Asymmetric Organocatalytic SOMO Activation: The Direct and Enantioselective α-Enolation of Aldehydes

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Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] All solvents were purified according to the method of Grubbs.[2] All aldehydes were purified by either distillation or silica gel chromatography prior to use. Starting silyl enolethers were prepared according to the literature from corresponding ketones and purified by distillation prior to use.[3] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile compounds. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still[4] and where noted, Davisil S-743-1 and Iatrobeads® 6RS-8060 were used in place of silica gel. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates.

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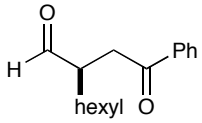
[1] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford, 1988.
[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
[3] Moriarty, R.; Prakash, O.; Duncan, M. P. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 559; Drewes, S. E.; Hogan, C. J.; Kaye, P. T.; Roos, G. H. P. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1585; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252.
[4] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Visualization of the developed chromatogram was performed by fluorescence quenching or by staining using either $KMnO_4$ or *p*-anisaldehyde stains.

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (300 MHz or 75 MHz), and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility by electron ionization, chemical ionization, or fast atom/ion bombardment techniques. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Varian CP-Chirasil-Dex-CB (30 m × 0.25 mm) column as noted. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a variable-wavelength UV detector using a Chiralcel AD-H column (25 cm × 0.46 cm) and AD guard (5 cm × 0.46 cm) or Chiralcel OJ-H column (25 cm × 0.46 cm) and OJ guard (5 cm × 0.46 cm) as noted. Optical rotations were measured on a Jasco P-1010 polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} dg cm^2 g^{-1}; concentration (c) is in g/100 ml.

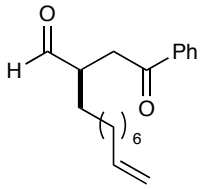
General procedure for enantioselective α-enolation of aldehydes (Table 1): A solution of the trifluoromethanesulfonic acid salt of (2*S*, 5*S*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (20 mol%) in acetone (0.0625 M) is prepared in a

scintillation vial equipped with a magnetic stir bar at -78 °C under argon. In this order, the aldehyde (1.0 eq), trimethyl-(1-phenyl-vinyloxy)-silane (2.0 eq), water (2.0 eq), CAN (2.0 eq), and 2,6-di-*tert*-butyl pyridine (2.0 eq) are added to this mixture. After purging the solution with argon for 1 minute, this mixture is warmed to -20 °C and stirred at constant temperature for 24 hours until no further reaction progression is observed. The cold reaction is poured into diethyl ether and filtered through davisil, washed with ether and concentrated *in vacuo*. The resulting residue is purified by column chromatography to provide the title compounds.

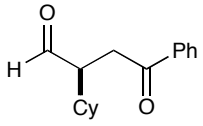


(*R*)-2-(2-oxo-2-phenyl ethyl) octanal (Table 1, entry 1): Prepared according to the general procedure from octanal (32.8 mg, 0.256 mmol) to provide the title compound as a colorless oil (52 mg, 85% yield, 90% ee) after purification by flash column chromatography on Davisil (3% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel OJ-H (25 cm × 0.46 cm) column (5% to 9.5% CH_3CN, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); t_r = 1.95 min and 2.12 min. IR (film) 2928, 2857, 1726, 1685, 1449, 1224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H, C**H**O), 8.00-7.96 (m, 2H, aryl **H**), 7.60-7.55 (m, 1H, aryl **H**), 7.50-7.44 (m, 2H, aryl **H**), 3.48 (dd, 1H, *J* = 7.65, 17.55 Hz, C**H**$_2$COPh), 3.15-2.99 (m, 2H, C**H**$_2$COPh & C**H**CHO), 1.86-1.74 (m, 1H, C**H**$_2$$CH_2CH_2CH_2CH_2CH_3$), 1.58-1.48 (m, 1H, C**H**$_2$$CH_2CH_2CH_2CH_2CH_3$), 1.41-1.25 (m, 8H, CH_2**$CH_2CH_2CH_2CH_2$**CH_3), 0.88 (t, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.66, 198.03, 136.55, 133.28, 128.62, 128.07, 46.73, 37.62, 31.57, 29.32, 28.85, 27.05, 22.54, 14.03; HRMS (EI^+) exact mass

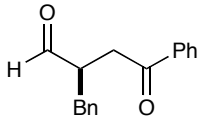
calculated for $[M]^+$ ($C_{16}H_{22}O_2$) requires *m/z* 246.1620, found *m/z* 246.1618; $[\alpha]_D$= +63.9 (c = 1.30, $CHCl_3$).



(*R*)-2-(2-oxo-2-phenyl ethyl)-undec-10-enal (Table 1, entry 2): Prepared according to the general procedure from 10-undecenal (43 mg, 0.256 mmol) to provide the title compound as a colorless oil (68 mg, 92% yield, 92% ee) after purification by flash column chromatography on Davisil (3% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel OJ-H (25 cm × 0.46 cm) column (5% to 9.5% CH_3CN, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); t_r = 2.66 min and 2.90 min. IR (film) 3583, 2927, 2855, 1726, 1685, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (bs, 1H, C**H**O), 7.99-7.95 (m, 2H, aryl **H**), 7.60-7.54 (m, 1H, aryl **H**), 7.49-7.44 (m, 2H, aryl **H**), 5.80 (m, 1H, C**H**=CH_2), 5.02-4.90 (m, 2H, CH=C**H**$_2$), 3.47 (dd, 1H, *J* = 7.5, 17.4 Hz, C**H**$_2$COPh), 3.14-2.98 (m, 2H, C**H**$_2$COPh & C**H**CHO), 2.03 (dt, 2H, *J* = 7.0, C**H**$_2$CH=CH_2), 1.79 (m, 1H, C**H**$_2$CHCHO), 1.53 (m, 1H, C**H**$_2$CHCHO), 1.36-1.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.58, 197.96, 139.04, 136.51, 133.25, 128.58, 128.04, 114.17, 46.69, 37.60, 33.69, 29.56, 29.17, 28.93, 28.79, 27.03; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{19}H_{26}O_2$) requires *m/z* 286.1933, found *m/z* 286.1920; $[\alpha]_D$= +56.5 (c = 0.66, $CHCl_3$).

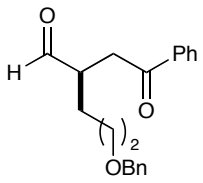


(*R*)-2-cyclohexyl-4-oxo-4-phenyl butyraldehyde (Table 1, entry 3): Prepared according to the general procedure from cyclohexylacetaldehyde (32.3 mg, 0.256 mmol) to provide the title compound as an white solid (46 mg, 74% yield, 93% ee) after purification by flash column chromatography on Davisil (3% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel OJ-H (25 cm × 0.46 cm) column (5% to 9.5% CH_3CN, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); t_r = 2.56 min and 2.77 min. IR (film) 2925, 2852, 2342, 2361, 1723, 1684, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H, C**H**O), 7.99-7.96 (m, 2H, aryl **H**), 7.60-7.43 (m, 3H, aryl **H**), 3.53 (dd, 1H, *J* = 9.15, 17.85 Hz, C**H**$_2$COPh), 3.11 (m, 1H, C**H**CHO), 2.94 (dd, 1H, *J* = 3.60, 18.00 Hz, C**H**$_2$COPh), 1.94-1.64 (m, 6H, cyclohexyl), 1.38-1.07 (m, 5H, cyclohexyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.96, 198.33, 136.65, 133.16, 128.55, 128.04, 52.14, 38.04, 34.74, 31.03, 30.10, 26.42, 26.10; HRMS (FAB^+) exact mass calculated for $[M]^+$ ($C_{16}H_{21}O_2$) requires *m*/*z* 245.1542, found *m*/*z* 245.1545; $[\alpha]_D$= +105.4 (c = 0.46, $CHCl_3$).



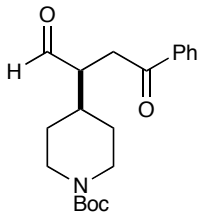
(*R*)-2-Benzyl-4-oxo-4-phenyl-butyraldehyde (Table 1, entry 4): Prepared according to the general procedure from hydrocinnamaldehyde (34.4 mg, 0.256 mmol) to provide the title compound as a colorless oil (50 mg, 77% yield, 91% ee) after purification by flash column chromatography on Davisil (7% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel OJ-H (25 cm × 0.46 cm) column (5% to 9.5% CH_3CN, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); t_r = 4.59 min and 5.02 min. IR (film) 3583, 1723, 1682, 1598, 1580, 1449, 1361, 1228

cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.90 (brs, 1H, C**H**O), 7.92-7.89 (m, 2H, aryl **H**), 7.59-7.54 (m, 1H, aryl **H**), 7.47-7.42 (m, 2H, aryl **H**), 7.33-7.19 (m, 5H), 3.47-3.35 (m, 2H), 3.21-3.14 (m, 1H), 3.06- 2.97 (m, 1H), 2.86-2.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.99, 197.81, 138.07, 136.37, 133.32, 129.00, 128.72, 128.58, 128.03, 126.70, 48.32, 37.21, 34.68; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{17}H_{16}O_2$) requires *m/z* 252.1150, found *m/z* 252.1148; $[\alpha]_D$= +25.4 (c = 0.55, $CHCl_3$).



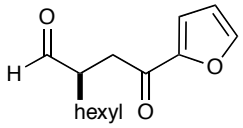
(*R*)-5-Benzyloxy-2-(2-oxo-2-phenylethyl)-pentanal (Table 1, entry 5): Prepared according to the general procedure from 5-(benzyloxy)pentanal (49 mg, 0.256 mmol) to provide the title compound as a colorless oil (56 mg, 71% yield, 90% ee) after purification by flash column chromatography on Davisil (20% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel OJ-H (25 cm × 0.46 cm) column (5% to 50% CH_3CN, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); t_r = 5.60 min and 6.18 min. IR (film) 2930, 2858, 2361, 2342, 1724, 1684, 1449, 1361, 1221, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (bs, 1H, C**H**O), 7.99-7.95 (m, 2H, aryl **H**), 7.61-7.55 (m, 1H, aryl **H**), 7.49-7.44 (m, 2H, aryl **H**), 7.38-7.26 (m, 5H, aryl **H**), 4.50 (s, 2H, OC**H**$_2$Ph), 3.53 -3.44 (m, 3H, C**H**$_2$COPh & C**H**$_2$OBn), 3.16-3.01 (m, 2H, C**H**$_2$COPh & C**H**CHO), 1.97-1.87 (m, 1H, C**H**$_2$CH$_2$CH$_2$OBn), 1.76-1.62 (3H, m, C**H**$_2$C**H**$_2$CH$_2$OBn); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.34, 197.83, 138.26, 136.42, 133.30, 128.60, 128.36, 128.05, 127.62, 127.59, 72.96, 69.71, 46.36, 37.64, 27.24,

25.55; HRMS (EI$^+$) exact mass calculated for [M]$^+$ ($C_{20}H_{22}O_3$) requires *m/z* 310.1569, found *m/z* 310.1562; $[\alpha]_D$= +44.3 (c = 0.55, $CHCl_3$).



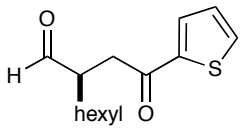
(*R*)-4-(1-Formyl-3-oxo-phenyl propyl)-piperidine-1-carboxylic acid *tert*-butyl ester (Table 1, entry 6): Prepared according to the general procedure from *tert*-butyl 4-(formylmethyl)piperidine-1-carboxlate (58 mg, 0.256 mmol) to provide the title compound as an white solid (75 mg, 84% yield, 95% ee) after purification by flash column chromatography on Davisil (25% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel OJ-H (25 cm × 0.46 cm) column (5% to 50% CH_3CN, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); t_r = 3.65 min and 4.20 min. IR (film) 2975, 2930, 2854, 1720, 1686, 1449, 1424, 1365, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (d, 1H, *J* = 0.6 Hz, C**H**O), 7.98-7.95 (m, 2H, aryl **H**), 7.61-7.55 (m, 1H, aryl **H**), 7.50-7.44 (m, 2H, aryl **H**), 4.15 (brs, 2H, C**H**$_2$NBoc), 3.52 (dd, 1H, *J* = 8.70, 18.0 Hz, C**H**$_2$COPh), 3.14 (m, 1H, C**H**CHO), 2.99 (dd, 1H, *J* = 3.75, 17.9 Hz, C**H**$_2$COPh), 2.68 (m, 2H, C**H**$_2$NBoc), 2.03 (m, 1H, C**H**cyclohexyl), 1.73-1.57 (m, 2H, C**H**$_2$CH$_2$NBoc), 1.44 (s, 9H, ^{t}Bu), 1.42-1.31 (m, 2H, C**H**$_2$CH$_2$NBoc); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.06, 197.77, 154.58, 136.32, 133.37, 128.61, 128.02, 79.55, 51.11, 36.19, 34.78, 29.94, 28.98, 28.36; HRMS (EI$^+$) exact mass calculated for [M]$^+$ ($C_{20}H_{28}NO_4$) requires *m/z* 346.2018, found *m/z* 346.2008; $[\alpha]_D$= +45.3 (c = 0.5, $CHCl_3$).

General procedure for enantioselective α-enolation of octanal with various silyl enolethers (Table 2): A solution of the trifluoromethanesulfonic acid salt of (2*S*, 5*S*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (20 mol%) in DME (0.25 M) is prepared in a scintillation vial equipped with a magnetic stir bar at -78 ºC under argon. In this order, octanal (1.0 eq), silyl enolether (1.5 or 2.0 eq as noted), water (2.0 eq), CAN (2.0 eq), and 2,6-di-*tert*-butyl pyridine (2.0 eq) are added to this mixture. After purging the solution with argon for 1 minute, this mixture is warmed to -20 ºC and stirred at constant temperature for 24 hours until no further reaction progression is observed. The cold reaction is poured into diethyl ether and filtered through davisil, washed with ether and concentrated *in vacuo*. The resulting residue is purified by column chromatography to provide the title compounds.



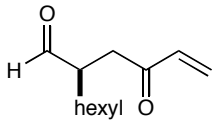
(*R*)-2-(2-(furan-2-yl)-2-oxoethyl)octanal (Table 2, entry 2): Prepared according to the general procedure from octanal (32.8 mg, 0.256 mmol) and *tert*-butyl(1-(furan-2-yl)vinyloxy)dimethylsilane (86.2 mg, 0.384 mmol) at -50 ºC reaction temperature to provide the title compound as a colorless oil (46.6 mg, 77% yield, 92% ee) after purification by flash column chromatography on Davisil (3% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel AD-H (25 cm × 0.46 cm) column (5% to 50% MeOH, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min) after oxidation of product to acid derivative; (*S*) isomer t_r = 3.78 min and (*R*) isomer t_r = 4.49 min. IR (film) 3135, 2929, 2857, 1726, 1677, 1570, 1469, 1397, 1263, 1164, 1084, 1018, 907 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H, C**H**O), 7.58 (dd,

1H, *J* = 0.9, 1.8 Hz, 5-**H** in furan), 7.21 (dd, 1H, *J* = 1.1, 3.6 Hz, 3-**H** in furan), 6.54 (m, 1H, 4-**H** in furan), 3.30 (dd, 1H, *J* = 7.8, 17.4 Hz, C**H**$_2$CO-furanyl), 3.11-3.02 (m, 1H, C**H**CHO), 2.87 (dd, 1H, *J* = 4.8, 17.4 Hz, C**H**$_2$CO-furanyl), 1.81-1.72 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.59-1.47 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.38-1.27 (m, 8H, CH$_2$**CH$_2$CH$_2$CH$_2$CH$_2$**CH$_3$), 0.89 (t, 3H, *J* = 6.9 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.32, 187.20, 152.46, 146.40, 117.16, 112.33, 46.55, 37.07, 31.56, 29.29, 28.71, 26.93, 22.53, 14.03; HRMS (EI$^+$) exact mass calculated for [M]$^+$ ($C_{14}H_{20}O_3$) requires *m*/*z* 236.1412, found *m*/*z* 236.1418; $[\alpha]_D$ = +70.1 (c = 1.03, CH_2Cl_2).



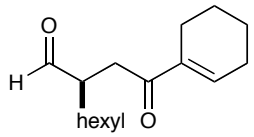
(*R*)-2-(2-oxo-2-(thiophen-2-yl)ethyl)octanal (**Table 2, entry 3):** Prepared according to the general procedure from octanal (32.8 mg, 0.256 mmol) and *tert*-butyldimethyl(1-(thiophen-2-yl)vinyloxy)silane (92.3 mg, 0.384 mmol) at -50 ºC reaction temperature to provide the title compound as a pale yellow oil (45.2 mg, 70% yield, 93% ee) after purification by flash column chromatography on Davisil (3% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel AD-H (25 cm × 0.46 cm) column (5% to 50% MeOH, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min) after oxidation of product to acid derivative; (*S*) isomer t_r = 5.06 min and (*R*) isomer t_r = 5.43 min. IR (film) 3092, 2928, 2857, 2719, 1725, 1663, 1518, 1459, 1416, 1357, 1235, 1058, 939 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (d, 1H, *J* = 0.6 Hz, C**H**O), 7.75 (dd, 1H, *J* = 0.9, 4.1 Hz, 5-**H** in thiophene), 7.64 (dd, 1H, *J* = 0.9, 4.9 Hz, 3-**H** in thiophene), 7.14 (dd, 1H, *J* = 3.6, 5.1 Hz, 4-**H** in thiophene), 3.41 (dd, 1H, *J* = 7.5, 17.1 Hz, C**H**$_2$CO-thiophenyl), 3.13-3.04 (m, 1H, C**H**CHO), 2.98 (dd, 1H, *J*

= 4.9, 17.2 Hz, C**H**$_2$CO-thiophenyl), 1.83-1.73 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.57-1.48 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.37-1.28 (m, 8H, CH$_2$**CH$_2$CH$_2$CH$_2$CH$_2$**CH$_3$), 0.89 (t, 3H, *J* = 6.9 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.37, 190.89, 143.72, 133.81, 132.07, 128.14, 46.87, 38.04, 31.56, 29.30, 28.78, 26.98, 22.54, 14.03; HRMS (EI$^+$) exact mass calculated for [M]$^+$ ($C_{14}H_{20}O_2S$) requires *m/z* 252.1184, found *m/z* 252.1173; $[\alpha]_D$ = +69.7 (c = 0.45, CH_2Cl_2).

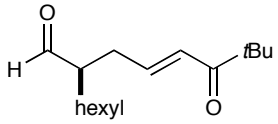


(*R*)-2-(2-oxobut-3-enyl)octanal (**Table 2, entry 4**)**:** Prepared according to the general procedure from octanal (32.8 mg, 0.256 mmol) and (1,3-butadien-2-yloxy)trimethylsilane (72.8 mg, 0.512 mmol) to provide the title compound as a colorless oil (30.6 mg, 61% yield, 90% ee) after purification by flash column chromatography on Davisil (3% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel AD-H (25 cm × 0.46 cm) column (5% to 50% MeOH, linear gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 2.52 min and (*R*) isomer t_r = 2.99 min. IR (film) 2929, 2858, 2718, 1727, 1702, 1683, 1616, 1467, 1402, 1245, 1198, 1084, 987 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (d, 1H, *J* = 0.9 Hz, C**H**O), 6.43-6.22 (m, 2H, C**H**=C**H**$_2$), 5.87 (dd, 1H, *J* = 1.4, 10.2 Hz, CH=C**H**$_2$), 3.08 (dd, 1H, *J* = 8.0, 17.4 Hz, C**H**$_2$COCH), 3.01-2.95 (m, 1H, C**H**CHO), 2.63 (dd, 1H, *J* = 4.4, 17.4 Hz, C**H**$_2$COCH), 1.76-1.69 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.50-1.42 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.31-1.27 (m, 8H, CH$_2$**CH$_2$CH$_2$CH$_2$CH$_2$**CH$_3$), 0.88 (t, 3H, *J* = 6.9 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.46, 198.47, 136.25, 128.66, 46.56, 38.28, 31.56, 29.29, 28.71, 26.96, 22.54, 14.03; HRMS (EI$^+$) exact mass

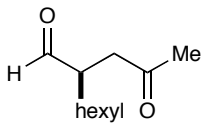
calculated for $[M]^+$ ($C_{12}H_{20}O_2$) requires *m/z* 196.1463, found *m/z* 196.1471; $[\alpha]_D$ = +83.7 (c = 0.82, CH_2Cl_2).



(*R*)-2-(2-cyclohexenyl-2-oxoethyl)octanal (Table 2, entry 5): Prepared according to the general procedure from octanal (32.8 mg, 0.256 mmol) and *tert*-butyl(1-cyclohexenylvinyloxy)dimethylsilane (91.6 mg, 0.384 mmol) to provide the title compound as a colorless oil (45.5 mg, 71% yield, 92% ee) after purification by flash column chromatography on Davisil (3% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel OJ-H (25 cm × 0.46 cm) column (5% MeCN, 100 bar, 35°C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 1.73 min and (*R*) isomer t_r = 1.79 min. IR (film) 2930, 2859, 2715, 1726, 1666, 1638, 1458, 1423, 1389, 1344, 1270, 1196, 1136, 1081, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, 1H, *J* = 1.2 Hz, C**H**O), 6.96-6.93 (m, 1H, C=C**H**CH_2), 3.11 (dd, 1H, *J* = 8.3, 17.1 Hz, C**H**$_2$COC), 2.95-2.90 (m, 1H, C**H**CHO), 2.70 (dd, 1H, *J* = 4.8, 17.1 Hz, C**H**$_2$COC), 2.28-2.21 (m, 4H, **H** in cyclohexenyl), 1.74-1.65 (m, 1H, C**H**$_2$$CH_2CH_2CH_2CH_2CH_3$), 1.64-1.56 (m, 4H, **H** in cyclohexenyl), 1.47-1.34 (m, 1H, C**H**$_2$$CH_2CH_2CH_2CH_2CH_3$), 1.34-1.21 (m, 8H, CH_2**CH$_2$CH$_2$CH$_2$CH$_2$**CH_3), 0.88 (t, 3H, *J* = 6.8 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.15, 198.86, 140.43, 139.0, 46.79, 36.35, 31.58, 29.32, 28.88, 27.06, 26.01, 23.01, 22.55, 21.87, 21.49, 14.04; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{16}H_{26}O_2$) requires *m/z* 250.1933, found *m/z* 250.1941; $[\alpha]_D$ = +53.0 (c = 0.45, CH_2Cl_2).

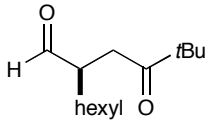


(*R*)-2-hexyl-7,7-dimethyl-6-oxooct-4-enal (Table 2, entry 6): Prepared according to the general procedure from octanal (32.8 mg, 0.256 mmol) and (*Z*)-*tert*-butyl(2,2-dimethylhexa-3,5-dien-3-yloxy)dimethylsilane (92.3 mg, 0.384 mmol) to provide the title compound as a colorless oil (47.9 mg, 74% yield, 96% ee) after purification by flash column chromatography on Davisil (3% ether/pentane). The enantiomeric ratio was determined by SFC analysis Chiralcel OJ-H (25 cm × 0.46 cm) column (5% MeCN, 100 bar, 35°C oven, flow = 4.0 mL/min); (*S*) isomer t_r = 1.05 min and (*R*) isomer t_r = 1.18 min. IR (film) 2930, 2859, 2716, 1726, 1690, 1626, 1477, 1466, 1395, 1366, 1280, 1200, 1081, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, 1H, *J* = 2.1 Hz, C**H**O), 6.88-6.79 (m, 1H, CH_2C**H**=CHCO), 6.55 (dt, 1H, *J* = 1.2, 15.0 Hz, CH_2CH=C**H**CO), 2.61-2.42 (m, 2H, C**H**$_2$CH=CHCO & C**H**CHO), 2.38-2.27 (m, 1H, C**H**$_2$CH=CHCO), 1.68-1.63 (m, 1H, C**H**$_2$$CH_2CH_2CH_2CH_2CH_3$), 1.54-1.42 (m, 1H, C**H**$_2$$CH_2CH_2CH_2CH_2CH_3$), 1.28-1.16 (m, 8H, CH_2**$CH_2CH_2CH_2CH_2$**CH_3), 1.14 (s, 9H, C(C**H**$_3$)$_3$), 0.88 (t, 3H, *J* = 6.9 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.69, 199.58, 143.29, 126.32, 50.62, 42.87, 31.56, 31.26, 29.28, 28.50, 26.56, 26.08, 22.53, 14.02; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{16}H_{28}O_2$) requires *m/z* 252.2089, found *m/z* 252.2095; $[\alpha]_D$ = +18.5 (c = 0.74, CH_2Cl_2).



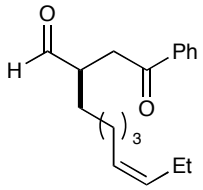
(*R*)-2-(2-oxopropyl)octanal (Table 2, entry 7): Prepared according to the general procedure from octanal (32.8 mg, 0.256 mmol) and *tert*-butyldiphenyl(prop-1-

en-2-yloxy)silane (152 mg, 0.512 mmol) to provide the title compound as a colorless oil (31.8 mg, 67% yield, 86% ee) after purification by flash column chromatography on Davisil (5% ether/pentane). The enantiomeric ratio was determined by GLC using a Chirasil-Dex-CB (30 m × 0.25 mm) column (130 °C isotherm for 30 minutes, 1 mL/min); (*S*) isomer t_r = 13.10 min and (*R*) isomer t_r = 14.02 min. IR (film) 2929, 2858, 2717, 1719, 1466, 1408, 1364, 1166, 963 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H, C**H**O), 2.92-2.84 (m, 2H, C**H**$_2$COMe & C**H**CHO), 2.45 (dd, 1H, *J* = 7.65, 20.7 Hz, C**H**$_2$COMe), 2.19 (s, 3H, COC**H**$_3$), 1.68-1.47 (m, 2H, C**H**$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.30-1.26 (m, 8H, CH$_2$**CH$_2$CH$_2$CH$_2$CH$_2$**CH$_3$), 0.89 (t, 3H, *J* = 6.9 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.73, 203.51, 46.74, 42.11, 31.56, 30.12, 29.28, 28.56, 26.95, 22.53, 14.03; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{11}H_{20}O_2$) requires *m/z* 184.1463, found *m/z* 184.1458; $[\alpha]_D$ = +76.6 (c = 0.96, CH_2Cl_2).



(*R*)-2-(3,3-dimethyl-2-oxobutyl)octanal (Table 2, entry 8): Prepared according to the general procedure from octanal (32.8 mg, 0.256 mmol) and *tert*-butyl(3,3-dimethylbut-1-en-2-yloxy)dimethylsilane (109.8 mg, 0.512 mmol) to provide the title compound as a colorless oil (31.8 mg, 55% yield, 92% ee) after purification by flash column chromatography on Davisil (3% ether/pentane). The enantiomeric ratio was determined by GLC using a Chirasil-Dex-CB (30 m × 0.25 mm) column (130 °C isotherm for 30 minutes, 1 mL/min); (*S*) isomer t_r = 29.05 min and (*R*) isomer t_r = 29.44 min. IR (film) 2958, 2929, 2859, 2715, 1725, 1702, 1478, 1459, 1396, 1365, 1068, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H, C**H**O), 2.98-2.86 (m, 2H,

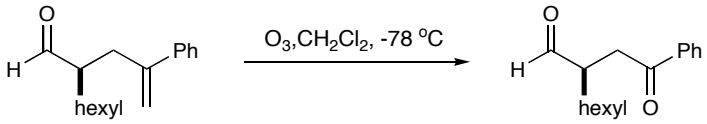
C**H**$_2$CO-*t*-Bu & C**H**CHO), 2.55 (dd, 1H, *J* = 3.9, 17.1 Hz, C**H**$_2$CO-*t*-Bu), 1.70-1.58 (m, 2H, C**H**$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.30-1.22 (m, 8H, CH$_2$**CH$_2$CH$_2$CH$_2$CH$_2$**CH$_3$), 1.16 (s, 9H, C(C**H**$_3$)$_3$), 0.88 (t, 3H, *J* = 6.6 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.07, 203.88, 46.58, 44.01, 36.02, 31.58, 29.32, 28.74, 27.07, 26.49, 22.54, 14.03; HRMS (EI$^+$) exact mass calculated for [M+H]$^+$ ($C_{14}H_{27}O_2$) requires *m/z* 227.2011, found *m/z* 227.2022; $[\alpha]_D$ = +67.6 (c = 0.26, CH_2Cl_2).



(*R*)-2-(2-oxo-2-phenyl ethyl)-dec-7-enal (eq. 6): A solution of the trifluoromethanesulfonic acid salt of (2*S*, 5*S*)-2-*tert*-butyl-5-benzyl-3-methyl-imidazolidin-4-one (18.0 mg, 0.05 mmol) in acetone (4 mL, 0.0625 M) is prepared in a scintillation vial equipped with a magnetic stir bar at -78 ºC under argon. In this order, *cis*-7-decenal (39.5 mg, 0.256 mmol), trimethyl-(1-phenyl-vinyloxy)-silane (96.6 mg, 0.512 mmol), water (18.0 mg, 0.512 mmol), CAN (274 mg, 0.512 mmol), and 2,6-di-*tert*-butyl pyridine (98.0 mg, 0.512 mmol) are added to this mixture. After purging the solution with argon for 1 minute, this mixture is warmed to -20 ºC and stirred at constant temperature for 24 hours until no further reaction progression is observed. The cold reaction is poured into diethyl ether and filtered through davisil, washed with ether and concentrated *in vacuo*. The resulting residue is purified by flash column chromatography on Davisil (3% ether/pentane) to provide the title compound as a colorless oil (55 mg, 79% yield, 91% ee). The enantiomeric ratio was determined by SFC analysis Chiralcel OJ-H (25 cm × 0.46 cm) column (5% to 9.5% CH_3CN, linear

gradient, 100 bar, 35°C oven, flow = 4.0 mL/min); t_r = 2.59 min and 2.91 min. IR (film) 3583, 2961, 2931, 1857, 1725, 1684, 1598, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (d, 1H, *J* = 0.9 Hz, C**H**O), 7.99-7.95 (m, 2H, aryl **H**), 7.60-7.55 (m, 1H, aryl **H**), 7.49-7.44 (m, 2H, aryl **H**), 5.41-5.24 (m, 2H, C**H**=C**H**), 3.47 (dd, 1H, *J* = 7.5, 17.4 Hz, C$\mathbf{H}_2$COPh), 3.14-2.98 (m, 2H, C$\mathbf{H}_2$COPh & C**H**CHO), 2.07-1.97 (m, 4H, C$\mathbf{H}_2$CH=CHC$\mathbf{H}_2$$CH_3$), 1.86-1.74 (m, 1H, C$\mathbf{H}_2$CHCHO), 1.60-1.49 (m, 1H, C$\mathbf{H}_2$CHCHO), 1.43-1.37 (m, 4H, C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_2$CH=CH$CH_2$$CH_3$), 0.95 (t, 3H, *J* = 7.2 Hz, CH=CHCH_2C$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.53, 197.94, 136.51, 133.27, 132.02, 128.60, 128.54, 128.05, 46.69, 37.61, 29.68, 28.73, 26.74, 26.65, 20.49, 14.33; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{18}H_{24}O_2$) requires *m/z* 272.1789, found *m/z* 272.1776; $[\alpha]_D$= +60.0 (c = 0.63, $CHCl_3$).

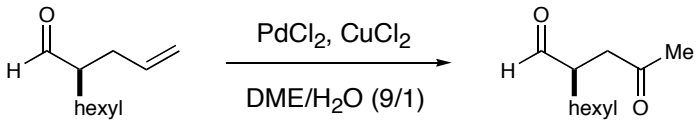
Determination of absolute configuration by chemical correlation:



(*R*)-2-(2-oxo-2-phenylethyl)octanal (Table 1, entry 1) was synthesized from (*R*)-2-(2-phenylallyl)octanal[5] by ozonolysis: To a 50 mL round-bottom-flask containing (*R*)-2-(2-phenylallyl)octanal[5] (20 mg, 0.082 mmol) was dissolved in dichloromethane (20 mL). O_3 was purged through the reaction solution at -78 °C for 30 min, at which point dimethylsulfide (2 mL) was added to quench the reaction. The resulting mixture was allowed to warm to room temperature while vigorous stirring (30 min). After concentration of reaction mixture *in vacuo*, purification by forced flow chromatography

[5] Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582-585.

on Iatrobeads (10-15% Et_2O/pentane) afforded (*R*)-2-(2-oxo-2-phenylethyl)octanal (Table 1, entry 1) as a colorless oil (6 mg, 30% yield, 90% ee). The observed optical rotation ($[\alpha]_D$= +60.4 (c = 0.53, $CHCl_3$)) displayed the sign of rotation, which is consistent with the designated (*R*)-configuration for 2-(2-oxo-2-phenylethyl)octanal ($[\alpha]_D$= +63.9 (c = 1.30, $CHCl_3$) for 90% ee).



(*R*)-2-(2-oxopropyl)octanal (Table 2, entry 7) was synthesized from (*R*)-2-allyloctanal[5,6] by Wacker oxidation[7]: To a 50 mL round-bottom-flask containing (*R*)-2-allyloctanal (50 mg, 0.299 mmol) and dissolved in DME/H_2O (9:1) was added $PdCl_2$ (5.3 mg, 0.03 mmol) and $CuCl_2$ (4.0 mg, 0.03 mmol) in one portion at room temperature. The reaction mixture was stirred under an oxygen atmosphere for 30 min, followed by aqueous extractive work-up with Et_2O. The organic layers were combined, dried and concentrated *in vacuo*. The resulting residue was purified by forced flow chromatography on Iatrobeads (30% Et_2O/pentane) afforded (*R*)-2-(2-oxopropyl)octanal (Table 2, entry 7) as a colorless oil (20.6 mg, 37% yield, 83% ee). The observed optical rotation ($[\alpha]_D$= +82.6 (c = 0.89, CH_2Cl_2)) displayed the sign of rotation, which is consistent with the designated (*R*)-configuration for 2-(2-oxopropyl)octanal ($[\alpha]_D$= +76.6 (c = 0.96, CH_2Cl_2) for 86% ee).

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[6] Hasegawa, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423.
[7] Kulkarni, M. G.; Davawala, S. I.; Doke, A. K.; Pendharkar, D. S. *Synthesis* **2004**, 2919-2926.