5*H*-Oxazol-4-ones as Building Blocks for Asymmetric Synthesis of α -Hydroxycarboxylic Acid Derivatives

Barry M. Trost*, Kalindi Dogra and Maurizio Franzini

Experimental section¹

All reactions were carried out in oven-dried flasks or pyrex test tube under a positive pressure of nitrogen, argon for Mo-catalyzed AAA. Anhydrous solvents and bases were obtained either from elution through alumina (DCM), or from refluxing on a suitable drying agent (and distilled under reduced pressure where required): CaH₂ for DCE, py; Na-benzophenone ketyl for THF; DMF and DMA were used directly from commercial sources (stored on 4 Å MS). THF solutions of LHMDS were freshly prepared by dissolving commercially available solid LHMDS (stored in dry box) in freshly distilled THF. Microwave assisted heating was carried out in a Smith Workstation US manufactured by Personal Chemistry AB. TLC was performed on precoated glass plates (Merck), flash chromatography with silica gel 60, 230-400 mesh, in compliance with Still's method. Detection of compounds on TLC was carried out either by visualization with a 254 nm lamp, or by exposure to an atmosphere of iodine (supported on sand), or by dipping into a suitable staining solution (**A**: 1.5% KMnO₄, 10% K₂CO₃, 2% NaOH in 200 mL H₂O; **B**: 0.42 mL *p*-anisaldehyde, 1.5 mL AcOH, 5 mL H₂SO₄, 135 mL EtOH; **C**: 0.05 g Ce(NH₄)₂(NO₂)₆, 2.4 g (NH₄)₂Mo₇O₂₄·4H₂O, 2.8 mL H₂SO₄, 50 mL H₂O). Enantiomeric excesses were determined by HPLC on Tsp Spectraseries P100/UV100 apparatus with a chiral stationary phase (see details where applies). Melting points (uncorrected) were determined in open capillary tubes using a Thomas-Hoover apparatus. ¹H-NMR (0 ppm as internal standard) and ¹³C-NMR (77 ppm as internal standard) spectra were recorded on Varian Gemini 2300 (300 MHz for ¹H-NMR), Mercury 400 (400 MHz for ¹H-NMR) and on Unity Inova 500 (500 MHz for ¹H-NMR). IR spectra (cm⁻¹) were obtained with a Perkin-Elmer FT-IR Paragon 500 spectrometer, either using neat sample on NaCl pad (for oils and liquids), or preparing a KBr pellet.

¹ Abbreviations used throughout the text: **AAA**, asymmetric allylic alkylation; **DCE**, 1,2-dichloroethane; **DCM**, dichloromethane; **DMA**, dimethylacetamide; **DMF**, dimethyl formamide; **Hept**, heptane; **Hex**, hexanes; **LHMDS**, lithium bis(trimethylsilyl)azide; **mp**, melting point; **PE**, petroleum ether; **py**, pyridine; **TLC**, thin layer chromatography.

Representative procedures for the preparation of diamides 2.

***N*-Benzoyl-2-bromopropanamide**

Commercially available 2-bromopropanoyl bromide (7.5 mL, 71 mmol) was added to a solution of benzamide (4.50 g, 37.1 mmol) and pyridine (6.0 mL, 74 mmol) in DCM (40 mL) at room temperature. A gentle reflux was set for 5 h. After cooling down to room temperature, most of the solvent was removed by rotary evaporation. The residual slurry, obtained after removal of most of solvents, was taken up in DCM, loaded onto a column of silica gel and eluted with 8:2 to 7:3 PE/EtOAc. A white crystalline solid was obtained (8.529 g, 33.3 mmol), along with a portion of mixed fractions, containing both the desired product and the corresponding, desired oxazolone (587 mg). Yield 90%.

$R_f = 0.55$ (75:25 PE/EtOAc; 254 nm, stain C). $^1\text{H-NMR}$ (500 MHz, CDCl_3), δ : 7.85 (2H, d, $J=7.5$ Hz), 7.61 (1H, t, $J=7.5$ Hz), 7.52 (2H, t, $J=7.5$ Hz), 5.44 (1H, q, $J=7$ Hz), 1.89 (3H, t, $J=7$ Hz), 1.57 (1H, br s). IR (neat): 3370, 2928, 1732, 1603, 1542, 1489, 1451, 1379, 1238, and 1172 cm^{-1} .

***N*-Benzoyl-2-bromopropanamide**

$^1\text{H-NMR}$ (500 MHz, CDCl_3), δ : 9.00 (1H, br s), 7.89 (2H, dt, $J=7$, $J=0.2$ Hz), 7.63 (1H, m), 7.53 (2H, dt, $J=14$, $J=0.5$ Hz), 5.37 (1H, dd, $J=8.5$, $J=6.5$ Hz), 2.17-2.21 (1H, m), 2.07-2.10 (1H, m), 1.36-1.46 (4H, m), 0.94 (3H, t, $J=7$ Hz). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3), δ : 171.0, 165.0, 133.6, 132.3, 129.1, 127.8, 48.0, 33.9, 29.4, 22.1, 13.9.

***N*-Benzoyl-2-bromo-3-phenylpropanamide**

2-Bromo-3-phenyl propanoyl chloride (380 mg, 2.75 mmol), benzamide (195 mg, 1.61 mmol) and pyridine (0.3 mL, 3.7 mmol) were heated in 1,2-DCE (10 mL) at 80 °C for 1.5 h, then at 60 °C for an additional 15 h. After cooling to r.t. and dilution with DCM (100 mL), the organic phase was washed with water (50 mL), brine (25 mL). After drying on MgSO₄, the clear solution was concentrated, loaded onto a column of silica gel and eluted with 75:25 to 6:4 PE/EtOAc. The desired product was isolated as a white solid (197 mg, 0.59 mmol). Yield 37%.

*R*_f = 0.5 (75:25 PE/EtOAc; 254 nm, stains A and C). ¹H-NMR (400 MHz, CDCl₃), δ: 8.84 (1H, br s), 7.81 (2H, d, *J*=7.5 Hz), 7.60 (1H, t, *J*=6.3 Hz), 7.49 (2H, t, *J*=7.5 Hz), 7.25-7.33 (5H, m), 5.70 (1H, t, *J*=7.2 Hz), 3.62 (1H, dd, *J* = 7.5 Hz, *J* = 14 Hz), 3.31 (1H, dd, *J* = 7.2 Hz, *J* = 14 Hz). ¹³C-NMR (100 MHz, CDCl₃), δ: 170.7, 165.1, 136.9, 133.7, 129.8, 129.6, 129.2, 128.8, 127.9, 127.4, 47.2, 40.3. IR (neat): 3282, 3167, 3063, 3030, 1748, 1715, 1694, 1682, 1504, 1455, 1372, 1260, 1145, 1074, and 695 cm⁻¹.

***N*-Benzoyl-2-bromo-3-methylbutanamide**

*R*_f = 0.60 (75:25 PE/EtOAc; 254 nm, stains A and C). ¹H-NMR (500 MHz, CDCl₃), δ: 9.34 (1H, br s), 7.85-7.89 (2H, m), 7.61-7.66 (1H, m), 7.50-7.55 (2H, m), 4.95 (1H, d, *J* = 8 Hz), 2.53-2.60 (1H, m), 1.14 (3H, d, *J* = 11.5 Hz), 1.06 (3H, d, *J* = 11.5 Hz). ¹³C-NMR (125 MHz, CDCl₃), δ: 169.0, 164.1, 133.7, 129.2, 127.9, 67.0, 57.3, 32.3, 20.2.

***N*-Benzoyl-2-bromo-4-methylpentanamide**

R_f = 0.63 (75:25 PE/EtOAc; 254 nm, stains A and C). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ : 9.30 (1H, br s), 7.88-7.90 (2H, m), 7.61-7.67 (1H, m), 7.48-7.54 (2H, m), 5.22 (1H, m), 1.87-1.98 (2H+1H, m+m), 1.00 (6H, d, J = 6 Hz). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3), δ : 170.7, 165.1, 133.7, 132.3, 129.2, 128.0, 58.1, 43.1, 25.3, 23.0, 21.1. IR (neat): 3282, 2960, 2872, 1740, 1693, 1601, 1508, 1487, 1371, 1263, 1156, and 707 cm^{-1} .

***N*-Benzoyl-2-bromo-2-cyclohexylacetamide**

R_f = 0.65 (95:5 $\text{CHCl}_3/\text{MeOH}$; 254 nm, stains A and C). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ : 9.30 (1H, br s), 7.86 (2H, dd, J = 1.4 Hz, J = 8.2 Hz), 7.62-7.66 (1H, m), 7.51-7.55 (2H, m), 4.87 (1H, d, J = 5.2 Hz), 1.77-1.82 (5H, m), 1.29-1.34 (5H, m). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3), δ : 168.8, 164.7, 133.7, 132.6, 129.3, 127.9, 65.9, 41.8, 30.3, 27.7, 26.0, 25.9, 25.7. IR (KBr): 3249, 2929, 2853, 1736, 1678, 1603, 1508, 1272 and 1154 cm^{-1} . HRMS for $\text{C}_{15}\text{H}_{18}^{79}\text{BrNO}_2$: found 323.05209, calc d 323.05148; for $\text{C}_{15}\text{H}_{18}^{81}\text{BrNO}_2$: found 325.05004, calc d 325.05342.

***N*-Benzoyl-2-bromopent-4-enamide**

R_f = 0.35 (8:2 PE/EtOAc; 254 nm, stains A and C). $^1\text{H-NMR}$ (500 MHz, CDCl_3), δ : 9.27 (1H, br s), 7.88-7.90 (2H, m), 7.62-7.65 (1H, m), 7.51-7.54 (2H, m), 5.82-5.91 (1H, m), 5.20-5.27 (2+1H, m), 2.90-2.96 (1H, m), 2.72-2.79 (1H, m). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3), δ : 169.6, 165.0, 133.8, 132.4, 132.1, 129.2, 128.0, 120.0, 58.3, 38.7. IR (neat): 3287, 3080, 2982, 1744, 1694, 1643, 1601, 1505, 1487, 1263, 1155, and 707 cm^{-1} .

Representative procedure for the preparation of oxalactims 3.

5H-5-Methyl-2-phenyl-2-oxazol-4-one

Mp: 63-65 °C. R_f = 0.4 (75:25 PE/EtOAc; 254 nm, stain C). $^1\text{H-NMR}$ (500 MHz, CDCl_3), δ : 8.22-8.24 (2H, m), 7.70 (1H, t, $J=7.5$ Hz), 7.55 (2H, t, $J=7.5$ Hz), 4.85 (1H, q, $J=7$ Hz), 1.65 (3H, t, $J=7$ Hz). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3), δ : 192.6, 186.5, 135.3, 130.3, 129.1, 127.9, 125.9, 78.2, 16.6. IR (KBr): 1758, 1605, 1589, 1549, 1490, 1451, 1368, 1276, 1186, 1030, and 710 cm^{-1} .

5H-5-Butyl-2-phenyl-2-oxazol-4-one

$^1\text{H-NMR}$ (300 MHz, CDCl_3), δ : 8.22 (2H, t, $J=7.5$ Hz), 7.71 (1H, t, $J=7.5$ Hz), 7.55 (2H, t, $J=7.5$ Hz), 4.79 (1H, dd, $J=7.5$ Hz, $J=4.5$ Hz), 2.05-2.15 (1H, m), 1.81-1.93 (1H, m), 1.34-1.54 (4H, m), 0.93 (3H, t, $J=7.5$ Hz). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3), δ : 191.9, 186.5, 135.1, 130.0, 128.9, 127.8, 125.7, 81.9, 30.8, 26.6, 22.1, 13.7. IR (neat): 3065, 2959, 2872, 1758, 1721, 1695, 1604, 1590, 1552, 1490, 1452, 1368, 1242, 1181, 1061, and 711 cm^{-1} .

5H-5-Phenylmethyl-2-phenyl-2-oxazol-4-one

Mp: 95-98 °C. R_f = 0.35 (75:25 PE/EtOAc; 254 nm, I_2 , stains A and C). $^1\text{H-NMR}$ (300 MHz, CDCl_3), δ : 8.14-8.16 (2H, m), 7.66-7.70 (1H, m), 7.51-7.53 (2H, m), 7.24-7.32 (5H, m), 5.00 (1H, dd, $J=4$ Hz, $J=7.5$ Hz), 3.44 (1H, dd, $J=4$ Hz, $J=15$ Hz), 3.13 (1H, dd, $J=7.5$ Hz, $J=15$ Hz). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3), δ : 191.1, 186.7, 135.4, 134.8, 130.2, 129.8, 129.5, 129.1, 128.8, 127.5, 125.8, 82.1, 37.4. IR (neat): 3063, 3031, 2925, 1756, 1604, 1590, 1549, 1490, 1451, 1371, 1180, 1064, and 700 cm^{-1} . Anal. Calc d for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.24; H, 5.09; N, 5.34.

5H-5-(Methyl)ethyl-2-phenyl-2-oxazol-4-one.

Mp: 79-81 °C. R_f = 0.40 (75:25 PE/EtOAc; 254 nm, I_2 , stains A and C). $^1\text{H-NMR}$ (500 MHz, CDCl_3), δ : 8.24 (2H, m), 7.71 (1H, m), 7.55 (2H, m), 4.66 (1H, d, $J=4$ Hz), 2.40 (1H, dsept, $J=4$ Hz, $J=7$ Hz), 1.19 (3H, d, $J=7$ Hz), 0.99 (3H, d, $J=7$ Hz). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3), δ : 191.4, 186.7, 135.3, 130.1, 129.1, 125.8, 86.1, 30.8, 18.5, 16.0. IR (neat): 2958, 1746, 1655, 1606, 1590, 1543, 1490, 1452, 1375, 1186, 1069, 1000, and 712 cm^{-1} . Anal. Calc d for $\text{C}_{12}\text{H}_{13}\text{NO}_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.14; H, 6.26; N, 6.87.

5H-5-(2-Methyl)propyl-2-phenyl-2-oxazol-4-one

Mp: 56-59 °C. R_f = 0.29 (85:15 PE/EtOAc; 254 nm, I_2 , stains A and C). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ : 8.22-8.24 (2H, m), 7.68-7.71 (1H, m), 7.53-7.57 (2H, m), 4.81 (1H, dd, J = 3.6, J = 10 Hz), 1.91-2.01 (2H, m), 1.66-1.73 (1H, m), 1.05 (6H, dd, J = 1.6, J = 6.4 Hz). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3), δ : 192.5, 186.5, 135.3, 130.2, 129.1, 126.0, 81.0, 40.4, 25.7, 23.0, 22.1. IR (neat): 3065, 2959, 2873, 1756, 1605, 1591, 1552, 1452, 1373, and 1182 cm^{-1} .

5H-5-Cyclohexyl-2-phenyl-2-oxazol-4-one

Mp: 106-9 °C. R_f = 0.35 (85:15 PE/EtOAc; 254 nm, I_2 , stains A and C). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ : 8.22-8.25 (2H, m), 7.69-7.73 (1H, m), 7.53-7.58 (2H, m), 4.63 (1H, d, J = 4.4 Hz), 2.07 (1H, m), 1.91-1.94 (1H, m), 1.62-1.83 (4H, m), 1.14-1.39 (5H, m). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3), δ : 191.6, 168.8, 135.3, 130.2, 129.1, 125.9, 85.9, 40.2, 29.0, 26.2, 25.9, 25.7. IR (neat): 2928, 2854, 1754, 1604, 1590, 1552, 1450, 1364, 1173, and 717 cm^{-1} . Anal. Calc d for $\text{C}_{15}\text{H}_{17}\text{NO}_2$: C, 74.97; H, 7.13; N, 5.83. Found: C, 74.88; H, 7.12; N, 5.76.

5H-5-(2-Propenyl)-2-phenyl oxazol-4-one

$R_f = 0.35$ (8:2 PE/EtOAc; 254 nm, I_2 , stain A). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 8.22-8.24 (2H, m), 7.60-7.63 (1H, m), 7.50-7.55 (2H, m), 5.77-5.84 (1H, m), 5.22 (1H, ddd, $J = 1.2$, $J = 2.5$, $J = 17$ Hz), 5.18 (1H, dt, $J = 1$, $J = 10$ Hz), 4.86 (1H, dd, $J = 7$, $J = 4.5$ Hz), 2.84-2.90 (1H, m), 2.62-2.68 (1H, m). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3), δ : 191.3, 186.7, 135.4, 130.3, 130.2, 129.1, 127.9, 125.8, 80.9, 35.2. IR (neat): 3072, 2923, 1757, 1604, 1551, 1451, 1369, 1284, and 1183 cm^{-1} .

General procedure for the preparation of Mo chiral catalyst and setting up of AAA reactions.

A solution of freshly distilled and degassed² THF (0.5 mL) of (*R,R*) [or (*S,S*) or ($\pm$), where applied] ligand **5** (4.9 mg, 0.015 mmol) and commercially available $[(\eta^3\text{-C}_7\text{H}_8)\text{Mo}(\text{CO})_3]$ (2.8 mg, 0.01 mmol) was gently refluxed under Ar atmosphere at 70 $^\circ\text{C}$ for 5 to 10 min (until deep purple color develops) in a pyrex test tube, sealed with a rubber septum and under Ar atmosphere. To this was added the solution of nucleophile **3** (prepared as indicated below), followed by addition of the chosen allylic carbonate **4** (0.11 mmol). Additions were done via syringe at 60 $^\circ\text{C}$ and the resulting mixture heated at THF reflux (oil bath temperature 70 $^\circ\text{C}$) for 8 hr. The reaction mixture was then poured onto a 1 N solution of 1:1 $\text{KH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$ (pH 7; 8 mL), DCM was added (15 mL). A further extraction with DCM followed, the combined organic layers were finally dried over MgSO_4 . After elimination of solvents *in vacuo*, a crude oil was obtained, which after $^1\text{H-NMR}$ (500 MHz) analysis underwent purification through silica gel (9:1 to 75:25 PE/EtOAc) affording the desired product as a thick oil or white solid, after concentration to dryness on a rotavapor and thorough elimination of solvents *in vacuo*.

² Freshly distilled THF was collected in a flame-dried flask and degassed by repeated (three times) freezing in liquid N_2 , vacuum pumping (pressure in the test tube submitted to degassing was 1 mbar or less) and Ar inflating. The catalyst is very sensitive to oxygen and thus thorough degassing needs to be performed.

Preparation of nucleophile. Test tube containing oxalactim **3** (0.1 mmol) was evacuated and flushed with argon three times; 0.5 mL of anhydrous, degassed THF was added, followed by dropwise addition of freshly prepared solution of LHMDs (1 M in THF; 0.1 mL, 0.1 mmol) with stirring at 0 °C.³ The resulting nucleophile was stirred for 5 to 10 min and directly added to the active catalyst.

5*H*-5-methyl-5-[1-(1-phenyl)prop-3-enyl]-2-phenyl oxazol-4-one.

R_f = 0.23 (9:1 PE/EtOAc; 254 nm, I_2 , stains A, C). ^1H NMR (500 MHz, CDCl_3), δ (major diastereomer): 8.23-8.26 (2H, m), 7.7-7.74 (1H, m), 7.55-7.59 (2H, m), 7.28-7.4 (5H, m), 5.99 (1H, ddd, J = 17, J = 10, J = 8.8 Hz), 5.00-5.21 (2H, m), 3.79 (1H, d, J = 8.8 Hz), 1.41 (3H, s). ^{13}C NMR (125 MHz, CDCl_3), δ (major diastereomer): 193.6, 185.3, 137.8, 135.2, 133.6, 130.0, 129.0, 128.9, 128.7, 127.5, 125.7, 119.8, 90.2, 56.2, 21.2. IR (neat): 2924, 2853, 1754, 1603, 1547, 1451, 1356, 1149, and 712 cm^{-1} . Anal. Calc d for $\text{C}_{19}\text{H}_{17}\text{NO}_2$: C, 78.33; H, 5.88; N, 4.81; found: C, 78.66; H, 6.71; N, 4.02. Daicel Chiralpak AD column at λ = 254 nm, 10 μL injection at 2 mg/mL, eluent 99:1 Hept/2-PrOH, flow rate 1 mL/min: t_R (1) 27.5 min, t_R (2) 34.1 min.

5*H*-5-butyl-5-[1-(1-phenyl)prop-3-enyl]-2-phenyl oxazol-4-one.

R_f = 0.26 (9:1 PE/EtOAc; 254 nm, I_2 , stains A, C). ^1H NMR (500 MHz, CDCl_3), δ (major diastereomer): 8.23-8.27 (2H, m), 7.68-7.74 (1H, m), 7.45-7.59 (2H, m), 7.24-7.38 (5H, m), 6.01 (1H, ddd, J = 18, J = 10, J = 8.8 Hz), 5.06-5.21 (2H, m), 3.8 (1H, d, J = 8.8 Hz), 1.82-1.90

³ For 5-methyl oxalactim (**3**, R = CH_3) a lower T (-78 °C) for the preparation of the lithium enolate was preferred.

(1H, m), 1.62-1.70 (1H, m), 1.06-1.21 (4H, m), 0.75 (3H, t, $J = 7$ Hz). ^{13}C NMR (125 MHz, CDCl_3), δ (major diastereomer): 193.2, 185.7, 137.9, 135.1, 133.6, 130.0, 129.0, 128.8, 128.7, 127.5, 125.6, 119.6, 93.6, 56.1, 34.5, 24.8, 22.4, 13.7. IR (neat): 2958, 1754, 1604, 1552, 1490, 1452, 1358, 1152, and 751 cm^{-1} . Anal. Calc d for $\text{C}_{22}\text{H}_{23}\text{NO}_2$: C, 79.25; H, 6.95; N, 4.2; found: C, 79.12; H, 7.29; N, 4.0. Daicel Chiralpak AD column at $\lambda = 254\text{ nm}$, 10 μL injection at 2 mg/mL, eluent 95:5 Hept/2-PrOH, flow rate 1 mL/min: t_{R} (1) 9.3 min, t_{R} (2) 10.6 min.

5*H*-5-methyl-5-[1-[1-(2,4-dimethoxyphenyl)]prop-3-enyl]-2-phenyl oxazol-4-one

$R_f = 0.45$ (8:2 PE/EtOAc; 254 nm, I_2 , stains A, C). ^1H -NMR (500 MHz, CDCl_3), major diastereoisomer, δ : 8.23-8.25 (2H, m), 7.69-7.73 (1H, m), 7.53-7.58 (2H, m), 7.37 (1H, d, $J = 8.5$ Hz), 6.57 (1H, dd, $J = 8.5$, $J = 2.5$ Hz), 6.47 (1H, d, $J = 2.5$ Hz), 5.90 (1H, ddd, $J = 17$, $J = 10$, $J = 8.5$ Hz), 5.17 (1H, ddd, $J = 17$, $J = 1.5$, $J = 1$ Hz), 5.04 (1H, ddd, $J = 10$, $J = 15$, $J = 0.5$ Hz), 4.46 (1H, d, $J = 8.5$ Hz), 3.83 (3H, s), 3.82 (3H, s), 1.40 (3H, s). ^{13}C -NMR (125 MHz, CDCl_3), major diastereoisomer, δ : 194.1, 185.2, 160.1, 158.5, 135.2, 133.9, 130.3, 130.1, 129.7, 129.1, 126.1, 119.5, 118.7, 104.9, 98.6, 91.3, 55.6, 55.5, 20.8. IR (neat): 2936, 2837, 1755, 1605, 1589, 1551, 1506, 1452, 1358, 1209, 1154, 1034, and 710 cm^{-1} . Daicel Chiralpak AD column at $\lambda = 254\text{ nm}$, 10 μL injection at 2 mg/mL, eluent 98:2 Hept/2-PrOH, flow rate 1 mL/min: t_{R} (1) 27.3 min, t_{R} (2) 29.6 min.

5*H*-5-methyl-5-[1-[1-(2-bromophenyl)]prop-3-enyl]-2-phenyl oxazol-4-one

R_f = 0.28 (9:1 PE/EtOAc; 254 nm, I_2 , stains A, C). ^1H NMR (500 MHz, CDCl_3), δ (major diastereomer): 8.23-8.27 (2H, m), 7.70-7.74 (1H, m), 7.54-7.61 (4H, m), 7.38 (1H, dt, J = 7.8, J = 1.2 Hz), 7.11-7.16 (1H, m), 5.91 (1H, ddd, J = 17, J = 10, J = 8.5 Hz), 5.10-5.27 (2H, m), 4.61 (1H, d, J = 8.5 Hz), 1.47 (3H, s). ^{13}C NMR (125 MHz, CDCl_3), δ (major diastereomer): 193.1, 185.2, 137.2, 135.2, 133.3, 132.5, 130.0, 129.4, 129.0, 128.9, 127.8, 125.8, 125.6, 120.6, 90.3, 53.8, 20.9. IR (neat): 2926, 1756, 1604, 1548, 1451, 1356, 1153, and 707 cm^{-1} .
Anal. Calc d for $\text{C}_{19}\text{H}_{16}\text{BrNO}_2$: C, 61.64; H, 4.36; N, 3.78; found: C, 61.86; H, 4.37; N, 3.68.
Daicel Chiralpak AD column at λ = 254 nm, 10 μL injection at 2 mg/mL, eluent 99:1 Hept/2-PrOH, flow rate 1 mL/min: t_R (1) 26.2 min, t_R (2) 30.3 min.

5*H*-5-methyl-5-[1-(1-cyclohexenyl)prop-3-enyl]-2-phenyl oxazol-4-one

R_f = 0.72 (8:2 PE/EtOAc; 254 nm, I_2 , stains A, C). ^1H -NMR (500 MHz, CDCl_3), major diastereoisomer, δ : 8.21-8.23 (2H, m), 7.68-7.73 (1H, m), 7.54-7.58 (2H, m), 5.75 (1H, ddd, J = 16, J = 10, J = 8.8 Hz), 5.71 (1H, m), 5.16 (1H, dt, J = 16, J = 0.8 Hz), 5.04 (1H, dd, J = 10, J = 0.8 Hz), 3.13 (1H, d, J = 8.8 Hz), 2.03-2.10 (4H, m), 1.55-1.62 (2+2H, m+m), 1.51 (3H, s). ^{13}C -NMR (125 MHz, CDCl_3), major diastereoisomer, δ : 194.3, 185.3, 135.2, 134.5, 132.7, 130.1, 129.1, 127.7, 126.1, 119.3, 90.4, 58.3, 26.9, 25.6, 23.1, 22.4, 21.1. IR (neat): 2929, 1757, 1065, 1591, 1552, 1451, 1356, and 1140 cm^{-1} . Anal. Calc d for $\text{C}_{19}\text{H}_{21}\text{NO}_2$: C, 77.26; H, 7.17, N, 4.74. Found: C, 77.12; H, 6.89, N, 4.75. Daicel Chiralpak AD column at λ = 254 nm, 10 μL

injection at 2 mg/mL, eluent 99:1 Hept/2-PrOH, flow rate 1 mL/min: t_R (1) 17.7 min, t_R (2) 21.9 min.

5*H*-5-methyl-5-[3-(5-methyl)hexa-1,4-dienyl]-2-phenyl oxazol-4-one

R_f = 0.67 (8:2 PE/EtOAc; 254 nm, I_2 , stains A, C). $^1\text{H-NMR}$ (400 MHz, CDCl_3), major diastereoisomer, δ : 8.21-8.23 (2H, m), 7.67-7.72 (1H, m), 7.52-7.56 (2H, m), 5.64 (1H, ddd, $J = 16, J = 10, J = 8$ Hz), 5.20 (1H, dt, $J = 10, J = 1.4$ Hz), 5.15 (1H, dd, $J = 16, J = 1.2$ Hz), 5.03 (1H, m), 3.47 (1H, d, $J = 8, J = 0.8$ Hz), 1.76 (3H, d, $J = 1.2$ Hz), 1.67 (3H, d, $J = 1.2$ Hz), 1.56 (3H, s). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3), major diastereoisomer, δ : 193.89, 185.4, 137.1, 135.1, 133.7, 130.1, 129.0, 126.1, 119.7, 118.5, 90.3, 49.2, 26.1, 20.8, 18.3. IR (neat): 3072, 2979, 2931, 1758, 1605, 1590, 1552, 1490, 1451, 1357, 1153, 1036, and 713 cm^{-1} . Anal. Calc d for $\text{C}_{17}\text{H}_{19}\text{NO}_2$: C, 75.81; H, 7.11, N, 5.20. Found: C, 75.60; H, 6.83, N, 5.10. Daicel Chiralpak AD column at $\lambda = 254$ nm, 10 μL injection at 2 mg/mL, eluent 99.5:0.5 Hept/2-PrOH, flow rate 1 mL/min: t_R (1) 24.5 min, t_R (2) 28.9 min.

5*H*-5-(3-propenyl)-5-[1-(1-phenyl)prop-3-enyl]-2-phenyl oxazol-4-one

R_f = 0.65 (8:2 PE/EtOAc; 254 nm, I_2 , stains A, C). $^1\text{H-NMR}$ (500 MHz, CDCl_3), major diastereoisomer, δ : 8.22 (2H, dd, $J = 8$ Hz, $J = 1$ Hz), 7.69-7.73 (1H, m), 7.56 (2H, t, $J = 8$ Hz), 7.36-7.38 (4H, m), 7.27-7.30 (1H, m), 6.02 (1H, ddd, $J = 10, J = 8, J = 7$ Hz), 5.49-5.57 (1H, m), 5.19 (1H, d, $J = 17$ Hz), 5.11 (1H, d, $J = 10$ Hz), 5.06 (1H, dd, $J = 17, J = 1.5$ Hz), 5.01 (1H, dd, $J = 10.5, J = 1$ Hz), 3.84 (1H, d, $J = 9$ Hz), 2.59 (1H, dd, $J = 7, J = 14$ Hz), 2.41 (1H, dd, $J = 7.5, J = 14$ Hz). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3), major diastereoisomer, δ : 192.7, 185.7, 137.8, 135.3,

133.6, 130.1, 129.2, 129.1, 129.1, 128.9, 127.8, 1254.7, 121.3, 120.0, 92.7, 55.8, 39.2.

IR (neat): 3064, 1755, 1604, 1551, 1452, 1359, 725, and 699 cm^{-1} . Daicel Chiralpak AD column at $\lambda = 254 \text{ nm}$, 10 μL injection at 2 mg/mL, eluent 99:1 Hept/2-PrOH, flow rate 1 mL/min:

t_R (1) 26.9 min, t_R (2) 30.9 min.

5H-3 -Phenyl-spiro[(2-phenyloxazol-4-one)-5,4 -cyclopentene] or 9-oxo-8-phenyl-3-oxa-1-aza-spiro[4.4]nona-1,6-diene

$R_f = 0.3$ (85:15 PE/EtOAc; I_2 , stains A, C). $^1\text{H-NMR}$ (500 MHz, CDCl_3), δ : 8.24 (2H, dt, $J = 8, J = 0.5 \text{ Hz}$), 7.70 (1H, t, $J = 7.5 \text{ Hz}$), 7.55 (2H, dd, $J = 7.5, J = 8 \text{ Hz}$), 7.25-7.30 (3H, m), 7.09-7.11 (2H, m), 6.13 (1H, dt, $J = 4, J = 2 \text{ Hz}$), 5.94 (1H, dt, $J = 4, J = 2 \text{ Hz}$), 4.42 (1H, s), 3.12 (1H, dt, $J = 15, J = 2 \text{ Hz}$), 2.91 (1H, dt, $J = 17, J = 2 \text{ Hz}$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3), δ : 190.5, 184.9, 135.8, 135.2, 131.3, 130.2, 129.5, 129.1, 128.6, 128.5, 128.0, 126.1, 94.8, 61.5, 42.6. IR (neat): 3062, 2924, 1757, 1604, 1590, 1552, 1451, 1355, 1035, and 697 cm^{-1} .

5H-5-(2-methyl)propyl-5-[1-(2-thienyl)prop-3-enyl]-2-phenyl oxazol-4-one

$R_f = 0.75$ (8:2 PE/EtOAc; 254 nm, I_2 , stains A, C). $^1\text{H-NMR}$ (400 MHz, CDCl_3), major diastereoisomer, δ : 8.19-8.22 (2H, m), 7.69-7.73 (1H, m), 7.54-7.58 (2H, m), 7.15 (1H, dd, $J = 1.4 \text{ Hz}, J = 3 \text{ Hz}$), 7.06 (1H, dd, $J = 1.4, J = 3 \text{ Hz}$), 6.02 (1H, ddd, $J = 8.8, J = 10 \text{ Hz}, J = 17 \text{ Hz}$), 5.16 (1H, dt, $J = 1.2, J = 17 \text{ Hz}$), 5.11 (1H, dt, $J = 10, J = 0.6 \text{ Hz}$), 3.95 (1H, d, $J = 8.8 \text{ Hz}$), 1.85-1.90 (1H, m), 1.72-1.78 (1H, m), 1.58-1.63 (1H, m), 0.85 (3H, d, $J = 6.4$). 0.78 (3H, d, $J = 6.8$). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3), major diastereoisomer, δ : 193.3, 185.8, 138.0, 135.3, 133.3, 130.1, 129.2, 127.7, 126.1, 125.9, 123.2, 119.7, 93.2, 52.2, 43.3, 24.3, 24.2, 24.0. IR (neat): 3088, 2958, 2872, 1753, 1604, 1590, 1551, 1490, 1451, 1357, and 715 cm^{-1} .

Anal. Calc d for C₂₀H₂₁NO₂S: C, 70.77; H, 6.24. Found: C, 71.14; H, 6.16. Daicel Chiralpak AD column at λ = 254 nm, 10 μ L injection at 2 mg/mL, eluent 99:1 Hept/2-PrOH, flow rate 1 mL/min: t_R (1) 12.7 min, t_R (2) 30.7 min.

5*H*-5-(methyl)ethyl-5-[1-(1-phenyl)prop-3-enyl]-2-phenyl oxazol-4-one

R_f = 0.69 (8:2 PE/EtOAc; 254 nm, I₂, stains A, C). ¹H-NMR (400 MHz, CDCl₃), major diastereoisomer, δ : 8.18-8.21 (2H, m), 7.68-7.71 (1H, m), 7.53-7.56 (2H, m), 7.36-7.38 (2H, m), 7.22-7.31 (3H, m), 6.12 (1H, ddd, J = 17, J = 10, J = 8.8 Hz), 5.17 (1H, d, J = 17 Hz), 5.12 (1H, dt, J = 10, J = 1 Hz), 4.01 (1H, d, J = 8.8 Hz), 2.20 (1H, sept, J = 6.8 Hz), 1.02 (3H, d, J = 6.8 Hz), 0.94 (3H, d, J = 6.8 Hz). ¹³C-NMR (100 MHz, CDCl₃), major diastereoisomer, δ : 192.6, 185.7, 138.1, 135.2, 130.0, 129.1, 128.8, 127.6, 125.7, 119.5, 95.6, 53.7, 32.1, 16.2, 15.6. IR (neat): 2973, 1750, 1604, 1591, 1552, 1490, 1451, and 1356 cm⁻¹. Daicel Chiralpak AD column at λ = 254 nm, 10 μ L injection at 2 mg/mL, eluent 99:1 Hept/2-PrOH, flow rate 1 mL/min: t_R (1) 21.6 min, t_R (2) 28.6 min.

5*H*-5-cyclohexyl-5-[1-(1-phenyl)prop-3-enyl]-2-phenyl oxazol-4-one

R_f = 0.67 (8:2 PE/EtOAc; 254 nm, I₂, stains A, C). ¹H-NMR (500 MHz, CDCl₃), major diastereoisomer, δ : 8.18-8.20 (2H, m), 7.67-7.71 (1H, m), 7.52-7.56 (2H, m), 7.34-7.36 (2H, m), 7.26-7.30 (2H, m), 7.20-7.23 (1H, m), 6.14 (1H, ddd, J = 17, J = 10, J = 9 Hz), 5.18 (1H, dt, J = 16, J = 1 Hz), 5.12 (1H, dd, J = 10, J = 1 Hz), 4.03 (1H, d, J = 9 Hz), 1.84-1.89 (1H, m), 1.75-1.77 (1H, m), 1.66-1.70 (3H, m), 1.57 (1H, m), 1.36-1.41 (1H, m), 0.99-1.10 (4H, m).

^{13}C -NMR (125 MHz, CDCl_3), major diastereoisomer, δ : 192.8, 185.6, 138.0, 135.1, 134.1, 130.0, 129.9, 129.1, 128.7, 127.5, 125.7, 119.5, 95.4, 53.0, 41.3, 26.1, 26.0, 25.9, 25.9, 25.3. IR (neat): 3063, 6061, 2933, 2855, 1750, 1604, 1591, 1552, 1490, 1451, 1359, and 721 cm^{-1} . Anal. Calc d for $\text{C}_{24}\text{H}_{25}\text{NO}_2$: C, 80.19; H, 7.01, N, 3.90. Found: C, 79.86; H, 6.98, N, 3.90. Daicel Chiralpak AD column at $\lambda = 254\text{ nm}$, 10 μL injection at 2 mg/mL, eluent 99:1 Hept/2-PrOH, flow rate 1 mL/min: t_R (1) 30.2 min, t_R (2) 52.2 min.

5*H*-5-methylphenyl-5-[1-(1-phenyl)prop-3-enyl]-2-phenyl oxazol-4-one

Mp: 111-118 $^{\circ}\text{C}$ (softening starts at 97 $^{\circ}\text{C}$). $R_f = 0.66$ (8:2 PE/EtOAc; 254 nm, I_2 , stains A, C). ^1H -NMR (400 MHz, CDCl_3), major diastereoisomer, δ : 8.04-8.06 (2H, m), 7.62-7.66 (1H, m), 7.36-7.50 (6H, m), 7.28-7.32 (1H, m), 7.06 (5H, m), 6.05 (1H, ddd, $J = 17$, $J = 10$, $J = 8.8\text{ Hz}$), 5.20 (1H, dt, $J = 17$, $J = 0.8\text{ Hz}$), 5.13 (1H, dd, $J = 10$, $J = 0.8\text{ Hz}$), 3.94 (1H, d, $J = 8.8\text{ Hz}$), 3.14 (1H, d, $J = 14\text{ Hz}$), 2.96 (1H, d, $J = 14\text{ Hz}$). ^{13}C -NMR (100 MHz, CDCl_3), major diastereoisomer, δ : 192.5, 185.5, 138.1, 135.1, 133.7, 133.2, 130.2, 130.1, 129.9, 129.7, 129.1, 129.0, 128.9, 128.8, 128.7, 128.4, 128.3, 127.8, 127.4, 125.6, 120.1, 93.3, 56.2, 41.1. IR (neat): 3031, 1753, 1604, 1589, 1550, 1452, and 1360 cm^{-1} . Anal. Calc d for $\text{C}_{25}\text{H}_{21}\text{NO}_2$: C, 81.72; H, 5.76, N, 3.81. Found: C, 82.12; H, 5.91, N, 3.81. Daicel Chiralpak AD column at $\lambda = 254\text{ nm}$, 10 μL injection at 2 mg/mL, eluent 98:2 Hept/2-PrOH, flow rate 1 mL/min: t_R (1) 39.6 min, t_R (2) 45.3 min.

General procedure for the hydrolysis to tertiary α -hydroxy carboxyamides.

To the 5,5-dialkylated oxazol-4-one **6** (0.1 mmol) 2.5 N NaOH (0.05 mL), and EtOH (0.2 mL) were added. The mixture was stirred for 30 min to 3 hr at 60 °C, after which the reaction was deemed complete from TLC. After correction of pH into acidic with 1 N NaHSO₄, extraction with CHCl₃ followed. The combined organic layers were then dried over MgSO₄. After elimination of solvents *in vacuo*, a crude oil was obtained, which underwent purification through silica gel (1:1 PE/EtOAc, 2% HOAc) affording the expected product, commonly as a white solid, after concentration to dryness on a rotavapor and thorough elimination of solvents *in vacuo*.

2-Hydroxy-2-methyl-3-phenylpent-4-enamide

¹H-NMR (500 MHz, CDCl₃), δ (major diastereomer): 7.25-7.38 (5H, m), 6.70 (1H, br s), 6.28 (1H, ddd, $J = 17, J = 10, J = 8.5$ Hz), 5.62 (1H, br s), 5.12-5.19 (2H, m), 3.78 (1H, d, $J = 8.5$ Hz), 2.29 (1H, br s), 1.26 (3H, s). ¹³C-NMR (125 MHz, CDCl₃), δ (major diastereomer): 177.7, 139.0, 136.2, 129.4, 128.6, 127.2, 118.2, 78.2, 57.0, 25.7. IR (neat): 3466, 3344, 2926, 1665, 1572, 1453, 1369, 1120, 925, and 702 cm⁻¹.

2-Hydroxy-2-methyl-3-(2-bromophenyl)pent-4-enamide

¹H-NMR (500 MHz, CDCl₃), δ (major diastereomer): 7.56-7.61 (2H, m), 7.30 (1H, dt, $J = 7.6, J = 1.5$ Hz), 7.05-7.14 (1H, m), 6.72 (1H, br s), 6.59 (1H, br s), 6.16 (1H, ddd, $J = 17,$

$J = 10, J = 8.5$ Hz), 5.11-5.17 (2H, m), 4.480 (1H, d, $J = 8.5$ Hz), 1.30 (3H, s).

^{13}C -NMR (125 MHz, CDCl_3), δ (major diastereomer): 179.0, 139.0, 135.7, 133.0, 130.3, 128.4, 127.4, 126.2, 118.6, 78.3, 54.4, 24.9. IR (neat): 3467, 3346, 2977, 1671, 1565, 1469, 1370, 1114, 926, and 751cm^{-1} .

2-Hydroxy-2-(2-methyl)propyl-3-(2-thienyl)pent-4-enamide

Mp: 123-124 $^{\circ}\text{C}$ (softening starts at 115 $^{\circ}\text{C}$). $R_f = 0.6$ (1:1 PE/EtOAc, 2% HOAc; I_2 , stains A, C). ^1H -NMR (500 MHz, CDCl_3), δ : 7.32 (1H, dd, $J = 5$ Hz, $J = 3$ Hz), 7.12 (1H, dd, $J = 3$, $J = 1.5$ Hz), 7.06 (1H, dt, $J = 3$, $J = 1.5$ Hz), 6.66 (1H, br s), 6.18 (1H, ddd, $J = 17$, $J = 10$, $J = 8.5$ Hz), 5.93 (1H, br s), 5.13 (1H, ddd, $J = 10$ Hz, $J = 1.5$ Hz, $J = 0.5$ Hz), 5.09 (1H, ddd, $J = 17$, $J = 1.5$, $J = 1$ Hz), 3.84 (1H, d, $J = 8.5$ Hz), 2.31 (1H, br s), 1.84 (1H, dd, $J = 5$, $J = 9$ Hz), 1.74 (1H, sept, $J = 7$ Hz), 1.12 (1H, dd, $J = 7$, $J = 14.5$ Hz), 0.89 (3H, d, $J = 7$ Hz), 0.86 (3H, d, $J = 7$ Hz). ^{13}C -NMR (125 MHz, CDCl_3), δ : 177.0, 139.3, 136.1, 128.5, 125.9, 122.7, 118.0, 81.0, 54.3, 46.6, 24.6, 24.2, 24.1. IR (neat): 3480, 3282, 3084, 2955, 2872, 1673, 1578, 1470, 1416, 1322, 1270, 1144, and 1036cm^{-1} .

2-Hydroxy-2-(methyl)ethyl-3-phenylpent-4-enamide

Mp: 98-101 $^{\circ}\text{C}$. $R_f = 0.65$ (1:1 PE/EtOAc, 2% HOAc; I_2 , stains A, C). ^1H -NMR (500 MHz, CDCl_3), δ : 7.26-7.35 (5H, m), 6.46 (1H, ddd, $J = 17$ Hz, $J = 9.5$ Hz, $J = 8.5$ Hz), 6.42 (1H, br s), 5.56 (1H, br s), 5.16 (1H, dt, $J = 9.5$, $J = 1$ Hz), 5.09 (1H, dt, $J = 17$, $J = 1$ Hz), 3.80 (1H, d, $J = 8.5$ Hz), 2.26 (1H, br s), 2.01 (1H, sept, $J = 7$ Hz), 0.99 (3H, d, $J = 7$ Hz), 0.97 (3H, d,

$J = 7$ Hz). ^{13}C -NMR (125 MHz, CDCl_3), δ : 176.3, 139.4, 137.3, 129.5, 128.7, 127.3, 117.9, 82.7, 55.7, 33.4, 17.8, 15.9. IR (neat): 3483, 3384, 2970, 1668, 1564, 1156, and 7021 cm^{-1} .

1-Hydroxy-2-phenylcyclopent-3-enylcarboxamide

$R_f = 0.3$ (1:1 PE/EtOAc, 2% HOAc; I_2 , stains A, C). ^1H -NMR (500 MHz, CDCl_3), δ : 7.16-7.30 (5H, m), 6.07 (1H, ddd, $J = 2$ Hz, $J = 4$ Hz, $J = 6$ Hz), 5.99 (1H, ddd, $J = 2$, $J = 4$, $J = 6$ Hz), 5.87 (1H, br s), 5.20 (1H, br s), 4.23 (1H, t, $J = 2$ Hz), 3.98 (1H, br s), 3.10 (1H, ddd, $J = 2$, $J = 4$, $J = 6$ Hz), 2.71 (1H, ddd, $J = 2$, $J = 6$, $J = 4$ Hz). ^{13}C -NMR (125 MHz, CDCl_3), δ : 175.7, 138.3, 132.4, 130.8, 129.2, 128.4, 128.4, 127.9, 127.4, 85.7, 63.0, 45.2. IR (neat): 3356, 2924, 1668, and 1456 cm^{-1} .