 141.2, 141.1, 128.3, 128.3, 127.9, 127.7, 126.6, 126.1, 74.3, 74.0, 67.8, 66.7, 53.7, 53.1, 38.5, 38.5, 35.4, 35.0, 34.0, 32.4, 31.3, 28.2, 27.6, 27.6, 27.5, 24.2, 24.0, 22.5, 22.5, 22.3, 22.3; HRMS Anal. Calcd for C₁₈H₂₆O₃Na (M+Na⁺) : 313.1780 Found: 313.1788.

(10a) 3-(hydroxy(phenyl)methyl)-4-isopropyl-tetrahydropyran-2-one. 1:1 mixture of trans-erythro and trans-threo diastereomers, relative configuration not determined. IR (neat): 3423 (br s), 2964 (s), 2924 (m), 2872 (w), 1714 (s), 1468 (w), 1410 (w), 1273 (s), 1209 (m), 1078 (m), 1055 (m), 774 (m), 705 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.39-7.26 (10H, m), 5.15 (1H, br s), 4.95 (1H, d, J = 5.6 Hz), 4.27-4.21 (2H, m), 4.18-4.13 (1H, m), 3.91 (1H, br s), 3.86 (1H, dt, J = 2.4, 11.2 Hz), 3.46 (1H, br s), 2.89-2.82 (2H, m), 1.91-1.74 (3H, m), 1.73-1.48 (4H, m), 1.34-1.27 (1H, m), 0.82 (3H, d, J = 6.8 Hz), 0.81 (3H, d, J = 6.8 Hz), 0.79 (3H, d, J = 6.8 Hz), 0.78 (3H, d, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 173.7, 141.6, 141.2, 128.6, 128.5, 128.1, 128.1, 126.6, 126.5, 74.8, 74.6, 68.2, 67.4, 51.8, 51.4, 38.7, 37.9, 30.1, 30.0, 23.4, 23.2, 20.7, 20.7, 16.9, 16.8; Calcd for C₁₅H₂₀O₃: 248.1412 Found: 248.1418.

(13a) 5-(hydroxy(phenyl)methyl)-4-methyl-4,5-dihydrobenzo[b]oxepin-2(3H)-one. Major diastereomer, relative configuration not determined. IR (neat): 3512 (bs s), 3070 (w), 3030 (w), 2973 (w), 2928 (w), 1747 (s), 1617 (w), 1577 (w), 1492 (m), 1458 (m), 1362 (m), 1237 (m), 1140 (s), 1118 (s), 998 (w), 703 (w) cm⁻¹; ¹H NMR (400 MHz): δ 7.32-7.15 (8H, m), 7.00 (1H, d, J = 7.6 Hz), 4.78 (1H, dd, J = 2.8, 10.8 Hz), 4.32 (1H, d, J = 10.8 Hz), 3.17 (1H, dd, J = 6.4, 14.0 Hz), 3.01-2.92 (1H, m), 2.48 (1H, dd, J = 3.2, 10.0 Hz), 2.43 (1H, dd, J = 1.2, 14.0 Hz), 1.01 (3H, d, J = 6.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 173.8, 150.6, 142.5, 131.1, 128.8, 128.5, 127.8, 127.5, 125.8, 125.6, 119.1, 71.6, 54.1, 36.2, 35.9, 17.9; Calcd for C₁₈H₂₁O₃: 282.1255 Found: 282.1263.

(14a) 4-ethyl-5-(hydroxy(phenyl)methyl)-4,5-dihydrobenzo[b]oxepin-2(3H)-one. Major diastereomer, relative configuration not determined. IR (neat): 3511 (bs s), 3061 (w), 3028 (w), 2973 (w), 2923 (w), 2867 (w), 1750 (s), 1489 (m), 1456 (m), 1362 (w), 1223 (s), 1134 (s), 1112 (s), 1000 (w), 700 (w), 673 (w) cm⁻¹; ¹H NMR (400 MHz): δ 7.31-7.10 (8H, m), 7.00 (1H, d, J = 7.6 Hz), 4.78 (1H, d, J = 8.0 Hz), 4.34 (1H, d, J = 10.8 Hz), 2.96 (1H, dd, J = 6.4, 14.4 Hz), 2.73 (1H, dd, J =
2.0, 14.4 Hz), 2.68-2.61 (1H, m), 2.56 (1H, dd, \( J = 3.2, 10.0 \) Hz), 1.56-1.48 (1H, m), 1.21-1.10 (1H, m), 1.02 (3H, t, \( J = 7.2 \) Hz); \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 173.8, 150.7, 142.7, 130.9, 128.8, 128.6, 128.2, 127.5, 125.9, 125.7, 119.1, 71.4, 53.7, 42.7, 31.4, 23.5, 11.9; Calcd for C\(_{19}\)H\(_{20}\)O\(_3\): 296.1412 Found: 296.1409.
Representative experimental procedure for oxidation with PCC:
Alcohol 5a (24.0 mg, 0.109 mmol) dissolved in undistilled CH\textsubscript{2}Cl\textsubscript{2} (4 mL), was added to a 10 mL round bottom flask charged with PCC (45.6 mg, 0.212 mmol), NaOAc (17.3 mg, 0.212 mmol), oven dried powdered 4 Å MS (10 mg) and Celite (~18 mg). The mixture was allowed to stir for 3 h, at which time Et\textsubscript{2}O (~6 mL) was added and the mixture was flushed through Celite layered on top of silica gel eluting with Et\textsubscript{2}O. Removal of solvent \textit{in vacuo} and exposure to high vacuum (~2.0 mmHg) for 1 h, to removed acetic acid, yielded pure 5b as a clear oil (22.7 mg, 0.104 mmol, 98%).

(5b) 3-Benzoyl-4-ethyl-dihydrofuran-2(3\textsubscript{H})-one. \textit{IR} (neat): 2967 (w), 2923 (w), 2879 (w), 1778 (s), 1677 (s), 1602 (m), 1457 (m), 1274 (m), 1230 (m), 1155 (s), 1016(m), 859 (m), 777 (w), 689 (m) cm\textsuperscript{-1}; \textit{\textsuperscript{1}H NMR} (400 MHz): δ 8.04 (2H, dd, \textit{J} = 0.8, 8.4 Hz), 7.61 (1H, tt, \textit{J} = 0.8, 6.8 Hz), 7.52-7.47 (2H, m), 4.58 (1H, dd, \textit{J} = 7.6, 8.8 Hz), 4.24 (1H, d, \textit{J} = 6.8 Hz), 4.04 (1H, dd, \textit{J} = 6.4, 8.8 Hz), 3.16-3.07 (1H, m), 1.62 -1.54 (2H, m), 0.92 (3H, t, \textit{J} = 7.6 Hz); \textit{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) δ 193.4, 172.9, 135.9, 134.2, 129.6, 129.0, 72.4, 54.5, 41.0, 25.9, 11.8; Anal. Calcd. for C\textsubscript{13}H\textsubscript{14}O\textsubscript{3}: C, 71.54; H, 6.47; Found: C, 71.38; H, 6.79; [\ensuremath{\alpha}]\textsubscript{D}\textsuperscript{20} –124.48° (c 0.853, CHCl\textsubscript{3}) for an optically enriched sample of 97% ee.

The optical purity of the conjugate addition was established by chiral HPLC analysis (Chiralpak AS, 78:22 hexanes/iPrOH, \textit{t}_{\text{minor}} = 11 min, \textit{t}_{\text{major}} = 16 min).

(6b) (3R,4S)-3-Benzoyl-4-isopropyl-dihydrofuran-2(3\textsubscript{H})-one. \textit{IR} (neat): 2961 (m), 2925 (w), 2889 (w), 1762 (s), 1690 (s), 1606 (w), 1576 (w), 1444 (w), 1228 (w), 1168 (s), 1024 (m), 688 (w) cm\textsuperscript{-1}; \textit{\textsuperscript{1}H NMR} (400 MHz): δ 8.04 (2H, d, \textit{J} = 8.4 Hz), 7.61 (1H, t, \textit{J} = 6.8 Hz), 7.50 (2H, d, \textit{J} = 8.4 Hz), 4.56 (1H, dd, \textit{J} = 8.0, 8.0 Hz), 4.33 (1H, d, \textit{J} = 8.0 Hz), 4.09 (1H, dd, \textit{J} = 8.0, 8.0 Hz), 3.09 (1H, \textit{q}, \textit{J} = 8.0 Hz), 1.78-1.70 (1H, m), 0.93 (3H, d, \textit{J} = 6.8 Hz), 0.84 (3H, d, \textit{J} = 6.8 Hz); \textit{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) δ 193.6, 173.1, 136.0, 134.1, 129.5, 128.9, 71.1, 52.7, 45.8, 31.6, 20.9, 19.8; Anal. Calcd for C\textsubscript{14}H\textsubscript{16}O\textsubscript{3}: C, 72.39; H, 6.94; Found: C, 72.06; H, 7.08; [\ensuremath{\alpha}]\textsubscript{D}\textsuperscript{20} –87.331° (c 1.353, CHCl\textsubscript{3}) for an optically enriched sample of 89% ee.

The optical purity of the conjugate addition was established by chiral HPLC analysis (Chiralpak AS, 80:20 hexanes/iPrOH, \textit{t}_{\text{minor}} = 9 min, \textit{t}_{\text{major}} = 14 min).
(8b) 3-Benzoyl-4-methyl-tetrahydropyran-2-one. IR (neat): 2961 (m), 2923 (m), 1740 (s), 1721 (s), 1696 (s), 1558 (m), 1262 (m), 1199 (m), 695 (m), 670 (m) cm⁻¹; ¹H NMR (400 MHz): δ 7.99-7.96 (2H, m), 7.58 (1H, tt, J = 1.2, 6.4 Hz), 7.50-7.46 (2H, m), 4.48-4.44 (2H, m), 4.15 (1H, d, J = 9.2 Hz), 2.71-2.63 (1H, m), 2.09-2.02 (1H, m), 1.75-1.65 (1H, m), 1.03 (3H, d, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 196.2, 168.3, 137.0, 133.9, 129.2, 128.9, 68.9, 56.7, 30.5, 30.2, 20.8; HRMS Anal. Calcd for C₁₃H₁₄O₃Na (M+Na⁺): 241.0845 Found: 241.0841; [α]D²⁰ –76.671° (c 0.226, CHCl₃) for an optically enriched sample of >98% ee.

The optical purity of the conjugate addition was established by chiral HPLC analysis (Chiralpak AS, 78:22 hexanes:iPrOH). Chromatograms are illustrated below:

(9b) (3R,4R)-3-Benzoyl-4-ethyl-tetrahydropyran-2-one. IR (neat): 3427 (br, w), 3075 (m), 2962 (s), 2930 (s), 2880 (s), 1734 (s), 1678 (s), 1596 (m), 1451 (m), 1413 (m), 1294 (m), 1262 (w), 1199 (w), 1073 (w), 998 (m), 935 (m), 778 (m), 696 (s) cm⁻¹; ¹H NMR (400 MHz): δ 8.02-7.88 (2H, m), 7.59 (1H, tt, J = 2.0, 7.6 Hz), 7.51-7.47 (2H, m), 4.48-4.45 (2H, m), 4.28, (1H, d, J = 8.4 Hz), 2.58-2.49 (1H, m), 2.17-2.10 (1H, m), 1.72-1.62 (1H, m), 1.49-1.41 (1H, m), 1.40-1.29 (1H, m), 0.89 (3H, t, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 196.1, 168.3, 136.6, 133.7, 129.1, 128.8, 68.5, 55.0, 36.5, 28.0, 27.1, 11.1; HRMS Calcd for C₁₄H₁₆O₃Na (M+Na⁺): 255.0994, Found: 255.0997; [α]D²⁰ –58.810° (c 1.05, CHCl₃) for an optically enriched sample of 93% ee.

The optical purity of the conjugate addition was established by chiral HPLC analysis (Chiralpak AS, 95:5 hexanes:iPrOH, t_minor = 50 min, t_major = 75 min).
(11b) 3-Benzoyl-4-(4-methylpentyl)-tetrahydropyran-2-one. IR (neat): 3522 (br, w) 3062 (w), 2955 (s), 2917 (s), 2867 (s), 1734 (s), 1678 (s), 1596 (w), 1476 (m), 1445 (s), 1413 (m), 1269 (m), 1193 (w), 1070 (m), 998 (m), 948 (m), 771 (s), 696 (s), 595 (w), 513 (w) cm\(^{-1}\); \(^1\)H NMR (400 MHz): \(\delta\) 8.05-7.98 (2H, m), 7.58 (1H, tt, \(J = 1.2, 7.6\) Hz), 7.50-7.46 (2H, m), 4.47-4.43 (2H, m), 4.26 (1H, d, \(J = 8.4\) Hz), 2.64-2.54 (1H, m), 2.16-2.09 (1H, m), 1.71-1.61 (1H, m), 1.47-1.37 (1H, m), 1.36-1.15 (4H, m), 1.05-1.04 (2H, m), 0.78 (3H, t, \(J = 3.2\) Hz), 0.77 (3H, t, \(J = 3.6\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 196.2, 186.2, 136.6, 133.7, 129.0, 128.7, 68.5, 55.3, 38.6, 35.5, 35.0, 27.7, 27.6, 24.3, 22.5, 22.3; Anal. Calcd for C\(_{18}\)H\(_{24}\)O\(_3\): C, 74.97; H, 8.39; Found: C, 74.96; H, 8.16; \([\alpha]_D^{20}\) = -56.5706° (c 1.017, CHCl\(_3\)) for an optically enriched sample of 94% ee.

The optical purity of the conjugate addition was established by chiral HPLC analysis (Chiralpak AS, 95:5 hexanes:iPrOH, \(t_{\text{minor}} = 38\) min, \(t_{\text{major}} = 48\) min).

(10b) 3-Benzoyl-4-isopropyl-tetrahydropyran-2-one. IR (neat): 2967 (m), 2919 (w), 2883 (s), 1744 (s), 1678 (s), 1606 (w), 1450 (m), 1294 (m), 1276 (m), 1198 (s), 1150 (m), 1078 (m), 946 (w) cm\(^{-1}\); \(^1\)H NMR (400 MHz): \(\delta\) 8.02 (2H, dd, \(J = 0.8, 8.4\) Hz), 7.58 (1H, tt, \(J = 0.8, 7.2\) Hz), 7.49-7.45 (2H, m), 4.47-4.38 (3H, m), 2.56 (1H, dddd, \(J = 5.6, 6.4, 13.6\) Hz), 1.99 (1H, dddd, \(J = 3.6, 6.0, 7.6, 13.6\) Hz), 1.77-1.67 (1H, m), 1.67-1.55 (1H, m), 0.86 (6H, d, \(J = 6.8\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 196.5, 168.8, 136.6, 133.9, 129.4, 129.0, 68.8, 53.3, 41.0, 31.2, 24.4, 20.5, 18.1; Anal. Calcd for C\(_{15}\)H\(_{18}\)O\(_3\): C, 73.15; H, 7.37; Found: C, 72.96; H, 7.47; \([\alpha]_D^{20}\) = -45.5203° (c 1.227, CHCl\(_3\)) for an optically enriched sample of 90% ee.

The optical purity of the conjugate addition was established by chiral HPLC analysis (Chiralpak AS, 80:20 hexanes:iPrOH). Chromatograms are illustrated below:
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### 3-Benzoyl-4-methyl-4,5-dihydro-3H-benzo[b]oxepin-2-one

IR (neat): 2961 (w), 2963 (w), 1759 (s), 1696 (w), 1482 (w), 1451 (w), 1130 (m), 1111 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.73-7.70 (2H, m), 7.52 (1H, dt, $J = 1.3$, 7.3 Hz), 7.43-7.38 (2H, m), 7.36-7.32 (1H, m), 7.24-7.20 (2H, m), 7.17 (1H, d, $J = 2.5$ Hz), 3.92 (1H, d, $J = 9.3$ Hz), 3.39-3.32 (1H, m), 3.21 (1H, dd, $J = 6.7$, 13.9 Hz) 2.46 (1H, dd, $J = 2.2$, 13.9 Hz), 0.96 (3H, d, $J = 6.6$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 192.1, 168.7, 151.1, 136.3, 133.8, 131.3, 129.0, 129.0, 128.6, 128.3, 126.4, 119.4, 56.2, 35.5, 35.3, 19.1; HRMS Calcd for C$_{18}$H$_{16}$O$_3$Na (M+Na$^+$): 303.0997, Found: 303.0989; [$\alpha$]$^{20}_{D}$ $+31.174^\circ$ (c 1.180, CHCl$_3$ for an optically enriched sample of 96% ee.

The optical purity of the conjugate addition was established by chiral HPLC analysis (Chiralpak AS, 98:2 hexanes:iPrOH) Chromatograms are illustrated below:

![Chromatogram 1](image1)

![Chromatogram 2](image2)

### 3-Benzoyl-4-ethyl-4,5-dihydro-3H-benzo[b]oxepin-2-one

IR (neat): 2962 (w), 2923 (w), 1753 (s), 1696 (s), 1482 (m), 1451 (m), 1218 (m), 1130 (m), 1111 (m), 758 (w), 689 (w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.73-7.71 (2H, m), 7.52 (1H, dt, $J = 1.3$, 7.5 Hz), 7.42-7.38 (2H, m), 7.33-7.28 (1H, m), 7.21-7.19 (2H, m), 7.11 (1H, d, $J = 7.9$ Hz), 3.99 (1H, d, $J = 8.6$ Hz), 3.15-3.05 (1H, m), 3.04 (1H, dd, $J = 6.4$, 13.9 Hz), 2.69 (1H, dd, $J = 2.7$, 13.9 Hz), 1.31-1.15 (2H, m), 0.98 (3H, t, $J = 7.3$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 192.2, 168.7, 150.9, 136.4, 133.7, 131.1, 129.0, 129.0, 128.8, 128.2, 126.3, 119.4, 55.8, 42.2, 31.2, 25.5, 12.1; HRMS Calcd for C$_{19}$H$_{18}$O$_3$Na (M+Na$^+$):
317.1154, Found: 317.1160; $[\alpha]_D^{20} +12.4987^\circ$ (c 1.493, CHCl$_3$) for an optically enriched sample of 93% ee.

The optical purity of the conjugate addition was established by chiral HPLC analysis (Chiralpak AS, 98.5:1.5 hexanes:iPrOH, $t_{\text{minor}} = 16$ min, $t_{\text{major}} = 19$ min).

The results of Cu-catalyzed ACA with various chiral phosphanes (1-3) and different substrate/alkylzinc combinations are summarized below. Optimal combinations are illustrated in bold.
Table S1. Three-Component Cu-Catalyzed Enantioselective Conjugate Addition of Dialkylzincs Reagent to Unsaturated Lactonesa

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>alkyl2Zn</th>
<th>product</th>
<th>chiral ligand</th>
<th>Ligand: Cu salt (mol %)</th>
<th>time (h)</th>
<th>Yield (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me2Zn</td>
<td>1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>n.rd</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>Et2Zn</td>
<td>3</td>
<td>20:8</td>
<td>48</td>
<td>10</td>
<td>n.de</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>Et2Zn</td>
<td>1</td>
<td>10:4</td>
<td>48</td>
<td>58</td>
<td>97</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>Et2Zn</td>
<td>2</td>
<td>10:4</td>
<td>48</td>
<td>67</td>
<td>97</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr2Zn</td>
<td>2</td>
<td>10:4</td>
<td>48</td>
<td>90</td>
<td>93</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>i-Pr2Zn</td>
<td>1</td>
<td>10:4</td>
<td>48</td>
<td>85</td>
<td>91</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

| 7     | Me2Zn     | 1        | 10:4    | 48           | 40f                    | >98      |            |        |
| 8     | Et2Zn     | 1        | 2.4:1   | 6            | 91                     | 98       |            |        |
| 9     | Et2Zn     | 3        | 2.4:1   | 6            | 90                     | 96       |            |        |
| 10    | i-Pr2Zn   | 1        | 2.4:1   | 12           | 93                     | 84       |            |        |
| 11    | i-Pr2Zn   | 2        | 2.4:1   | 12           | 91                     | 90       |            |        |
| 12    |            | 3        | 2.4:1   | 12           | 78                     | 96       |            |        |

| 13    | Me2Zn     | 3        | 10:4    | 12           | <2                     | --       |            |        |
| 14    | Me2Zn     | 1        | 10:4    | 12           | 66                     | 98       |            |        |
| 15    | Et2Zn     | 1        | 10:4    | 6            | 75                     | 89       |            |        |
| 16    | Et2Zn     | 3        | 10:4    | 6            | 84                     | 94       |            |        |

a 3 equiv Et2Zn, N2 atm  b Isolated yield of ACA product. Products from entries 1-12 are isolated as a mixture of trans-erythro and trans-threo in ratios of not greater than 4:1. Relative configuration not determined. Oxidation proceeds in >85% yield for all substrates. c Determined by Chiral HPLC (Chiralpak AS). d no reaction e not determined. f -15 °C, 67% conv.
Representative experimental procedure for retroaldol fragmentation with $\text{K}_2\text{CO}_3$: The conjugate addition adduct 9a (23.6 mg, 0.100 mmol) dissolved in undistilled toluene (2.0 mL) was added to a 10 mL round bottom flask charged with $\text{K}_2\text{CO}_3$ (15.3 mg, 0.110 mmol) and equipped with a reflux condenser. The mixture was allowed to stir at 120 °C for 1h at which time it was cooled to 22 °C and passed through a short plug of silica gel eluting with EtOAc. The filtrate was then concentrated in vacuo. Purification by silica gel chromatography (25% diethyl ether/hexanes) yielded 16 as a clear oil (12.3 mg, 0.0960 mmol, 96%) (15) (R)-4-Isopropyl-dihydrofuran-2(3H)-one. IR (neat): 2974 (m), 2930 (s), 2854 (w), 1784 (s), 1476 (w), 1180 (m), 1029 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.39 (1H, dd, $J = 7.6$, 8.8 Hz), 3.94 (1H, dd, $J = 8.8$, 8.8 Hz), 2.55 (1H, dd, $J = 8.0$, 16.8 Hz), 2.33-2.17 (2H, m), 1.67-1.55 (1H, m), 0.94 (3H, d, $J = 6.8$ Hz), 0.89 (3H, d, $J = 6.8$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 177.5, 72.2, 42.9, 33.1, 31.9, 20.8, 20.1; Anal. Calcd for C$_7$H$_{12}$O$_2$: C, 65.60; H, 9.44; Found: C, 65.37; H, 9.49; $[\alpha]_D^{20} +10.2756^\circ$ (c 0.240, CHCl$_3$) for an optically enriched sample of 89% ee. Proof of Stereochemistry: literature: $^4$ $[\alpha]_D^{20} -11^\circ$ (c 0.52, CHCl$_3$) for 96% ee in the S enantiomer.

The optical purity of the conjugate addition was established by chiral GLC analysis (Chiraldex GTA, 15 psi, 100 °C). Chromatograms are illustrated below:

Table S2. Optimization of the Retroaldol Transformation

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>solvent</th>
<th>temp. ($^\circ$C)</th>
<th>base</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>PhMe</td>
<td>120$^a$</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>PhMe</td>
<td>--</td>
<td>n.r.$^b$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>PhMe</td>
<td>120$^a$</td>
<td>DBU</td>
<td>dec.$^c$</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>THF</td>
<td>50</td>
<td>NaH</td>
<td>dec.$^c$</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>MeOH/H$_2$O$^d$</td>
<td>40</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>dec.$^c$</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>PhMe$^e$</td>
<td>120</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>PhMe$^e$</td>
<td>120$^a$</td>
<td>$\text{K}_2\text{CO}_3$</td>
<td>96</td>
</tr>
</tbody>
</table>

$^a$ no reaction at lower temperatures $^b$ no reaction $^c$ decompostion $^d$ 1:1 $^e$ undistilled toluene
(16) \((R)-4\text{-Ethyl-tetrahydropyran-2-one}\). IR (neat): 2962 (m), 2924 (m), 2874 (w), 1737 (s), 1462 (w), 1412 (w), 1262 (m), 1231 (m), 1175 (w), 1106 (m), 1081 (m) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 4.41-4.36 (1\text{H, m}), 4.26-4.19 (1\text{H, m}), 2.67 (1\text{H, ddd, } J = 1.6, 6.0, 17.6 \text{ Hz}), 2.12 (1\text{H, dd, } J = 10.4, 17.6 \text{ Hz}), 1.97-1.81 (2\text{H, m}), 1.54-1.44 (1\text{H, m}), 1.37 (2\text{H, dddd, } J = 7.2, 7.2, 7.2, 14.4 \text{ Hz}), 0.92 (3\text{H, t, } J = 7.6 \text{ Hz}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 171.7, 68.7, 36.5, 33.3, 29.1, 28.7, 11.1\); HRMS Calcd for C\(_7\)H\(_{12}\)O\(_2\)Na (M+Na\(^+\)): 151.0735, Found: 151.0733; \([\alpha]\)\(_D\)\(^{20}\) +21.994° (c 0.51, CHCl\(_3\)) for an optically enriched sample of 98% ee. **Proof of Stereochemistry:** literature: \(^5\) (-) value was assigned to the S enantiomer, but the exact value was not provided.

The optical purity of the conjugate addition was established by chiral GLC analysis (\(\beta\)-Dex, 15 psi, 110 °C). Chromatograms are illustrated below:
Experimental Procedures for the Preparation of 2H-pyran-3(6H)-one (17):

\[ A \xrightarrow{1) \text{MeOH, 65 \degree C}} B \xrightarrow{2) \text{CH}_2\text{Cl}_2, 45 \degree C} 17 \]

A 250 mL RBF equipped with a reflux condenser was charged with dibutyltinoxide (3.22 g, 13.0 mmol). Reagent grade MeOH (100 mL) followed by 3,4-dihydroxy-1-butene (A) (1.09 mL, 13.0 mmol) were added and the reaction allowed to reflux for 1 h (Reaction becomes homogeneous). The volatiles were removed and CH\(_2\)Cl\(_2\) (100 mL) followed by allyl bromide (1.18 mL, 14.0 mmol) were added. The solution was allowed to reflux for 72 h at which time silica gel was added. The volatiles were removed in vacuo and the resulting solid was purified by silica gel chromatography (30% ether/pentane) to yield B as a pale yellow oil (0.62 g, 4.84 mmol, 37%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_{1} 5.93-5.77 (2H, m), 5.35-5.15 (4H, m), 4.34-4.26 (1H, m), 4.01 (2H, d, J = 5.6 Hz), 3.50-3.47 (1H, m), 3.33-3.29 (1H, m), 2.54 (1H, d, J = 2.8 Hz).

To a 250 mL round bottom flask charged with Ru-catalyst C (15.2 mg, 0.024 mmol), was added CH\(_2\)Cl\(_2\) (100 mL). To this green solution, diene B (312.0 mg, 2.43 mmol) was added neat and the reaction allowed to stir for 2 h at rt. Once complete, ethylvinyl ether (~2mL) was added to decompose C. Volatiles were removed and the crude reaction was purified by silica gel chromatography (50% ether/pentane) to afford D as a clear oil (244 mg, 2.43 mmol, >98%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta_{1} 5.99-5.89 (2H, m), 4.17-3.71 (5H, m), 1.83 (1H, d, J = 9.6 Hz).
To a 50 mL round bottom flask charged with tetrapropylammonium perruthenate (TPAP) (68.0 mg, 0.193 mmol), 4-methylmorpholine N-oxide (NMO) (1.50 g, 12.8 mmol), and powdered 4Å MS (~1 g) was added CH₂Cl₂ (20 mL). Alcohol D (390 mg, 3.90 mmol) was added neat and the reaction allowed to stir at 22 °C. Once complete by TLC analysis (~7h) the reaction was purified directly by silica gel chromatography to afford 17 as an unstable clear oil (265 mg, 2.70 mmol, 69%). ¹H NMR (400 MHz, CDCl₃) δ 7.11 (1H, tt, J = 3.2, 10.4 Hz), 6.19 (1H, tt, J = 2.0, 10.4 Hz), 4.38-4.37 (2H, m), 4.18 (2H, s).

Representative experimental procedure for Cu-catalyzed conjugate addition of dialkylzincs to 2H-6H-pyran-3-one (17): (CAUTION: Me₂Zn IS PYROPHORIC! USE EXTREME CAUTION!) An oven-dried 13x100 mm test tube charged with 1 (4.4 mg, 0.0074 mmol) and (CuOTf)₂•C₆H₆ (1.5 mg, 0.0029 mmol), weighed out under a N₂ atmosphere in a glove box, was sealed with a septum and removed from the glove box. 2H-6H-pyran-3-one (17) (14.7 mg, 0.150 mmol) dissolved in THF (1.0 mL) was added, the reaction was cooled to –30 °C and Me₂Zn (31.0 µL, 0.450 mmol) was added. The reaction was allowed to stir at –30 °C for 6 h at which time the reaction was quenched by addition of a saturated solution of aqueous NH₄Cl (2 mL) then H₂O (2 mL). The aqueous layer was washed with Et₂O (2 x 4 mL). The combined organic layers were passed through a short plug of silica gel with Et₂O and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (15% diethyl ether/pentane) yielded 19 as a clear oil (10.0 mg, 0.087 mmol, 58%).

(19) 5-methyl-dihydro-2H-pyran-3(4H)-one. IR (neat): 2949 (m), 2921 (s), 2847 (m), 1733 (m), 1716 (m), 1458 (m), 1372 (w), 1245 (w), 1106 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.04-3.86 (3H, m), 3.36 (1H, dd, J = 8.8, 11.2 Hz), 2.61 (1H, ddt, J = 1.6, 5.2, 16.0 Hz), 2.35-2.30 (1H, m), 2.11 (1H, dd, J = 9.6, 16.0 Hz), 0.99 (3H, d, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 207.5, 74.5, 72.4, 46.2, 31.7, 17.7; HRMS Calcd for C₆H₁₀O₂: 114.0681, Found: 114.0683; [α]₀° +8.482° (c 0.667, CDCl₃) for an optically enriched sample of >98% ee.

The optical purity of the conjugate addition was established by chiral GLC analysis (α-Dex, 15 psi, 70 °C). Chromatograms are illustrated below:
The optical purity of the conjugate addition was established by chiral GLC analysis (α-Dex, 15 psi, 70 °C). Chromatograms are illustrated below:
For representative Cu-catalyzed conjugate addition experimental procedure, please see Page 2 of the Supporting Information:

(21a) 5-ethyl-4-(hydroxy(phenyl)methyl)-2,2-dimethyl-dihydrofuran-3(2H)-one. >30:1 mixture of trans-erythro and trans-threo diastereomers, relative configuration not determined. IR (neat): 3461 (br, s), 3067 (w), 3039 (m), 2984 (m), 2939 (m), 2878 (m), 1756 (s), 1506 (w), 1462 (m), 1384 (m), 1339 (w), 1234 (m), 1195 (m), 1117 (m), 1050 (m), 995 (m), 712 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.26 (5H, m), 4.84 (1H, d, J = 8.0 Hz), 3.93 (1H, br s), 3.83-3.78 (1H, m), 2.56 (1H, dd, J = 7.6, 9.6 Hz), 1.28 (3H, s), 1.21-1.10 (1H, m), 1.14 (3H, s), 1.08-0.97 (1H, m), 0.78 (3H, t, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 221.4, 140.5, 128.7, 128.6, 126.7, 80.4, 75.9, 74.0, 56.4, 27.0, 24.6, 22.1, 8.9; HRMS Calcd for C₁₅H₂₀O₃: 248.1412 Found: 248.1414.

(23a) 2-ethyl-3-(hydroxy(phenyl)methyl)-2,3-dihydrochromen-4-one. 9:1 mixture of trans-erythro and trans-threo diastereomers. Major diastereomer: IR (neat): 3445 (bs, s), 3064 (w), 3042 (w), 2933 (w), 2884 (w), 1688 (s), 1612 (s), 1465 (s), 1323 (s), 1215 (m), 1144 (w), 1111 (w), 1035 (w), 1002 (w), 774 (m), 703 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.79 (1H, dd, J = 1.6, 7.6 Hz), 7.52-7.23 (6H, m), 7.02-6.94 (2H, m), 4.97 (1H, d, J = 8.8 Hz), 4.05-4.01 (1H, m), 2.71 (1H, dd, J = 2.4, 9.2 Hz), 1.84-1.72 (1H, m), 1.49-1.39 (1H, m), 0.83 (3H, s), 1.08-0.97 (1H, m), 0.78 (3H, t, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 193.9, 159.2, 141.2, 136.8, 128.9, 128.6, 127.4, 121.5, 118.4, 79.9, 74.0, 56.4, 27.0, 24.9, 10.0; HRMS Calcd for C₁₈H₁₈O₃: 282.1255 Found: 282.1265.

(24a) 3-(hydroxy(phenyl)methyl)-2-isopropyl-2,3-dihydrochromen-4-one. 9:1 mixture of trans-erythro and trans-threo diastereomers. Relative configuration not determined. Major diastereomer: IR (neat): 3454 (br, s), 3064 (w), 2933 (w), 2884 (w), 1688 (s), 1612 (s), 1465 (s), 1323 (s), 1215 (m), 1144 (w), 1111 (w), 1035 (w), 1002 (w), 774 (m), 703 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.89 (1H, dd, J = 2.0, 8.0 Hz), 7.52-7.21 (6H, m), 7.00 (1H, td, J = 0.8, 8.0 Hz), 6.95 (1H, d, J = 8.8 Hz), 4.96 (1H, d, J = 9.2 Hz), 3.63 (1H, dd, J = 2.0, 9.6 Hz), 2.93 (1H, dd, J = 2.0, 8.8 Hz), 2.57 (1H, br s), 2.04-1.92 (1H, m), 0.85 (3H, s), 0.73 (3H, d, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 193.9, 159.4, 141.2, 136.8, 129.0, 128.7, 127.4, 127.0, 121.4, 120.7, 118.3, 84.2, 73.5, 56.1, 28.7, 19.1, 18.5; HRMS Calcd for C₁₉H₂₃O₃: 296.1412 Found: 296.1413.
For representative retroaldol fragmentation experimental procedure, please see Page 11 of the Supporting Information:

(21b) 5-Ethyl-2,2-dimethyl-dihydrofuran-3(2H)-one.

(Note: The general procedure for retroaldol fragmentation stated above is followed except the reaction is performed in a sealed tube due to product volatility.) IR (neat): 2970 (m), 2926 (m), 2873 (w), 1763 (s), 1734 (w), 1627 (w), 1457 (w), 1379 (w), 1184 (m), 1116 (m), 1014 (w), 985 (w), 698 (w) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 4.10 (1H, dddd, J = 6.0, 6.0, 10.0, 12.4 Hz), 2.53 (1H, dd, J = 6.0, 18.0 Hz), 2.19 (1H, dd, J = 10.0, 18.0 Hz), 1.79-1.71 (1H, m), 1.68-1.57 (1H, m), 1.26 (3H, s), 1.19 (3H, s), 0.96 (3H, t, J = 7.6 Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 218.3, 80.9, 74.2, 41.6, 28.9, 24.5, 21.9, 9.6; HRMS Calcd for C\(_8\)H\(_{14}\)O\(_2\): 142.0994, Found: 142.0996; [α]\(^D\)\(_{20}\) +99.72\(^\circ\) (c 0.413, CHCl\(_3\)) for an optically enriched sample of >98% ee.

The optical purity of the conjugate addition was established by chiral GLC analysis (ChiralDex GTA, 15 psi, 70°C) Chromatograms are illustrated below:

(23b) 2-Ethyl-2,3-dihydrochromen-4-one. IR (neat):
2965 (w), 2921 (w), 2878 (w), 1695 (s), 1608 (m), 1466 (s), 1316 (m), 1228 (w), 1150 (w), 1116 (w), 1028 (w), 956 (w), 873 (w), 766 (m) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.86 (1H, dd, J = 1.6, 7.6 Hz), 7.47-7.43 (1H, m), 7.00-6.95 (2H, m), 4.40-4.33 (1H, m), 2.67 (2H, d, J = 8.4 Hz), 1.94-1.71 (2H, m), 1.06 (3H, t, J = 7.2 Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 192.9, 161.9, 136.1, 127.1, 121.3, 121.2, 118.1, 79.2, 42.7, 28.1, 9.5; Anal. Calcd for C\(_{11}\)H\(_{12}\)O\(_2\): C, 74.98; H, 6.86; Found: C, 75.11; H, 7.05; [α]\(^D\)\(_{20}\) +80.271\(^\circ\) (c 0.093, CHCl\(_3\)) for an optically enriched sample of >98% ee.
The optical purity of the conjugate addition was established by chiral GLC analysis (Chiraldex GTA, 15 psi, 100 °C). Chromatograms are illustrated below:

(24b) 2-Isopropyl-2,3-dihydrochromen-4-one. IR (neat): 2965 (w), 2926 (w), 2878 (w), 1695 (s), 1608 (m), 1462 (s), 1306 (m), 1233 (m), 1111 (w), 1028 (w), 887 (w), 761 (m), 664 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.88-7.84 (1H, m), 7.47-7.42 (1H, m), 6.99-6.95 (2H, m), 4.17 (1H, ddd, J = 3.6, 6.0, 12.4 Hz), 2.73-2.60 (2H, m), 2.04 (1H, qdd, J = 6.8, 6.8, 13.6 Hz), 1.06 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 193.2, 162.1, 136.0, 127.0, 121.2, 121.1, 118.0, 82.6, 40.2, 32.3, 18.0, 17.9; HRMS Calcd for C₁₂H₁₅O₂H (M+H): 191.1076, Found: 191.1072; [α]₂₀° +49.566° (c 0.433, CHCl₃) for an optically enriched sample of 91% ee.

The optical purity of the conjugate addition was established by chiral HPLC analysis (Chiralpak AS, 98:2 hexanes/iPrOH, tₘₐᵢₐᵢₒᵣₜᵢₐᵢᵠᵢₐᵢᵠᵠ = 5 min, tₘₐᵢₐᵢᵐᵢᵠᵠ = 6 min).

**Determination of relative stereochemistry of 2-ethyl-3-(hydroxy(phenyl)methyl)-2,3-dihydrochromen-4-one (23a).**

2-Ethyl-3-(hydroxy(phenyl)methyl) chroman-4-ol (G): To a flask charged with Na(OAc)₃BH (21.0 mg, 0.0991 mmol), CH₂Cl₂ (2.0 mL) followed by HOAc (40.0 µL, 0.699 mmol) were added. To this solution, 23a (25.0 mg, 0.0886 mmol, 9:1 d.r.) dissolved in CH₂Cl₂ (2.0 mL) was added and the mixture was allowed to stir at 22 °C for 24 h. The reaction was quenched by the addition of
saturated aqueous NaHCO$_3$ (2 mL) and washed with CH$_2$Cl$_2$ (3 x 2 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by silica gel chromatography (10% EtOAc/pentane) yielded G as a clear oil (8.0 mg, 0.028 mmol, 33% yield, 50% conv, >30:1 d.r.). IR (neat): 3360 (br), 2988 (m), 2931 (m), 1719 (w), 1616 (m), 1588 (m), 1491 (s), 1462 (s), 1228 (s), 1136 (w), 1062 (m), 987 (m), 759 (s), 713 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44-7.31 (6H, m), 7.20 (1H, dt, $J = 1.6$, 8.0 Hz), 6.97 (1H, dt, $J = 1.2$, 7.2 Hz), 6.86 (1H, dd, $J = 1.2$, 8.4 Hz), 5.17 (1H, d, $J = 4.4$ Hz), 4.71 (1H, d, $J = 4.4$, 8.8 Hz), 2.31 (1H, dt, $J = 4.8$, 8.4 Hz), 2.20 (1H, br s), 1.80-1.69 (1H, m), 1.62-1.52 (1H, m), 0.87 (3H, t, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 152.8, 142.8, 129.3, 129.2, 129.0, 128.4, 126.7, 124.9, 121.3, 117.4, 74.6, 65.3, 50.9, 26.0, 14.3, 10.3; HRMS Calcd for C$_{18}$H$_{20}$O$_3$: 284.1412, Found: 284.1412.

5-ethyl-2,2-dimethyl-4-phenyl-4,4a,5,10b-tetrahydro-[1,3]dioxino[5,4-c]chromene (H): To a flame dried one dram vial containing 4Å MS (small spatula tip) was added G (6.0 mg, 0.021 mmol) dissolved in benzene (800 µL). To this vial pTsOH (one small crystal) and 2,2 dimethoxy propane (5.9 µL, 0.047 mmol) were added and the mixture allowed to stir at 22°C for 20 min. At this time the solution was passed through a short plug of silica eluting with EtOAc. The filtrate was concentrated in vacuo. Purification by silica gel chromatography (1% EtOAc/Pentane) afforded pure H as a colorless oil (>30:1 d.r.). IR (neat): 2995 (m), 2924 (m), 2904 (m), 1618 (w), 1588 (w), 1492 (s), 1462 (s), 1386 (s), 1260 (s), 1210 (s), 1129 (m), 1084 (s), 1013 (m), 968 (m), 902 (m), 766 (m), 710 (m), 675 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40-7.30 (6H, m), 7.14 (1H, tq, $J = 0.8$, 7.6 Hz), 6.94 (1H, td, $J = 1.2$, 7.6 Hz), 6.77 (1H, dd, $J = 1.2$, 8.4 Hz), 4.99 (1H, d, $J = 10.0$ Hz), 4.76 (1H, d, $J = 10.0$ Hz), 4.00-3.95 (1H, m), 1.99 (1H, q, $J = 10.0$ Hz), 1.69 (3H, s), 1.57 (3H, s), 1.31-1.16 (1H, m), 0.88-0.76 (1H, m), 0.65 (3H, t, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 153.6, 140.3, 128.9, 128.8, 128.5, 128.1, 125.8, 123.8, 120.8, 116.5, 100.1, 67.9, 46.4, 34.3, 30.4, 29.9, 27.8, 20.0, 9.4; HRMS Calcd for C$_{21}$H$_{24}$O$_3$: 324.1725, Found: 324.1719.
Representative experimental procedure for three-component in situ generation of catalyst for conjugate addition of dialkylzinc reagents to unsaturated lactones with benzaldehyde in the presence of CuCl and CuI: (CAUTION: Et₂Zn IS PYROPHORIC! USE EXTREME CAUTION!) An oven-dried 13x100 mm test tube charged with 1 (8.9 mg, 0.0150 mmol) and CuCl (1.17 mg, 0.0118 mmol) in air. The test tube was sealed with a septum and purged with N₂. Toluene (1.0 mL) was added followed by 5,6-dihydro-2H-pyran-2-one (7) (13.0 µL, 0.150 mmol) and benzaldehyde (29.0 µL, 0.300 mmol). The mixture was cooled to -30 °C and Et₂Zn (46.0 µL, 0.450 mmol) was added. The mixture was allowed to stir at -30 °C for 12 h at which time the reaction was quenched through addition of a saturated solution of aqueous NH₄Cl (1 mL) then H₂O (1 mL). The aqueous layer was washed with EtOAc (2 x 2 mL). The combined organic layers were passed through a short plug of silica gel with EtOAc and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (30% diethyl ether/hexanes) yielded a clear oil (18.1 mg, 0.0773 mmol, 51%).

The general procedure for PCC oxidation (cf. Pg 6 of the Supporting Information) was followed to yield 9b as a clear oil (15.7 mg, 0.0680 mmol, 88%).

Representative experimental procedure for preparation of peptide•CuCl and peptide•CuI complexes (25, 26): An oven-dried 13x100 mm test tube was charged with CuCl (9.89 mg, 0.100 mmol) and 1 (59.2 mg, 0.100 mmol) in air. The test tube was sealed with a septum, purged with N₂, and CH₂Cl₂ (4 mL) was added. The reaction was allowed to stir at rt (22°C) for 12 h and which time the orange solution was filtered through filter paper and concentrated to afford an orange solid. The orange solid (25) could either be used for catalytic ACA, without further purification, by dissolving in toluene (0.012 N) or recrystallized from CH₂Cl₂/pentane and used as a pale orange powder (51.1 mg, 0.739 mmol, 74%)

(26) CuI-1-complex: IR (neat): 3307 (bs m), 3049 (m), 2967 (s), 2873 (m), 1658 (s), 1532 (m), 1438 (m), 1262 (w), 1092 (w), 771 (m), 695 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.68 (1H, br s); 7.77 (1H, br s), 7.51-7.13 (18H, m), 6.91 (1H, t, J = 7.6 Hz), 6.06 (1H, br s), 4.53 (1H, br q, J = 6.8 Hz), 4.05 (1H, br s), 3.09-2.99 (3H, br s), 2.15 (1H, br s), 1.68 (1H, br s), 1.30-1.19 (3H, m), 1.12-1.03 (2H, m), 0.73 (3H, t, J = 7.2 Hz), 0.60-0.45 (6H, br s); ³¹P NMR
(162 MHz, CDCl$_3$): $\delta$ -14.67; HRMS Calcd for C$_{37}$H$_{42}$ICuN$_3$O$_2$PNa (M+Na): 804.1253, Found: 804.1260.

(25) CuCl-1-complex: mp = 108-115 (dec.);
IR (neat): 3301 (br s), 3056 (w), 2959 (m), 2925 (m), 2862 (w), 1654 (s), 1523 (m), 1437 (w), 1375 (w), 1266 (w), 1227 (w), 1101 (w), 1033 (w), 753 (m), 696 (s), 668 (w), 520 (bs w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.45 (1H, br s), 7.92 (1H, br s), 7.60-7.01 (19 H, br m), 6.41 (1H, br s), 4.60 (1H, br s), 3.67 (1H, br s), 3.24 -3.02 (4H, br m), 2.35 (1H, br s), 1.25-1.17 (2H, br m), 1.12-1.02 (2H, br m), 0.64 (3H, t, $J$ = 7.2 Hz), 0.45 (3H, br d, $J$ = 5.2 Hz), 0.41 (3H, br d, $J$ = 5.6 Hz); $^{31}$P NMR (162 MHz, CDCl$_3$): $\delta$ -11.37; HRMS Calcd for C$_{37}$H$_{42}$ICuN$_3$O$_2$PNa (M+Na): 712.1897, Found: 712.1891.

(27) CuCl-2-complex: IR (neat): 3312 (br), 3057 (w), 2965 (m), 2927 (m), 2867 (w), 1652 (s), 1511 (s), 1376 (m), 1245 (m), 1164 (m), 1099 (w), 893 (w), 746 (m), 692 (m), 508 (w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.87 (br s), 7.87 (br s), 7.54 -7.24 (br m), 7.11 (br s), 6.84 (br s), 6.34 (br s), 4.66 (br s), 3.70 (br s), 3.06 (br s), 1.26 (br s), 1.06 (br s), 0.69 (br s), 0.60 (br s); $^{31}$P NMR (162 MHz, CDCl$_3$): $\delta$ -8.19; LRMS Calcd for C$_{37}$H$_{42}$ICuN$_3$O$_2$PNa (M+Na): 798.26, Found: 798.31; $[\alpha]_D^{20}$ -106.9° (c 0.533, CHCl$_3$) for an optically enriched sample of >98% ee.

Representative experimental procedure for three-component Cu-catalyzed conjugate addition of dialkylzinc reagents to unsaturated lactones with benzaldehyde using CuI or CuCl complexes: (CAUTION: Et$_2$Zn IS PYROPHORIC! USE EXTREME CAUTION!) An oven-dried 13x100 mm test tube was charged with 25 (8.27 mg, 0.0120 mmol) in air. The test tube was sealed with a septum and purged with N$_2$. Toluene (1.0 mL) was added followed by 5,6-dihydro-2H-pyran-2-one (7) (13.0 µL, 0.150 mmol) and benzaldehyde (29.0 µL, 0.300 mmol). The mixture was cooled to -30 °C and Et$_2$Zn (46.0 µL, 0.450 mmol) was added. The mixture was allowed to stir at -30 °C for 12 h, at which time the reaction was quenched through addition of a saturated solution of aqueous NH$_4$Cl (1 mL) then H$_2$O (1 mL). The aqueous layer was washed with EtOAc (2 x 2 mL). The combined organic layers were passed through a short plug of silica gel with EtOAc and the filtrate was concentrated in vacuo. Purification by silica gel
chromatography (30% diethyl ether/hexanes) yielded a clear oil (30.4 mg, 0.130 mmol, 87%). The general procedure for PCC oxidation (cf. page 6 of the Supporting Information) was followed to afford 9b as a clear oil (26.4 mg, 0.114 mmol, 87%).


