Supporting Online Material for

Enantioselective Organocatalysis Using SOMO Activation

Teresa D. Beeson, Anthony Mastracchio, Jun-Bae Hong, Kate Ashton, David W. C. MacMillan*

*To whom correspondence should be addressed. E-mail: dmacmill@princeton.edu

Published 29 March 2007 on *Science* Express
DOI: 10.1126/science.1142696

This PDF file includes:

Enantioselective Organocatalysis Using SOMO Activation

Teresa D. Beeson, Anthony Mastracchio, Jun Bae Hong, Kate Ashton and David W. C. MacMillan*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Supporting Information

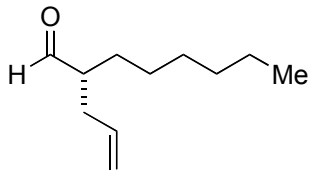
General Information. Commercial reagents were distilled prior to use following the guidelines of Perrin and Armarego (*S1*). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on Iatrobeads 6RS–8060 according to the method of Still (*S2*). Filtration of reactions was perfomed using EMD Silica Gel 60 230-400 mesh. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching using anisaldehyde, ceric ammonium molybdenate, potassium permanganate or iodine stain. Supercritical Fluid Chromatography (SFC) and Gas liquid chromatography (GLC) assays to determine enantiometric excess were developed using racemic samples.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 (300 MHz and 75 MHz respectively) unless otherwise noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H and ^{13}C 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. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR 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 unless otherwise noted. Gas liquid chromatography

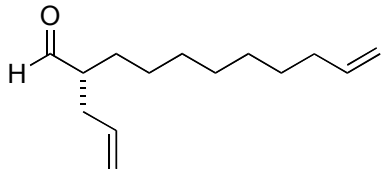
(GLC) was performed on a Hewlett-Packard 6850 Series gas chromatograph equipped with a split-mode capillary injection system and flame ionization detectors using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column or Hewlett Packard HP-1 (30m x 0.32mm) column. Supercritical Fluid Chromatography (SFC) was perfomed on a Berger Minigram equipped with a variable-wavelength UV detector using a Chiralcel® OJH, ODH and Chiralpak®ADH column (25 cm) as noted (4.0 mL/min.). Optical rotations were recorded on a Jasco P-1010 Polarimeter.

General Procedure for the α-Allylation of Aldehydes: To an oven-dried 25 mL round-bottom flask equipped with a magnetic stir bar and charged with (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one trifluoroacetic acid salt **1** (72 mg, 0.20 mmol), ceric ammonium nitrate (CAN) (1.37g, 2.5 mmol) and oven-dried sodium bicarbonate (126 mg, 1.5 mmol) was added dimethoxyethane (*S3*) (DME) (4.0 mL). The suspension was cooled to –50 ºC and deoxygenated by stirring vigorously under vacuum for 3-5 min (*S4*). The mixture was back-filled with argon and degassed twice more. The allyltrimethylsilane substrate (2.5 mmol) was added followed by the aldehyde substrate (1.0 mmol). The reaction was warmed to –20 ºC and stirred for 24 h under an argon atmosphere. The reaction was then cooled to –50 ºC and quickly filtered through a pad of silica gel, eluting with Et_2O. The flask was washed with a minimal amount of DME to transfer any remaining yellow solid to the silica pad. The filtrate was concentrated *in vacuo* and purified by forced flow chromatography to afford the title compounds. The enantioselectivity was determined either by chiral GLC analysis or chiral SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride.

α-Allyl Aldehydes

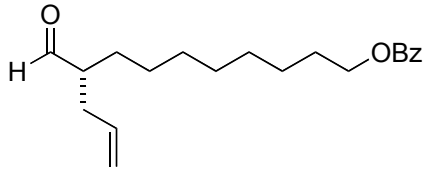


(*R*)-2-Allyloctanal (Table 1, entry 1): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) to afford a yellow oil. Purification on Iatrobeads (2-10% Et_2O/Pentanes) afforded (*R*)-2-allyloctanal as a colorless oil (137 mg, 81% yield, 91% ee). IR (film) 3075, 2928, 2858, 2703, 1728, 1708, 1641, 1458, 992.6, 915.5, 724.0 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.59 (d, *J* = 2.4 Hz, 1H, C**H**O), 5.69-5.84 (m, 1H, C**H**=CH_2), 4.97-5.10 (m, 2H, CH=C**H**$_2$), 2.30-2.46 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 2.17-2.28 (m, 1H, CHC**H**$_2$CH), δ 1.38-1.72 (dm, 2H, C**H**$_2$$(CH_2)_4$), 1.20-1.38 (m, 8H, CH_2(C**H**$_2$)$_4$), 0.87 (t, *J* = 6.9 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 136.4, 116.9, 51.7, 33.5, 32.2, 29.9, 28.8, 27.4, 23.1, 14.2. HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_{11}H_{20}O$) requires *m/z* 168.1514, found *m/z* 168.1508. $[\alpha]_D$ = +12.7 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column (100 °C isotherm); (*S*) isomer t_r = 23.2 min and (*R*) isomer t_r = 23.8 min.



(*R*)-2-Allyl-undec-10-enal (Table 1, entry 2): Prepared according to the general procedure from undecylenic aldehyde (200 μL, 1.00 mmol) to afford a yellow oil. Purification on Iatrobeads (2-10% Et_2O/Pentanes) afforded (*R*)-2-allyl-undec-10-enal as a colorless oil (156 mg, 75% yield, 92% ee). IR (film) 3077, 2927, 2855, 2704, 1728, 1641, 1441, 993.1, 912.1, 721.4 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.59 (d, *J* = 2.2 Hz, 1H, C**H**O), 5.69-5.86 (m, 2H, $CHCH_2$C**H**=CH_2, CH_2CH_2C**H**=CH_2), 4.86-5.10 (m, 4H, $CHCH_2CH$=C**H**$_2$, CH_2CH_2CH=C**H**$_2$), 2.30-2.46 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 2.17-2.28 (m, 1H, CHC**H**$_2$CH), 1.98-2.06 (m, 2H, CH_2C**H**$_2$CH=CH_2), 1.20-1.72 (m, 12H, CH(C**H**$_2$)$_6$); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 139.7, 136.5, 116.9, 114.6, 51.7, 34.4, 33.5, 29.9, 29.6, 29.5, 28.8, 27.5. HRMS (FAB+) exact mass calculated for $[M+\bullet]^+$ ($C_{14}H_{24}O$) requires *m/z* 208.1827, found *m/z* 208.1822. $[\alpha]_D$ = +12.1 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to

the primary alcohol and acylation with 2-naphthoylchloride. (Chiralcel®OJH 5% Isocratic MeCN). t_S(minor) = 3.9 min. t_R(major) = 4.4 min.

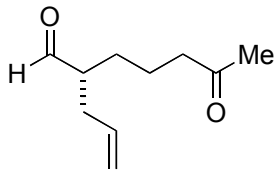


(*R*)-9-Formyldodec-11-enyl benzoate (Table 1, entry 3): Prepared according to the general procedure from 9-formylnonyl benzoate (138 mg, 0.5 mmol) to afford a yellow oil. Purification on Iatrobeads (10-50% Et_2O/Pentanes) afforded (*R*)-9-formyldodec-11-enyl benzoate as a colorless oil (114 mg, 72% yield, 95% ee). IR (film) 3077, 2927, 2855, 2704, 1728, 1641, 1441, 993.1, 912.1, 721.4 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.59 (d, *J* = 2.1 Hz, 1H, C**H**O), 7.99-8.04 (m, 2H, Ph), 7.59-7.66 (m, 1H, Ph), 7.47-7.54 (m, 2H, Ph), 5.69-5.84 (m, 1H, C**H**=CH_2), 4.97-5.10 (m, 2H, CH=C**H**$_2$), 4.30 (t, *J* = 6.5 Hz, 2H, C**H**$_2$OBz), 2.30-2.46 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 2.17-2.28 (m, 1H, CHC**H**$_2$CH), 1.20-1.82 (m, 14H, (C**H**$_2$)$_7$$CH_2$OBz); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 166.6, 136.5, 133.7, 131.4, 130.0, 129.3, 116.9, 65.4, 51.7, 33.5, 30.2, 29.9, 29.8, 29.3, 28.8, 27.4, 26.6. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{20}H_{28}O_3$) requires *m/z* 316.2039, found *m/z* 316.2041. $[\alpha]_D$ = +5.8 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after acetal formation with (*R,R)*-pentadiol of both (*R*)-9-formyldodec-11-enyl benzoate and (*S*)-9-formyldodec-11-enyl benzoate, separately. (Chiralcel®ODH 5-10% MeCN). (*R,R,S*) isomer t_r = 6.2 min and (*R,R,R*) isomer t_r = 6.9 min.

9-Formylnonyl Benzoate: A solution of 10-hydroxydecyl benzoate (2.9 g, 10.4 mmol) in dichloromethane (DCM) (40 mL) was cooled to 0 ºC and pyridinium chlorochromate (PCC) was added (3.4 g, 15.6 mmol). The reaction was warmed to ambient temperature and stirred for 4 h. The reaction was filtered through Florisil®, washing with Et_2O and concentrated in vacuo. Purification by forced flow chromatography (30% Et_2O/Pentanes) affored the title compound (1.58 g, 55% yield). IR (film) 2922, 2851, 1714, 1451, 1386, 1309, 1269, 1173, 1105, 1070, 1024, 708 cm^{-1}; ^{1}H

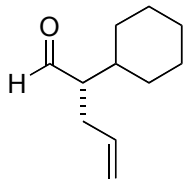
NMR (600 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.83 Hz, 1H, C**H**O), 8.04-8.06 (m, 2H, *ortho*-phenyl), 7.54-7.58 (m, 1H, *para*-phenyl), 7.43-7.46 (m, 2H, *meta*-phenyl), 4.32 (t, *J* = 6.78 Hz, 2H, C$\mathbf{H_2}$OC(O)Ph), 2.34-2.44 (m, 2H, C$\mathbf{H_2}$CHO), 1.75-1.79 (m, 2H, C$\mathbf{H_2}$$CH_2$OC(O)Ph), 1.62-1.65 (m, 2H, C$\mathbf{H_2}$$CH_2$CHO), 1.33-1.47 (m, 10H, CH_2(C$\mathbf{H_2}$)$_\mathbf{5}$$CH_2$); ^{13}C NMR (125 MHz, acetone-d_6) δ 202.9, 166.7, 133.8, 131.5, 130.1, 129.4, 64.6, 44.3, 34.2, 30.1, 30.0, 29.9, 26.8, 25.7, 22.7. HRMS (EI+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}O_3$) requires *m/z* 277.1804, found *m/z* 277.1795 (*S4*).

10-Hydroxydecyl benzoate: To a solution of 1,10-decanediol (5.0 g, 28.7 mmol) in 100 mL of tetrahydrofuran (THF) was added triethylamine (TEA) (4.8 mL, 34.4 mmol) and the reaction mixture was cooled to 0 ºC. Benzoyl chloride (1.7 mL, 14.3 mmol) was slowly added and the reaction mixture was stirred at 0 ºC for 45 min. then at ambient temperature overnight. The reaction was concentrated in vacuo until 15 mL of solvent remained, then filtered and washed with Et_2O. The filtrate was concentrated in vacuo and filtered a second time, and the filtrate purified by forced flow chromatography (30-100% Et_2O/Pentanes) (2.91 g, 73% yield). IR (film) 3362, 2922, 2851, 1717, 1451, 1383, 1312, 1269, 1173, 1110, 1067, 1024, 706 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.04 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H, *ortho*-phenyl), 7.62-7.66 (m, 1H, *para*-phenyl), 7.50-7.55 (m, 2H, *meta*-phenyl), 4.32 (t, *J* = 6.8 Hz, 2H, C$\mathbf{H_2}$OC(O)Ph), 3.51-3.55 (m, 2H, C$\mathbf{H_2}$OH), 3.38-3.44 (m, 1H, O**H**), 1.75-1.82 (m, 2H, C$\mathbf{H_2}$$CH_2$OC(O)Ph), 1.31-1.54 (m, 14H, (C$\mathbf{H_2}$)$_\mathbf{7}$$CH_2$OH; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 133.0, 130.7, 129.7, 128.5, 65.3, 63.3, 33.0, 29.7, 29.6 29.6, 29.4, 28.9 26.2, 25.9. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{17}H_{26}O_3$) requires *m/z* 278.1882, found *m/z* 278.1879 (*S5*).



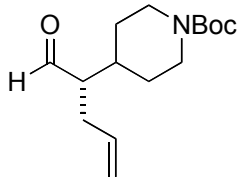
(*R*)-2-Allyl-6-oxoheptanal (Table 1, entry 4): Prepared according to the general procedure from 6-oxoheptanal (*S6*) (128 mg, 1.0 mmol) to afford a yellow oil.

Purification on Iatrobeads (20-60% Et_2O/Pentanes) afforded (*R*)-2-allyl-6-oxoheptanal as a colorless oil (121 mg, 72% yield, 87% ee). IR (film) 3418, 3079, 2931, 2862, 2720, 1718, 1642, 1416, 1361, 1164, 996.4, 919.5, 725.7 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.60 (d, *J* = 2.1 Hz, 1H, C**H**O), 5.69-5.84 (m, 1H, C**H**=CH_2), 4.97-5.11 (m, 2H, CH=C**H**$_2$), 2.46 (t, *J* = 6.9 Hz, 2H, C**H**$_2$$OCH_3$), 2.32-2.44 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 2.18-2.28 (m, 1H, CHC**H**$_2$CH), 2.06 (s, 3H, C**H**$_3$), 1.39-1.68 (m, 4H, CH(C**H**$_2$)$_2$); ^{13}C NMR (75 MHz, acetone-d_6) δ 207.6, 204.6, 136.3, 117.0, 51.6, 43.4, 33.4, 29.6, 28.1, 21.6. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{10}H_{16}O_2$) requires *m/z* 168.1150, found *m/z* 168.1149. $[\alpha]_D$ = –8.0 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC analysis after acetal formation with (*R,R)*-pentadiol of both (*R*)-2-allyl-6-oxoheptanal and (*S*)-2-allyl-6-oxoheptanal, separately. Varian Chirasil-Dex-CB (25M x 0.25mm) column (115 ^{0}C isotherm); (*R,R,R*) isomer t_r = 93.5 min and (*R,R,S*) isomer t_r = 96.6 min.

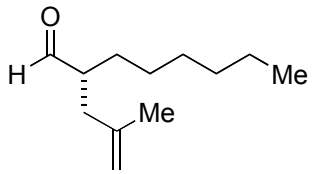


(*S*)-2-Cyclohexylpent-4-enal (Table 1, entry 5): Prepared according to the general procedure from 2-cyclohexylacetaldehyde (15.6 mg, 0.125 mmol) and methyl cyclohexanecarboxylate (19.9 mg, 0.140 mmol) as an internal standard (75% GC yield, 94% ee). Purification on Iatrobeads for characterization (10-50% Et_2O/Pentanes) afforded (*S*)-2-cyclohexylpent-4-enal as a volatile colorless oil containing Et_2O. IR (film) 3078, 2927, 2854, 2706, 1726, 1642, 1449, 994.1, 914.8, 851.6 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.62 (d, *J* = 2.7 Hz, 1H, C**H**O), 5.68-5.81 (m, 1H, C**H**=CH_2), 4.94-5.08 (m, 2H, CH=C**H**$_2$), 2.36-2.47 (m, 1H, CHC**H**$_2$CH), 2.16-2.30 (m, 2H, CHC**H**$_2$CH, C**H**CHO), 1.60-1.78 and 1.02-1.33 (m, 11H, cyclohexyl); ^{13}C NMR (75 MHz, acetone-d_6) δ 205.0, 137.1, 116.5, 57.4, 38.4, 31.1, 30.8, 30.6, 27.0, 27.0, 26.8. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{11}H_{18}O$) requires *m/z* 166.1358, found *m/z* 166.1361. $[\alpha]_D$ = +33.9 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC

using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column (100 °C isotherm); (*S*) isomer t_r = 36.3 min and (*R*) isomer t_r = 37.7 min.

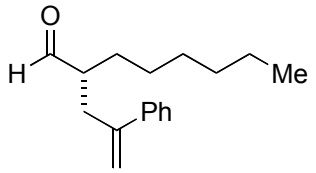


***tert*-Butyl 4-((*S*)-1-formylbut-3-enyl)piperidine-1-carboxylate (Table 1, entry 6):** Prepared according to the general procedure from *tert*-butyl 4-(formylmethyl)piperidine-1-carboxylate (*S7*) (114 mg, 0.5 mmol) to afford a yellow oil. Purification on Iatrobeads (25-50% Et_2O/Pentanes) afforded *tert*-butyl 4-((*S*)-1-formylbut-3-enyl)piperidine-1-carboxylate as a colorless oil (94 mg, 70% yield, 93% ee). IR (film) 2977, 2932, 2854, 2713, 1726, 1692, 1423, 1366, 1281, 1249, 1172, 918.0, 866.6, 769.3 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.65 (d, *J* = 2.7 Hz, 1H, C**H**O), 5.69-5.84 (m, 1H, C**H**=CH_2), 4.98-5.10 (m, 2H, CH=C**H**$_2$), 4.08 (bs, 2H, (C**H**$_a$H$_b$)$_2$NBoc), 2.67 (bs, 2H, (CH$_a$**H**$_b$)$_2$NBoc), 2.24-2.46 (m, 3H, CHC**H**$_2$CH, C**H**CHO), 1.84-1.98 (m, 1H, C**H**CHCHO), 1.58-1.72 (m, 2H, (C**H**$_a$H$_b$CH$_2$)$_2$NBoc), 1.41 (s, 9H, (C**H**$_3$)$_3$), 1.13-1.31 (m, 2H, (CH$_a$**H**$_b$CH$_2$)$_2$NBoc); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.7, 154.8, 136.7, 116.9, 79.1, 56.5, 36.5, 30.8, 28.4. HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_{15}H_{24}NO_3$) requires *m/z* 266.1756, found *m/z* 266.1762. $[\alpha]_D$ = +7.8 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride. (Chiralcel®ODH 5-50% MeCN). t_R(major) = 5.9 min. t_S(minor) = 6.2 min.



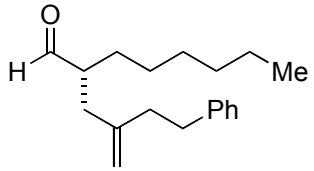
(*R*)-2-(2-Methylallyl)octanal (Table 1, entry 7): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) and methallyltrimethylsilane

(440μL, 2.50 mmol) to afford a yellow oil. Purification on Iatrobeads (2-10% Et_2O/Pentanes) afforded (*R*)-2-(2-methylallyl)octanal as a colorless oil (160 mg, 88% yield, 91% ee). IR (film) 3075, 2929, 2857, 2703, 1729, 1651, 1456, 1377, 892.5, 724.0 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.56 (d, *J* = 2.7 Hz, 1H, C**H**O), 4.74-4.77 (m, 1H, C=C**H$_a$**H$_b$), 4.70-4.72 (m, 1H, C=CH$_a$**H$_b$**), 2.35-2.52 (m, 2H, CHC**H$_2$**C=, C**H**CHO), 2.10-2.16 (m, 1H, CHC**H$_2$**C=), 1.70 (s, 3H, CC**H$_3$**), 1.40-1.66 (dm, 2H, C**H$_2$**(CH$_2$)$_4$), 1.22-1.34 (m, 8H, CH$_2$(C**H$_2$**)$_4$), 0.86 (t, *J* = 6.6 Hz, 3H, C**H$_3$**); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.9, 143.7, 112.6, 50.1, 37.7, 32.3, 29.3, 27.5, 23.1, 22.3, 14.2. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{12}H_{22}O$) requires *m/z* 182.1671, found *m/z* 182.1663. $[\alpha]_D$ = +14.5 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Varian Chirasil-Dex-CB (25 m x 0.25 mm) column (100 °C isotherm); (*S*) isomer t_r = 35.4 min and (*R*) isomer t_r = 36.1 min.

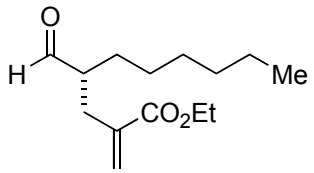


(*R*)-2-(2-Phenylallyl)octanal (Table 1, entry 8): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) and trimethyl(2-phenylallyl)silane (*S8*): (476 mg, 2.50 mmol) to afford a yellow oil. Purification on Iatrobeads (3-30% Et_2O/Pentanes) afforded (*R*)-2-(2-phenylallyl)octanal as a colorless oil (213 mg, 87% yield, 90% ee). IR (film) 3082, 3057, 3025, 2955, 2929, 2857, 2710, 1727, 1628, 1600, 1574, 1495, 1456, 1378, 1303, 1076, 1028, 900.6, 778.7, 705.8 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.58 (d, *J* = 2.7 Hz, 1H, C**H**O), 7.12-7.30 (m, 5H, **Ph**), 5.32 (d, *J* = 1.3 Hz, 1H, C=C**H$_a$**H$_b$), 5.13 (q, *J* = 1.3 Hz, 1H, C=CH$_a$**H$_b$**), 2.96 (ddd, *J* = 14.6 Hz, 7.4 Hz, 1.3 Hz, 1H, CHOCHC**H$_a$**H$_b$), 2.63 (ddd, *J* = 14.6 Hz, 6.9 Hz, 1.1 Hz, 1H, CHOCHCH$_a$**H$_b$**), 2.31-2.42 (m, 1H, C**H**CHO), 1.42-1.68 (m, 2H, CH$_2$(C**H$_2$**)$_4$), 1.18-1.34 (m, 8H, CH$_2$(C**H$_2$**)$_4$), 0.84 (t, *J* = 7.2 Hz, 3H, C**H$_3$**); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.5, 147.0, 141.3, 129.2, 128.4, 127.0, 114.7, 50.4, 35.2, 32.2, 29.9, 29.0, 27.2, 23.1, 14.2. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{17}H_{24}O$) requires *m/z* 244.1827,

found *m/z* 244.1837. $[\alpha]_D$ = +13.4 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol. (Chiralcel®OJH 2-5% IPA). t_R(major) = 5.2 min. t_S(minor) = 6.1 min.



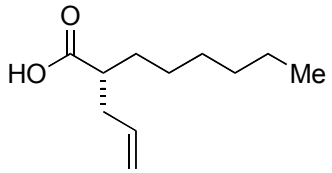
(*R*)-2-Hexyl-4-phenethyl-pent-4-enal (Table 1, entry 9): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) and trimethyl(2-methylene-4-phenylbutyl)silane (*S9*) (546 mg, 2.50 mmol) to afford a yellow oil. Purification on Iatrobeads (3-30% Et_2O/Pentanes) afforded (*R*)-2-hexyl-4-phenethyl-pent-4-enal as a colorless oil (209 mg, 77% yield, 88% ee). IR (film) 3085, 3027, 2955, 2929, 2857, 2708, 1727, 1645, 1604, 1496, 1454, 1077, 1031, 895.9, 747.2, 698.7 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.57 (d, *J* = 2.9 Hz, 1H, C**H**O), 7.13-7.30 (m, 5H, **Ph**), 4.84 (app. d, *J* = 1.3 Hz, 1H, C=C**H$_a$**H$_b$), 4.79 (app. d, *J* = 1.1 Hz, 1H, C=CH$_a$**H$_b$**), 2.76 (dd, *J* = 8.2 Hz, 8.0 Hz, 2H, C**H$_2$**Ph), 2.14-2.57 (m, 5H, C**H**CHO, CHC**H$_2$**C=C, C**H$_2$**CH$_2$Ph), 1.38-1.68 (dm, 2H, C**H$_2$**(CH$_2$)$_4$), 1.20-1.38 (m, 8H, CH$_2$(C**H$_2$**)$_4$), 0.86 (t, *J* = 6.9 Hz, 3H, C**H$_3$**); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.9, 147.2, 142.7, 129.1, 129.0, 126.5, 112.0, 50.2, 38.3, 36.1, 34.8, 32.3, 29.4, 27.5, 23.1, 14.2. HRMS (EI+) exact mass calculated for $[M+\bullet]^+$ ($C_{19}H_{28}O$) requires *m/z* 272.2140, found *m/z* 272.2129. $[\alpha]_D$ = +11.6 (c = 1.0, $CHCl_3$). Enantiopurity was determined by SFC analysis after reduction to the primary alcohol and acylation with 2-naphthoylchloride. (Chiralpak®ADH 2-25% IPA). t_S(minor) = 7.4 min. t_R(major) = 7.8 min.



(*R*)-Ethyl 4-formyl-2-methylenedecanoate (Table 1, entry 10): Prepared according to the general procedure from octanal (156 μL, 1.00 mmol) to afford a yellow oil. Purification on Iatrobeads (10-50% Et_2O/Pentanes) afforded (*R*)-ethyl 4-formyl-2-

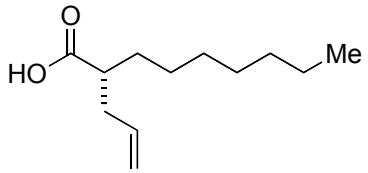
methylenedecanoate as a colorless oil (194 mg, 81% yield, 90% ee). IR (film) 2930, 2858, 2712, 1720, 1630, 1466, 1370, 1302, 1185, 1153, 1027, 948.7, 854.3, 818.8, 724.7 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.58 (d, *J* = 2.7 Hz, 1H, C**H**O), 6.16 (d, *J* = 1.3 Hz, 1H, C=C**H$_a$**H$_b$), 5.66 (d, *J* = 1.3 Hz, 1H, C=CH$_a$**H$_b$**), 4.16 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 2.64-2.73 (m, 1H, C**H$_a$**H$_b$C=CH**$_2$**), 2.47-2.58 (m, 1H, C**H**CHO), 2.37-2.45 (m, 1H, CH$_a$**H$_b$**C=CH**$_2$**), 1.38-1.72 (dm, 2H, C**H$_2$**(CH$_2$)$_4$), 1.26 (t, *J* = 7.2 Hz, 3H, OCH_2C**H$_3$**), 1.22-1.36 (m, 8H, CH$_2$(C**H$_2$**)**$_4$**), 0.86 (t, *J* = 6.6 Hz, 3H, C**H$_3$**); ^{13}C NMR (75 MHz, acetone-d_6) δ 204.3, 166.9, 139.2, 126.9, 61.1, 51.2, 32.2, 31.8, 29.9, 29.2, 27.4, 23.1, 14.3, 14.2. HRMS (EI+) exact mass calculated for $[M-H]^+$ ($C_{14}H_{23}O_3$) requires *m/z* 239.1647, found *m/z* 239.1659. $[\alpha]_D$ = +13.0 (c = 1.0, $CHCl_3$). Enantiopurity was determined by achiral GLC after acetal formation with (*R,R*)-pentanediol and (*S,S*)-pentanediol, separately. Hewlett Packard HP-1 (30 m x 0.32 mm) column (140 °C isotherm); (*R,R,R*) and (*S,S,S)* isomer t_r = 91.5 min and (*R,R,S*) and (*S,S,R)* isomer t_r = 93.7 min.

Determination of Absolute Stereochemistry

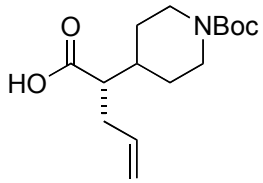


(*R*)-2-Allyloctanoic acid: To a flask containing (*R*)-2-allyloctanal (45 mg, 0.267 mmol, 91% ee) and dissolved in *tert*-butanol (800 μL) and water (300 μL) at 0 ºC was added sodium dihydrogenphosphate hydrate (9.2 mg, 0.067 mmol) followed by 2-methyl-2-butene (124 μL, 1.17 mmol). Separately, sodium chlorite (42 mg, 0.374 mmol) was dissolved in water (500 μL) and cooled to 0 ºC, and the solution added to the aldehyde solution. The reaction was allowed to warm to ambient temperature over 4 h. Saturated sodium sulfite (1.00 mL) was added and stirred vigorously 5 min. The reaction was acidified to pH~2, extracted with Et_2O (3 x 25 mL), and dried over Na_2SO_4. Purification by forced flow chromatography on Iatrobeads (5-50% Et_2O/Pentanes) afforded a colorless oil (31 mg, 63% yield), which corresponded to the reported literature compound

(*S10*). $[\alpha]_D$ = +12.7 (c = 1.0, EtOH), Lit. (*S*)-2-allyloctanoic acid $[\alpha]_D$ = –11.1 (c = 1.0, EtOH).

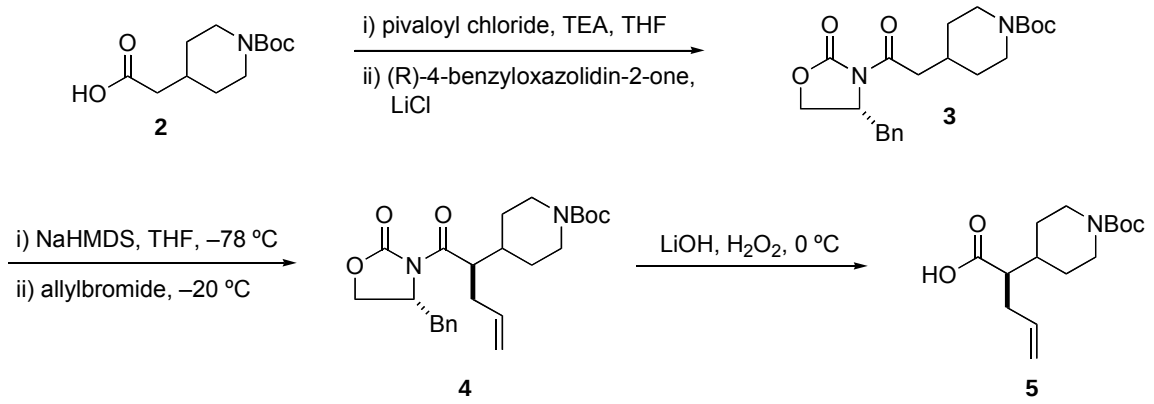


(*R*)-2-Allylnonanoic acid: Prepared according to the oxidation procedure for (*R*)-2-allyloctanoic acid from (*R*)-2-allylnonanal (*S11*) (45 mg, 0.250 mmol, 91% ee). Purification by forced flow chromatography on Iatrobeads (5-50% Et_2O/Pentanes) afforded a colorless oil (37 mg, 76% yield). Spectral data for the title compound matched the reported literature compound (*S12*). $[\alpha]_D$ = +5.99 (c = 1.0, $CHCl_3$), Lit. (*S*)-2-allylnonanoic acid $[\alpha]_D$ = –8.1 (c = 2.78, $CHCl_3$).



(*S*)-2-(1-*tert*-Butoxycarbonyl)piperidin-4-yl)pent-4-enoic acid: Prepared according to the oxidation procedure for (*R*)-2-allyloctanoic acid from *tert*-butyl 4-((*S*)-1-formylbut-3-enyl)piperidine-1-carboxylate (52 mg, 0.194 mmol, 93% ee). The reaction was extracted with EtOAc (3 x 25 mL) in place of Et_2O (40 mg, 73% yield). IR (film) 3073, 2977, 2934, 2861, 1733, 1659, 1428, 1367, 1282, 1249, 1167, 1138, 993.8, 916.7, 866.4, 766.3 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 5.74-5.85 (m, 1H, C**H**=CH_2), 4.96-5.10 (m, 2H, CH=C$\mathbf{H_2}$), 4.08 (bs, 2H, (C$\mathbf{H_a}H_b)_2$NBoc), 2.67 (bs, 2H, ($CH_a\mathbf{H_b}$)$_2$NBoc), 2.24-2.38 (m, 3H, CHC$\mathbf{H_2}$CH, C**H**CHO), 1.58-1.80 (m, 3H, (C$\mathbf{H_a}H_bCH_2)_2$NBoc, C**H**CHCHO), 1.41 (s, 9H, (C$\mathbf{H_3}$)$_3$), 1.10-1.32 (m, 2H, ($CH_a\mathbf{H_b}CH_2)_2$NBoc); ^{13}C NMR (Bruker Avance II 500, APT experiment, 125 MHz, acetone-d_6) δ 176.2, 155.8, 137.8, 117.6, 80.1, 52.1, 39.6, 35.1, 31.4, 29.4. HRMS (FAB+) exact mass calculated for

$[M+H]^+$ ($C_{15}H_{26}NO_4$) requires *m/z* 284.1862, found *m/z* 284.1872. $[\alpha]_D$ = +12.23 (c = 1.0, EtOH).



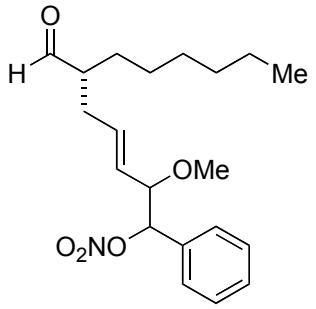
(*R*)-2-(1-*tert*-Butoxycarbonyl)piperidin-4-yl)pent-4-enoic acid: *tert*-Butyl 4-(formylmethyl)piperidine-1-carboxylate (*S6*) (500 mg, 2.2 mmol) was converted to the corresponding carboxylic acid **2** using the procedure described for (*R)*-2-allyloctanoic acid (473 mg, 88% yield).

The carboxylic acid **2** was converted to the 4-[2-((*R*)-4-benzyl-2-oxo-oxazolidin-3-yl)-2-oxo-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester **3** in like manner as described by Fuwa *et al* (*S13*). The carboxylic acid **2** (217 mg, 0.89 mmol) was dissolved in dry THF (7.0 mL) and TEA (248 μL, 1.78 mmol) and cooled to –78 ºC. Pivaloyl chloride (132 μL, 1.07 mmol) was added and the reaction was gradually warmed to 0 ºC over 90 min. (*R*)-4-benzyloxazolidin-2-one (158 mg, 0.89 mmol) was added followed by lithium chloride (113 mg, 2.67 mmol) and the reaction was warmed to ambient temperature and stirred overnight. The reaction was diluted with ethyl acetate (EtOAc) (25 mL) and washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by forced flow chromatography (silica gel, 10-50% EtOAc/Hexanes) afforded **3** (215 mg, 60% yield).

Allylation of **3** was performed in like manner to Evans *et al.* (*S14*), **3** (172 mg, 0.427 mmol) was dissolved in THF (4 mL) and cooled to –78 ºC. $NaN(SiMe_3)_2$ (641 μL, 0.64 mmol) was added and the reaction was stirred for 1 h. Allylbromide (145 μL, 1.71 mmol) was then added and the reaction was warmed to –20 ºC over 6 h. A saturated NH_4Cl solution (5 mL) was added and the reaction stirred overnight. The reaction was

diluted with EtOAc (25 mL) and washed with saturated aqueous NH4Cl (10 mL), and brine (10 mL). Dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by forced flow chromatograpy (silica gel, 5-50% EtOAc/hexanes) afforded 4-[(*R*)-1-((*R*)-4-benzyl-2-oxo-oxazolidine-3-carbonyl)-but-3-enyl]-piperidine-1-carboxylic acid *tert*-butyl ester **4** (60 mg, 32% yield).

The allylated oxazolidinone **4** was converted to the title compound **5** in like manner to the method of Stončius *et al.* (*S15*) **4** (40 mg, 0.09 mmol) was dissolved in THF (1 mL) and cooled to 0 ºC. H_2O_2 (30% aqueous, 44 µL, 0.39 mmol) was added dropwise followed by a solution of LiOH hydrate (8.4 mg, 0.20 mmol) in water (500 µL). Stirring was continued at 0 ºC for 3 h. Saturated Na_2SO_3 (500 µL) and saturated $NaHCO_3$ (500 µL) aqueous solutions were added and the mixture stirred vigorously allowing to warm to ambient temperature overnight. The reaction was acidified with 1N HCl to pH~2, and extracted with EtOAc (3 x 10 mL). Dried over Na_2SO_4, filtered and concentrated in vacuo to afford the title compound **5** (20 mg, 80% yield). Spectral data was identical to the (*S*)-enantiomer synthesized above. $[\alpha]_D = -11.07$ (c = 1.0, EtOH).



2-((*E*)-4-methoxy-5-nitrooxy-5-phenylpent-2-enyl)octanal (Figure 3c): Prepared according to the general procedure, in acetone-d_6 with water (18mg, 1.0 mmol), from octanal (78 µl, 0.5 mmol) and (*trans, trans*-2-methoxy-3-phenylcyclopropyl)ethylene (*S16)* to afford a yellow oil. Purification on Iatrobeads (5-50% Et_2O/Pentanes) afforded 2-((*E*)-4-methoxy-5-nitrooxy-5-phenylpent-2-enyl)octanal as a colorless oil. The product obtained is a 2 : 1 : 1 : 0.5 mixture of diastereomers. Data reported for the major diastereomer only. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.59 (d, 1H, *J* = 2.4 Hz, C**H**O), 7.26-7.44 (m, 5H, Ph), 5.94 (d, 1H, *J* = 5.2, Hz, C**H**ONO_2), 5.66-

5.73 (m, 1H, C**H**=CH), 5.35-5.42 (m, 1H, C**H**=CH), 4.04-4.09 (m, 1H, C**H**-OMe), 3.21 (s, 3H, OC**H**$_3$), 2.36-2.46 (m, 3H, C**H**CHO, C**H**$_2$CH=CH), 1.29-1.66 (m, 10H, (C**H**$_2$)$_5$CH$_3$) 0.87-0.89 (m, 3H, C**H**$_3$); ^{13}C NMR (150 MHz, acetone-d$_6$) δ 205.3, 135.9, 130.29, 130.0, 129.7, 129.4, 129.1, 87.5, 83.9, 57.2, 52.3, 34.7, 32.8, 32.5, 30.0, 28.0, 23.8, 14.9.

***tert*-butyl 2-(1-hydroxyoctan-2-yl)-1H-pyrrole-1-carboxylate (Figure 3a):** A solution of the trifluoromethanesulfonic acid salt of (2*S*, 5*S*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (18.0 mg, 0.05 mmol) in DME (1 mL) was prepared in a scintillation vial equipped with a magnetic stir bar at –78 °C under argon. In this order, octanal (32 mg, 0.25 mmol), Boc-pyrrole (125.4 mg, 0.75 mmol), water (18 mg, 1.0 mmol) and CAN (274.1 mg, 0.5 mmol) were added to this mixture. After purging the solution with argon for 1 minute, the reaction mixture was warmed to –30 °C and stirred for 12 hours until the reaction was judged to be complete by TLC. The cold reaction mixture was poured into diethyl ether and filtered through iatrobeads and concentrated *in vacuo*. The resulting residue was dissolved in EtOH (3 mL), cooled to 0 °C and stirred with $NaBH_4$ (19.0 mg, 0.5 mmol) for 1 hour. The reaction was quenched by dropwise addition of saturated NH_4Cl (5 mL) and the aqueous layer was extracted with Et_2O (2× 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% ether/pentane) to provide the title compound as colorless oil (62 mg, 84% yield, 84 %ee). The enantiomeric ratio was determined by SFC analysis using a Chiralcel AD-H (25 cm × 0.46 cm) column (5% to 50% MeOH, linear gradient, 100 bar, 35 °C oven, 4.0 mL/min); (*R*) isomer t_r = 1.55 min and (*S*) isomer t_r = 1.91 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.2 (dd, 1H, *J* = 1.8, 3.4 Hz, pyrrole 5**H**), 6.12 (t, 1H, *J* = 3.4 Hz, pyrrole 3**H**), 6.07 (dd, 1H, *J* = 1.8, 3.4, Hz, pyrrole 4**H**), 3.7 (m, 3H, C**H**$_2$OH & C**H**), 1.68 (m, 2H, C**H**$_2$), 1.6 (s, 9H, C(C**H**$_3$)$_3$), 1.20-1.36 (m, 8H, CH$_2$**CH$_2$CH$_2$CH$_2$CH$_2$**CH$_3$), 0.87 (t, 3H, *J* = 7.0 Hz, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.81, 136.95, 121.56, 110.77, 110.11, 83.72, 66.22, 39.95, 31.76, 31.41, 29.52, 28.04, 27.27, 22.66, 14,11; $[\alpha]_D$= –9.6° (c = 1.5, $CHCl_3$, 25 °C).

(1*R*,2*R*,1'*S*)-2-(1'-Chloropropyl)cyclopentanecarbaldehyde (Figure 3b): A 25 mL round bottomed flask equipped with a large magnetic stir bar was charged with LiCl (125 mg, 5.0 mmol, 5.0 equiv.) and catalyst **1** (42 mg, 0.12 mmol, 0.2 equiv.) in distilled acetone (10 ml, 0.0625M) and water (22 μl, 1.2 mmol, 2.0 equiv.). The resultant slurry was degassed at low temperature prior to being stirred at room temperature for 1 hour. The reaction mixture was then cooled to -20 °C, *cis*-6-nonenal (100 ml, 0.6 mmol, 1 equiv.) added and Ceric Ammonium Nitrate (725 mg, 1.32 mmol, 2.2 equiv.) and the solvent degassed via an evacuation/argon flush which was performed three times, for a period of at least a minute each time. The hetereogenous reaction mixture was stirred at between -20 °C and -10 °C for 2 hours, ensuring constant agitation throughout the time period. No monitoring of the reaction was performed as exposure to either air or moisture resulted in a compromised yield of desired product. Upon completion the reaction mixture was diluted with Et_2O to precipitate the catalyst, flushed through a small pad of fluorosil, eluting with Et_2O and a small amount of acetone, and then concentrated *in vacuo*. The product was purified by silica gel chromatography (5% Et_2O/pentane) to yield the title compound as a colourless oil (87 mg, 85% isolated yield, 95% ee for major diastereomer and 90% for minor, ≥8:1 dr) following silica gel chromatography (5% Et_2O/pentane). IR (film) 2963, 2873, 1721, 1452, 1218, 808, 668 cm^{-1}; ^1H NMR (300 MHz, ($CDCl_3$) Major diastereomer δ 1.04 (t, 3H, *J* = 7.5 Hz, -$CH_2C\mathbf{H_3}$), 1.45-1.96 (m, 8H, -$C\mathbf{H_2}C\mathbf{H_2}C\mathbf{H_2}$- and –$C\mathbf{H_2}CH_3$), 2.69 (m, 1H, -C**H**$CH(Cl)CH_2$-), 2.85 (m, 1H, -C**H**C(O)H), 3.85 (ddd, 1H, *J* = 3.3, 6.6, 9.0 Hz, -C**H**Cl), 9.71 (d, 1H, *J* = 2.1 Hz, -C(O)**H**). Minor diastereomer δ 1.04 (m, 3H, -$CH_2C\mathbf{H_3}$), 1.45-1.96 (m, 8H, -$C\mathbf{H_2}C\mathbf{H_2}C\mathbf{H_2}$- and –$C\mathbf{H_2}CH_3$), 2.60 (m, 1H, -C**H**$CH(Cl)CH_2$-), 2.80 (m, 1H, -C**H**C(O)H), 3.94 (ddd, 1H, *J* = 4.5, 4.5, 9.0 Hz, - C**H**Cl), 9.67 (d, 1H, *J* = 1.8 Hz, -C(O)**H**); ^{13}C NMR (75 MHz, CDCl3) Major diastereomer δ 11.1, 25.8, 27.6, 30.4, 31.3, 46.5, 54.8, 69.8, 203.2. Minor diastereomer δ 11.7, 25.2, 27.4, 30.5, 31.3, 45.5, 55.2, 68.9, 203.1; HRMS (EI) exact mass calculated for ($C_9H_{15}OCl$) requires *m/z* 174.0811, found *m/z* 174.0813; $[\alpha]_D$ = -20.7º (c = 2.0, $CHCl_3$); The enantiomeric ratio was determined by GLC using a Γ-TA column (100ºC isotherm for 160 minutes, 1 ml/min); major enantiomer t_r= 45.75 min and minor enantiomer t_r = 29.89 min. The diastereomeric ratio was determined by the same

assay; minor diastereomer, major enantiomer t_r= 40.45 min and minor diastereomer, minor enantiomer t_r= 33.49 min.

References and Notes

S1. D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals* (Pergamon Press, Oxford, 1988) [third edition].

S2. W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **43**, 2923 (1978).

S3. Wet, non-distilled DME. Alternatively, 0.3 equiv. H_2O can be added to dry DME.

S4. The method of freeze-pump thaw, when used to deoxygenate the reaction mixture, showed less consistent results and lower yields, possibly due to the heterogeneity of the reactions.

S5. Mass spectra were obtained from the Princeton University Mass Spectral Facility.

S6. B.-C. Hong, F.-L. Chen, S.-H. Chen, J.-H. Liao, G.-H. Lee, *Org. Lett.* **7**, 557 (2005).

S7. T. Sato, K. Okamoto, Y. Nakano, J. Uenishi, M. Ikeda, *Heterocycles*, ***54***, 747 (2001).

S8. B. A. Narayanan, W. H. Bunnelle, *Tetrahedron Lett.* **28**, 6261 (1987).

S9. J. S. Clark, et al. *J. Org. Chem*, **69**, 3886 (2004).

S10. T. Hasegawa, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **73**, 423 (2000).

S11. (*R*)-2-Allylnonanal was prepared according to the general procedure from nonanal (132 mg, 73% yield, 91% ee).

S12. A. Expósito, M. Fernández-Suárez, T. Iglesias, L. Muñoz, R. Riguera, *J. Org. Chem.* **66**, 4206 (2001**)**.

S13. H. Fuwa, Y. Okamura, H. Natsugari, *Tetrahedron* **60**, 5341 (2004).

S14. D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **104**, 1737 (1982).

S15. A. Stončius, M. Nahrwold, N. Sewald *Synthesis* **11**, 1829 (2005).

S16. M-H. Le Tadic, M. Newcomb *J. Chem. Soc. Perkin Trans. 2* 1467 (1996).