The Enantioselective Organocatalytic 1,4-Addition of Electron-Rich Benzenes to α,β-Unsaturated Aldehydes.

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Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Armarego and Perrin.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Methylene chloride was distilled from calcium hydride prior to use. $CHCl_3$ was distilled from calcium sulfate and potassium carbonate and passed through an alumina plug prior to use. 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.[2] 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, anisaldehyde stain, potassium permanganate stain or dinitrophenylhydrazine stain.

^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 spectrometers (300 MHz and 75 MHz respectively) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). 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 UC Irvine Mass Spectral facility. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard

[1] Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals;* 4th ed., Butterworth-Heinemann: Oxford, 1996.
[2] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

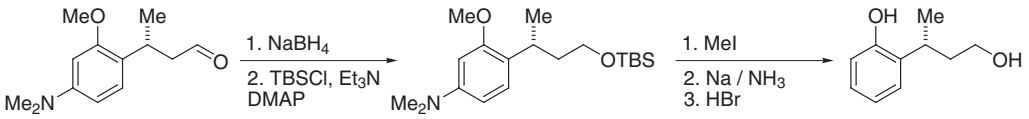
1100 Series chromatographs using Chiralpak AD column (0.46 x 25 cm) and AD guard (0.46 x 5 cm). Optical rotations were taken using a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25 °C).

Catalyst Preparation: (2*S*,5*S*)-5-Benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (2). To a solution of ethanolic $MeNH_2$ (8.0 M, 50 ml) was added (*S*)-phenylalanine methyl ester (23.0 g, 130 mmol). The resulting solution was stirred at room temperature until the amino ester was judged to be consumed by TLC analysis. The resulting solution was then concentrated to provide (*S*)-phenylalanine *N*-methyl amide (18 g, 82% yield) as a white solid. To a flask containing (*S*)-phenylalanine *N*-methyl amide (8.9 g, 50 mmol) was added THF (100 ml), trimethylacetaldehyde (5.4 g, 50 mmol), $FeCl_3$ (1.7 g, 10 mmol) and 4Å MS (5.0 g). The resulting mixture was stirred at room temperature for 36 h, then washed with H_2O (3 x 100 mL). The combined organics were concentrated and the resulting residue was treated with HCl (27 mL, 1*N* in ether). The resulting hetereogenous mixture was filtered to removed the undesired *trans* isomer•HCl salt and the resulting solution was concentrated. The residue was recrystallized (9:1 pentane / CH_2Cl_2) to provide the product as a crystalline solid (2.88 g, 23% yield, >99% ee). IR (film) 3343, 2958, 1605, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H, ArH), 4.04 (s, 1H, NCHN), 3.72-3.65 (m, 1H, C**H**CH_2), 3.13 (dd, *J* = 4.1, 13.7 Hz, 1H, CH_2), 2.92 (dd, *J* = 7.7, 13.7 Hz, 1H, CH_2), 2.90 (s, 3H, NCH_3), 0.82 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 138.0, 129.8, 128.7, 126.8, 82.7, 77.8, 77.4, 76.9, 59.7, 38.6, 35.4, 31.0, 25.7; $[\alpha]_D = -39.6$ (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC using a Chiralpak OD-H and OD guard column (3.0% *i*-PrOH / hexanes, 1 mL/min); (5*S*) isomer t_r = 16.7 min, (5*R*) isomer t_r = 20.1 min.

The *trans* (2*R*,5*S*) isomer of catalyst **2** can be converted to the desired *cis* (2*S*,5*S*) isomer as follows: A solution of *trans*-(*2R*,*5S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one•HCl salt (6.0 g, 27.9 mmol) in Et_2O (100 mL) was washed with saturated aqueous $NaHCO_3$ (100 mL) before the organics were separated and concentrated. To a flask containing the resulting residue was added THF (50 ml) and $FeCl_3$ (0.95 g, 5.6 mmol). The resulting solution was maintained at room temperature for 14 h, then washed with H_2O (3 x 50 mL). The combined organics were concentrated and the resulting residue was treated with HCl (13 mL, 1*N* in ether). The resulting hetereogenous mixture was filtered to removed the undesired *trans* isomer•HCl salt and the

resulting solution was concentrated. The residue was recrystallized (9:1 pentane/CH_2Cl_2) to provide the product as a crystalline solid (1.65 g, 22% yield, >99% ee).

(*R*)-3-(4-Dimethylamino-2-methoxy-phenyl)-butyraldehyde (Table 1, entry 1). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.050 mmol, 0.100 equiv), CH_2Cl_2 (0.50 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.050 mmol, 0.100 equiv), and *N,N*-dimethyl-*m*-anisidine (73.3 μL, 0.500 mmol, 1.00 equiv). The solution was cooled to –40 °C before crotonaldehyde (124 μL, 1.50 mmol, 3.00 equiv) was added. After 36 h, the reaction mixture was subjected directly to silica gel chromatography. Elution with 20% EtOAc in hexanes followed by concentration and removal of residual crotonaldehyde under vacuum afforded the product as a colorless oil in 86% yield (94.9 mg, 0.429 mmol); 89% ee. IR (film) 2958, 2874, 2834, 2719, 1721, 1615, 1568, 1516, 1462, 1441, 1352, 1238, 1133, 1034, 979.6, 814.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (t, *J* = 2.7 Hz, 1H, CHO), 7.03 (d, *J* = 8.2 Hz, 1H, ArH), 6.31 (dd, *J* = 2.5, 8.2 Hz, 1H, ArH), 6.27 (d, *J* = 2.5 Hz, 1H, ArH), 3.83 (s, 3H, OCH_3), 3.63 (dq, *J* = 7.1, 7.1 Hz, 1H, ArCH), 2.94 (s, 6H, $N(CH_3)_2$), 2.68 (ddd, *J* = 2.5, 6.9, 15.9 Hz, 1H, C**H**$_2$CO), 2.55 (ddd, *J* = 2.8, 7.7, 15.9 Hz, 1H, C**H**$_2$CO), 1.27 (d, 3H, CH**CH**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 157.8, 150.9, 127.5, 121.7, 15.1, 96.6, 55.4, 51.2, 41.0, 27.6, 20.9. HRMS (CI) exact mass calcd for ($C_{13}H_{19}NO_2$) requires *m/z* 222.1494 for $[M+H]^+$, found *m/z* 222.1497. $[\alpha]_D$ = − 9.5 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (3.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 21.6 min, *R* isomer t_r = 23.1 min.



S1

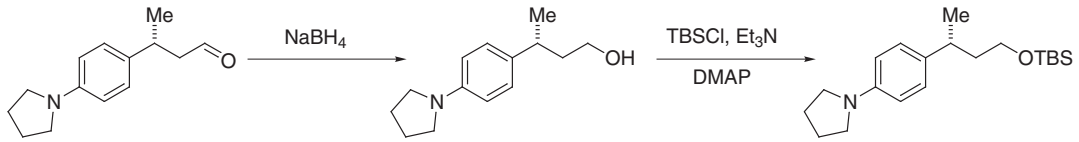
Determination of the absolute configuration (*R*)-3-(4-Dimethylamino-2-methoxy-phenyl)-butyraldehyde by correlation to (*S*)-2-phenyl-butanol. A solution of (*R*)-3-(4-dimethylamino-2-methoxy-phenyl)-butyraldehyde (520 mg, 2.35 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) was added to a stirring solution of sodium borohydride (86.9 mg, 2.35 mmol, 1.00

equiv) in ethanol (5.0 mL). After 5 min, the reaction was diluted with saturated aqueous $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL). The organic layer was separated and washed with saturated solutions of $NaHCO_3$ and NaCl. The resulting solution was then dried over Na_2SO_4 and concentrated *in vacuo.* The residual oil (525 mg, 2.35 mmol, 1.00 equiv) was exposed to *tert*-butyldimethylsilyl chloride (700 mg, 4.70 mmol, 2.00 equiv), triethylamine (0.70 mL, 5.0 mmol, 2.1 equiv), and DMAP (10 mg) in CH_2Cl_2 (3.0 mL). After 1 h, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 2-20% EtOAc in hexanes followed by concentration *in vacuo* afforded **S1** as a colorless oil in 72% yield (568 mg, 1.68 mmol), $[\alpha]_D = -13.3$ (c = 1.12, $CHCl_3$). This oil was dissolved in CH_3I (0.52 mL, 8.4 mmol, 5 equiv) and stirred for 10 h. The resulting mixture was then diluted with Et_2O (20 mL), filtered and dried *in vacuo* to provide a white microcrystaline solid in 88% yield (706 mg, 1.47 mmol). The resulting ammonium salt (479 mg, 1.00 mmol, 1.00 equiv) was dissolved in freshly condensed liquid ammonia (20 ml) at –78 °C and treated with sodium (72 mg, 3.0 mmol, 3.0 equiv). After 3 min, the reaction mixture was quenched with excess methanol, diluted with ether (20 mL) and allowed to warm to ambient temperature. The ethereal solution was washed with aqueous HCl (1N) and saturated NaCl and subsequently dried over Na_2SO_4. The solvents were removed *in vacuo* and this oil was exposed to refluxing 48% HBr. After 8 h the reaction was partitioned between Et_2O and water. The aqueous layer was extracted three times with EtOAc and the combined organics were washed with saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was purified by silica gel chromatography (50% EtOAc in hexanes) to afford 6.40 mg (38 μmol, 3.8% yield from ammonium salt) of a colorless oil that was spectroscopically identical in all respects to the compound (*S*)-2-phenyl-butanol[3]. $[\alpha]_D$ (literature) = +16 (c = 25, acetone); $[\alpha]_D$ (observed) = –6.1 (c = 0.128, acetone), the opposite sign of the rotation indicating that we had produced the enantiomer of the known compound.

(*R*)-3-(4-Pyrolidin-1-yl-phenyl)-butyraldehyde (Table 1, entry 2). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (49.3 mg, 0.200 mmol, 0.200 equiv) CH_2Cl_2 (0.33 ml), HCl (as a 4N solution in 1,4-dioxane, 50 μL, 0.200 mmol, 0.200 equiv), and 1-phenylpyrrolidine (144 μL, 1.00 mmol, 1.00 equiv). The solution was cooled to –20 °C before crotonaldehyde (166 μL, 2.00

[3] Loiodice, et. al. *Tet. Asymm.* **1995**, 1001-1012.

mmol, 2.00 equiv) was added. After 48 h, the reaction mixture was subjected directly to silica gel chromatography. Elution with 20% EtOAc in hexanes followed by concentration *in vacuo* and removal of residual crotonaldehyde under high vacuum afforded the product as a pale yellow oil in 70% yield (147 mg, 0.676 mmol); 87% ee. IR (film) 2962, 2927, 2829, 2717, 1721, 1616, 1522, 1372, 814.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 2.2 Hz, 1H, CHO), 7.10 (d, *J* = 8.8 Hz, 2H, ArH), 6.54 (d, *J* = 8.8 Hz, 2H, ArH), 3.32-3.21 (m, 5H, ArCH, $N(CH_2)_2$), 2.71 (ddd, *J* = 2.2, 7.1, 16.5 Hz, 1H, C**H**$_2$CO), 2.61 (ddd, *J* = 2.2, 7.7, 16.0 Hz, 1H, C**H**$_2$CO), 2.03-1.96 (m, 4H, CH_2(**C**$\mathbf{H_2}$)$_2$$CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 146.7, 132.0, 127.5, 111.8, 52.3, 47.8, 33.8, 25.7, 22.8. HRMS (CI) exact mass calcd for ($C_{14}H_{19}NO$) requires *m/z* 217.1467, found *m/z* 217.1467. $[\alpha]_D = -33.9$ (c = 0.539, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *R* isomer t_r = 20.9 min, *S* isomer t_r = 24.4 min.

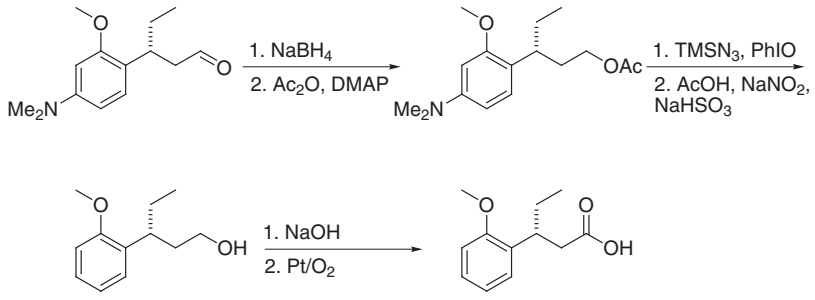


S2 **S3**

Determination of the absolute configuration (*R*)-3-(4-Pyrolidin-1-yl-phenyl)-butyraldehyde by correlation to (*R*)-3-(4-Pyrolidin-1-yl-phenyl)-butanol-*tert*-butyldimethylsilyl ether. A solution (*R*)-3-(4-pyrolidin-1-yl-phenyl)-butyraldehyde (201 mg, 0.923 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added to a stirring solution of sodium borohydride (37.1 mg, 1.00 mmol, 1.08 equiv) in ethanol (3.0 mL). After 5 min, the reaction was diluted with saturated aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (30 mL). The organic layer was separated and washed with saturated solutions of $NaHCO_3$ and NaCl. The resulting solution was then dried over Na_2SO_4 and concentrated *in vacuo.* The residual oil (201 mg, 0.915 mmol, 1.00 equiv) was exposed to *tert*-butyldimethylsilyl chloride (276 mg, 1.83 mmol, 2.00 equiv), triethylamine (0.28 mL, 2.0 mmol, 2.2 equiv), and DMAP (10 mg) in CH_2Cl_2 (1.5 mL). After one hour, the reaction mixture was subjected directly to silica gel chromatography. Elution with 10% Et_2O in hexanes followed by concentration of two fractions *in vacuo* afforded 35 mg of **S3** as a colorless oil (0.10 mmol, 11% yield) that was spectroscopically identical in all respects to **S3**

generated below from (*S*)-4-benzoyloxy-3-(4-pyrolidin-1-yl-phenyl)-butyraldehyde. $[\alpha]_D$ (reference) = –28.7 (c = 1.20, $CHCl_3$); $[\alpha]_D$ (observed) = –34.8 (c = 0.994, $CHCl_3$).

(*R*)-3-(4-Dimethylamino-2-methoxy-phenyl)-pentanal (Table 1, entry 3). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv), CH_2Cl_2 (0.50 ml), HCl (as a 4N solution in 1,4-dioxane, 25.0 μL, 0.100 mmol, 0.200 equiv), and *N,N*-dimethyl-*m*-anisidine (73.3 μL, 0.500 mmol, 1.00 equiv). The solution was cooled to –50 °C before pentenal (98.0 μL, 1.00 mmol, 2.00 equiv) was added. After 62 h, the reaction mixture was subjected directly to silica gel chromatography. Elution with 20% EtOAc in hexanes followed by concentration and removal of residual pentenal under vacuum afforded the product as a colorless oil in 68% yield (79.5 mg, 0.338 mmol); 88% ee. IR (film) 2959, 2926, 2871, 2839, 2800, 2721, 1718, 1616, 1569, 1517, 1351, 1237, 1136, 1034, 979.5, 812.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (t, *J* = 2.8 Hz, 1H, CHO), 6.97 (d, *J* = 8.2 Hz, 1H, ArH), 6.30 (dd, *J* = 2.5, 8.3 Hz, 1H, ArH), 6.26 (d, *J* = 2.5 Hz, 1H, ArH), 3.81 (s, 3H, OCH_3), 3.40 (dt, *J* = 7.3, 7.4 Hz, 1H, ArCH), 2.94 (s, 6H, $N(CH_3)_2$), 2.66 (dd, *J* = 2.7, 7.4 Hz, 2H, CH_2CO), 1.72-1.61 (m, 2H, $C\mathbf{H_2}CH_3$), 0.83 (t, *J* = 7.4 Hz, 3H, $CH_2\mathbf{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) 203.8, 158.2, 150.6, 128.4, 119.8, 105.0, 96.5, 55.5, 49.7, 1.1, 34.9, 28.4, 12.4. HRMS (CI) exact mass calcd for ($C_{14}H_{21}NO_2$) requires *m/z* 236.1650 for $[M+H]^+$, found *m/z* 236.1649. $[\alpha]_D$ = –18.9 (c = 0.970, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (3.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 11.5 min, *R* isomer t_r = 12.4 min.

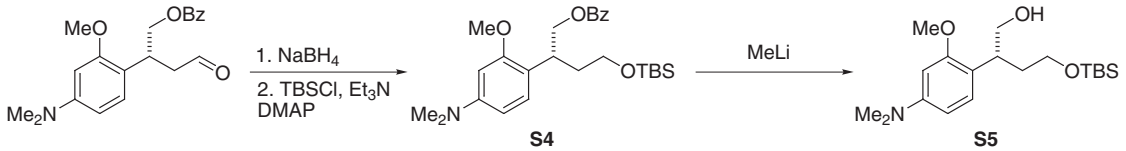


Determination of the absolute configuration of (*R*)-3-(4-dimethylamino-2-methoxy-phenyl)-pentanal by correlation to (*R*)-3-ethyl-*o*-methoxy-dihydrocinnamic acid. A solution of (*R*)-3-(4-dimethylamino-2-methoxy-phenyl)-pentanal (318 mg, 1.35 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) was added to a stirring solution of sodium borohydride (50.1 mg, 1.35 mmol, 1.00 equiv) in ethanol (5.0 mL). After 5 min, the reaction was diluted with saturated aqueous $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL). The organic layer was then separated and washed with saturated solutions of $NaHCO_3$ and NaCl. The resulting solution was then dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was exposed to acetic anhydride (0.254 mL, 2.70 mmol, 2.00 equiv), triethylamine (0.42 mL, 3.0 mmol, 2.2 equiv), and DMAP (10 mg) in CH_2Cl_2 (5.0 mL). After one hour, the reaction mixture was subjected directly to silica gel chromatography. Elution with 25% EtOAc in hexanes followed by concentration *in vacuo* afforded 370 mg (1.32 mmol, 98% yield) of a colorless oil which was treated with iodosylbenzene (1.16 g, 5.28 mmol, 4.00 equiv) and trimethylsilylazide (0.74 ml, 5.6 mmol, 4.2 equiv) in CH_2Cl_2 (32 mL) at –40 °C according to the procedure of Jørgensen[4]. After 2 h, the reaction was warmed to room temperature and treated with THF and saturated aqueous $NaHCO_3$. The resulting mixture was stirred for 12 h then it was diluted with EtOAc, the organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. This residue was dissolved in a mixture of ethanol/AcOH (50 mL: 7.5 mL) and treated with excess $NaNO_3$ (0.93 g in 15 mL H_2O) and $NaHSO_3$ (1.40 g in 15 mL H_2O). This mixture was extracted with $CHCl_3$ and the organic phase was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was dissolved in methanol (2.0 mL) and treated with an excess of NaOH (108 mg). After 15 min, the reaction mixture was diluted with Et_2O (20 mL) and H_2O (20 mL) then the organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated in vacuo. Silica gel chromatography of the residue (5-50% EtOAc in hexanes) afforded 41 mg of a colorless oil (0.21 mmol, 16% yield from dialkyl aniline). Finally, this material was taken up in EtOAc (3.4 mL) and added to a suspension of activated PtO_2 (150 mg, 0.060 mmol, 0.30 equiv) in H_2O/isopropanol (0.7 ml : 0.4 mL). This suspension was stirred under an O_2 atmosphere at 40 °C for 24 h. The reaction mixture was then filtered through Celite with additional EtOAc. The resulting solution was dried over Na_2SO_4 and concentrated *in vacuo* to afford 19.2 mg of a clear oil that was spectroscopically identical in all respects to the known compound (*R*)-3-ethyl-*o*-

[4] Jørgensen, et. al. *J. Am. Chem. Soc.* **2000**, *122*, 12517.

methoxy-dihydrocinnamic acid.[5] [α] (literature) = –21.3 (c = 11.2, $CHCl_3$); $[\alpha]_D$ (observed) = –3.1 (c = 1.0, $CHCl_3$).

(*S*)-4-Benzoyloxy-3-(4-dimethylamino-2-methoxy-phenyl)-butyraldehyde (Table 1, entry 4). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.100 equiv), *N,N*-dimethyl-*m*-anisidine hydrochloride (18.8 mg, 0.100 mmol., 0.100 equiv), $CHCl_3$ (1.00 ml), and *N,N*-dimethyl-*m*-anisidine (132 μL, 0.900 mmol, 0.900 equiv). The solution was cooled to –20 °C before 4-benzoyloxy-crotonaldehyde (0.380, 2.00 mmol, 2.00 equiv) was added as a solid. After 24 h, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 10-25% EtOAc in hexanes followed by concentration and removal of residual pentenal under vacuum afforded the product as a colorless oil in 89% yield (304 mg, 0.889 mmol); 92% ee. IR (film) 2940, 2892, 2836, 2724, 1719, 1615, 1518, 1273, 1240, 1117, 712.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.1 Hz, 1H, CHO), 8.01 (ddd, *J* = 0.6, 1.1, 6.3 Hz., 2H, ArH), 7.58-7.40 (m, 3H, ArH), 7.08 (d, *J* = 8.2 Hz, 1H, ArH), 6.30 (dd, *J* = 2.5, 8.5 Hz, 1H, ArH), 6.25 (d, *J* = 2.4 Hz, 1H, ArH), 4.51 (dd, *J* = 5.5, 10.7 Hz, 1H, C**H**$_2$O), 4.42 (dd, *J* = 8.2, 10.7 Hz, 1H, C**H**$_2$O), 4.08-3.98 (m, 1H, ArCH), 3.83 (s, 3H, OCH_3), 2.98-2.80 (m, 2H, CH_2CO), 2.95 (s, 6H, $N(CH_3)$; ^{13}C NMR (75 MHz, $CDCl_3$) 202.2, 166.6, 158.2, 151.3, 133.1, 130.3, 129.8, 129.0, 128.6, 115.6, 104.9, 96.3, 67.9, 55.4, 46.3, 50.0, 33.5. HRMS (CI) exact mass calcd for ($C_{20}H_{23}NO_4$) requires *m/z* 342.1705 for $[M+H]^+$, found *m/z* 342.1705. $[\alpha]_D$ = –16.9 (c = 0.751, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *R* isomer t_r = 15.2 min, *S* isomer t_r = 24.0 min.



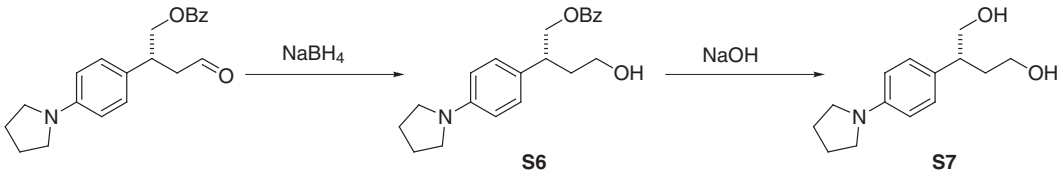
Determination of the absolute configuration (*S*)-4-Benzoyloxy-3-(4-dimethylamino-2-methoxy-phenyl)-butyraldehyde by correlation to (*R*)-3-*tert*-butyldimethylsiloxy-2-

[5] Meyers, A. I. et al, *J. Org. Chem.* **1979**, *44*, 2250-2256.

(dimethylamino-2-methoxy-phenyl)-butanol. A solution (*S*)-4-benzoyloxy-3-(4-dimethylamino-2-methoxy-phenyl)-butyraldehyde (311 mg, 0.911 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added to a stirring solution of sodium borohydride (37.1 mg, 1.00 mmol, 1.10 equiv) in ethanol (3.0 mL). After 5 min, the reaction was diluted with saturated aqueous $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL). The organic layer was then separated and washed with saturated solutions of $NaHCO_3$ and NaCl. The resulting solution was then dried over Na_2SO_4 and concentrated *in vacuo.* The residual oil (303 mg, 0.883 mmol, 1.00 equiv) was exposed to *tert*-butyldimethylsilyl chloride (266 mg, 1.77 mmol, 2.00 equiv), triethylamine (0.27 mL, 1.9 mmol, 2.2 equiv), and DMAP (10 mg) in CH_2Cl_2 (1.0 mL). After one hour, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 10-25% Et_2O in hexanes followed by concentration *in vacuo* afforded 400 mg of **S4** as a colorless oil (0.874 mmol, 99% yield). To a solution of **S4** (50 mg, 0.11 mmol, 1.0 equiv) in Et_2O (0.55 mL) at 0 °C was added MeLi (1.6 M in hexanes, 0.21 mL, 0.33 mmol, 3.0 equiv). After 5 min, the reaction was treated with saturated aqueous NH_4Cl (20 mL) and Et_2O (20 mL). The organic phase was washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel chromatography of the resulting residue (50-100% Et_2O in hexanes) afforded 25.4 mg (72.0 μmol, 65% yield) of **S5** that was spectroscopically identical in all respects to **S5** generated below from (*R*)-4-oxo-2-(4-dimethylamino-2-methoxyphenyl)-butyric acid methyl ester. $[\alpha]_D$ (reference) = –20.1 (c = 1.00, $CHCl_3$); $[\alpha]_D$ (observed) = –21.6 (c = 1.12, $CHCl_3$).

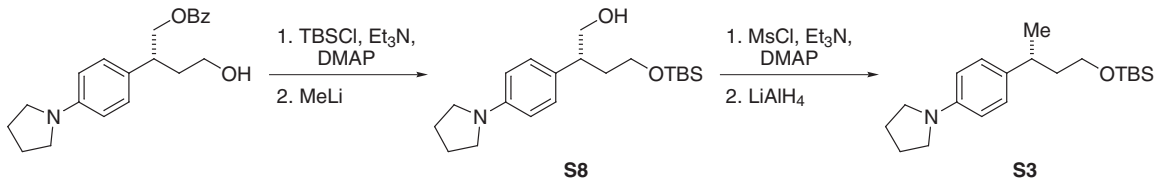
(*S*)-4-Benzoyloxy-3-(4-pyrolidin-1-yl-phenyl)-butyraldehyde (Table 1, entry 5). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (6.13 mg, 0.025 mmol, 0.100 equiv) $CHCl_3$ (0.25 ml), HCl (as a 4N solution in 1,4-dioxane, 6.25 μL, 0.025 mmol, 0.100 equiv), 1-phenylpyrrolidine (36.1 μL, 0.025 mmol, 1.00 equiv). To the stirring solution at room temperature was added 4-benzoyloxy-crotonaldehyde (95.0 mg, 0.5 mmol, 2.00 equiv). After 24 h, the reaction mixture was subjected directly to silica gel chromatography. Elution with 20-40% EtOAc in hexanes followed by concentration *in vacuo* afforded the product as a pale yellow oil in 73% yield (61.3 mg, 0.182 mmol); 90% ee. IR (film) 2961, 2888, 2825, 1717, 1715, 1616, 1522, 1487, 1450, 1374, 1271, 1176, 1115, 1069, 1026, 964.1, 812.7, 711.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H, CHO), 7.99 (d, *J* = 7.1 Hz, 2H, ArH), 7.56 (t, *J* = 7.7 Hz, 1H, ArH), 7.44 (t, *J* = 7.7 Hz,

2H, ArH), 7.17 (d, *J* = 8.8 Hz, 2H, ArH), 6.54 (d, *J* = 8.8 Hz, 2H, ArH), 4.49 (dd, *J* = 6.1, 11.0 Hz, 1H, OC**H**$_2$), 4.34 (dd, *J* = 8.2, 10.4 Hz, 1H, OC**H**$_2$), 3.72-3.60 (m, 1H, ArCH), 3.30-3.21 (m, 4H, N(CH$_2$)$_2$), 2.94 (ddd, *J* = 1.7, 6.6, 16.5 Hz, 1H, C**H**$_2$CO), 2.84 (ddd, *J* = 2.2, 8.3, 17.1 Hz, 1H, C**H**$_2$CO), 2.03-1.95 (m, 4H, CH$_2$(**CH$_2$**)$_2$CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.5, 166.5, 147.3, 133.2, 130.2, 129.8, 128.6, 128.6, 126.1, 112.1, 69.0, 47.9, 47.2, 38.8, 25.8. HRMS (CI) exact mass calcd for ($C_{21}H_{23}NO_3$) requires *m/z* 338.1756, found *m/z* 338.1747. $[\alpha]_D = -5.1$ (c = 0.50, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *R* isomer t_r = 31.4 min, *S* isomer t_r = 37.8 min.



S6 **S7**

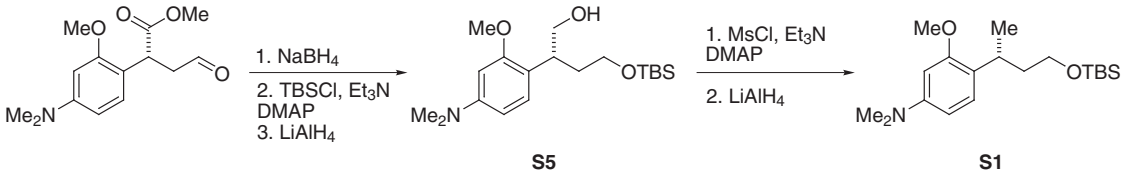
Determination of the absolute configuration of (*S*)-4-Benzoyloxy-3-(4-pyrolidin-1-yl-phenyl)-butyraldehyde by correlation to (*S*)-2-(4-pyrolidin-1-yl-phenyl)-butan-1,4-diol. A solution of (*S*)-4-benzoyloxy-3-(4-pyrolidin-1-yl-phenyl)-butyraldehyde (508 mg, 1.51 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) was added to a stirring solution of sodium borohydride (55.9 mg, 1.51 mmol, 1.00 equiv) in ethanol (5.0 mL). After 5 min, the reaction was diluted with saturated aqueous $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL). The organic layer was separated and washed with saturated solutions of $NaHCO_3$ and NaCl. The resulting solution was then dried over Na_2SO_4 and concentrated *in vacuo* to afford 464 mg (1.37 mmol, 91% yield) of a colorless oil. A portion of this substance (46.4 mg, 0.138 mmol, 1.00 equiv) was dissolved in methanol (2.0 mL) and treated with an excess of NaOH (100 mg, 2.50 mmol, 18.1 equiv). After one hour, the reaction mixture was partitioned between CH_2Cl_2 and H_2O, the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (100% EtOAc) followed by concentration *in vacuo* to afford 24.6 mg of **S7** as a white glassy solid (0.105 mmol, 76% yield) that was spectroscopically identical in all respects to **S7** generated below from (*R*)-4-oxo-2-(4-pyrrolidin-1-yl-phenyl)-butyric acid methyl ester. $[\alpha]_D$ (reference) = –19.1 (c = 1.03, $CHCl_3$); $[\alpha]_D$ (observed) = –15.9 (c = 1.32, $CHCl_3$).



Conversion of (*S*)-4-benzoyloxy-3-(4-pyrolidin-1-yl-phenyl)-butyraldehyde to (*R*)-3-(4-Pyrolidin-1-yl-phenyl)-butanol-*tert*-butyldimethylsilyl ether. A solution of (*S*)-4-benzoyloxy-3-(4-pyrolidin-1-yl-phenyl)-butanol (464 mg, 1.37 mmol, 1.00 equiv) was exposed to *tert*-butyldimethylsilyl chloride (412 mg, 2.73 mmol, 2.00 equiv), triethylamine (0.42 mL, 3.0 mmol, 2.2 equiv), and DMAP (10 mg) in CH_2Cl_2 (1.5 mL). After one hour, the reaction mixture was subjected directly to silica gel chromatography. Elution with 10-25% Et_2O in hexanes followed by concentration of two fractions *in vacuo* afforded 544 mg of a colorless oil (1.20 mmol, 87% yield). This compound was dissolved in Et_2O (6.0 mL), cooled to 0 °C and treated with MeLi (1.6 M in hexanes, 3.75 mL, 6.0 mmol, 5.0 equiv). After 5 min, the reaction was treated with saturated aqueous NH_4Cl (50 mL) and Et_2O (50 mL). The organic phase was then washed with saturated aqueous NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel chromatography of the resulting residue (10-50% Et_2O in hexanes) afforded 326 mg (0.932 mmol, 78% yield) of **S8** as a colorless oil. A portion of this substance (0.193 mg, 0.551 mmol, 1.00 equiv) was treated with methanesulfonyl chloride (0.055 mL, 0.716 mmol, 1.30 equiv), triethylamine (0.12 mL, 0.83 mmol, 1.5 equiv), and DMAP (10 mg) in THF (10 mL). After 12 h, the resulting suspension was carefully added to a stirring suspension of lithium aluminumhydride (105 mg, 2.76 mmol, 5.0 equiv) in Et_2O (10 mL). After 6 h, this mixture was diluted with saturated aqueous sodium potassium tartrate (50 mL) and Et_2O (50 mL) and allowed to stir for an additional 8 h. The organic layer was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography (10% Et_2O in hexanes) to afford 12.0 mg of **S3**; $[\alpha]_D = -28.7$ (c = 1.20, $CHCl_3$).

(*R*)-4-Oxo-2-(4-dimethylamino-2-methoxyphenyl)-butyric acid methyl ester (Table 1, entry 6). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (6.13 mg, 0.0250 mmol, 0.100 equiv), $CHCl_3$ (0.25 ml), HCl (as a 4N solution in 1,4-dioxane, 6.25 μL, 0.0250 mmol, 0.100 equiv), and 3-

dimethylamino-anisole (44 μL, 0.30 mmol, 1.2 equiv). The solution was cooled to –20 °C before oxobuteneoic acid methyl ester (28.5 mg, 0.250 mmol, 1.00 equiv) was added. The resulting solution was maintained at –20 °C for 8 h and then subjected directly silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a colorless oil in 73% yield (48.2 mg, 0.182 mmol); 91% ee. IR (film) 2950, 2903, 2838, 2727, 1730, 1616, 1569, 1519, 1462, 1440, 1356, 1242, 1171, 1114, 1033, 979.4, 814.6, 642.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.1 Hz, 1H, CHO), 6.99 (d, *J* = 8.2 Hz, 1H, ArH), 6.27 (dd, J = 2.5, 8.5 Hz, 1H, ArH), 6.22 (d, *J* = 2.5 Hz, 1H, ArH), 4.38 (dd, *J* = 5.2, 9.1 Hz, 1H, ArCH), 3.81 (s, 3H, $ArOCH_3$), 3.66 (s, 3H, CO_2CH_3), 3.52 (ddd, *J* = 1.4, 9.1, 18.1 Hz, 1H, C**H**$_2$CO), 2.94 (s, 6H, $N(CH_3)_2$), 2.67 (ddd, *J* = 0.8, 4.9, 17.8 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 174.4, 157.5, 151.5, 129.3, 114.6, 104.9, 96.2, 55.6, 52.5, 46.7, 40.9, 39.2. HRMS (CI) exact mass calcd for ($C_{21}H_{23}NO_3$) requires *m/z* 266.1392 for $[M+H]^+$, found *m/z* 266.1387. $[\alpha]_D = -149.0$ (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 26.0 min, *R* isomer t_r = 27.8 min.



Determination of the absolute configuration (*R*)-4-Oxo-2-(4-dimethylamino-2-methoxyphenyl)-butyric acid methyl ester by correlation to (*R*)-3-(4-dimethylamino-2-methoxyphenyl)-butanol *tert*-butyldimethylsilyl ether. A solution of (*R*)-4-oxo-2-(4-dimethylamino-2-methoxyphenyl)-butyric acid methyl ester (288 mg, 1.30 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added to a stirring solution of sodium borohydride (48.3 mg, 1.30 mmol, 1.00 equiv) in ethanol (3.0 mL) at 0 °C. After 5 min, the reaction was diluted with saturated aqueous $NaHCO_3$ (15 mL) and CH_2Cl_2 (15 mL). The organic layer was separated and washed with saturated solutions of $NaHCO_3$ and NaCl. The resulting solution was then dried over Na_2SO_4 and concentrated *in vacuo*. The residual oil was exposed to *tert*-butyldimethylsilyl chloride (392 mg, 2.60 mmol, 2.00 equiv), triethylamine (0.40 mL, 2.9 mmol, 2.2 equiv), and

DMAP (10 mg) in CH_2Cl_2 (2.6 mL). After one hour, the reaction mixture was subjected directly to silica gel chromatography. Elution with 10-50% Et_2O in hexanes followed by concentration *in vacuo* afforded 453 mg of a colorless oil (1.19 mmol, 91% yield from aldehyde). This compound was dissolved in Et_2O (5.0 mL) and added to a suspension of lithium aluminumhydride (100 mg, 2.63 mmol, 2.21 equiv) in Et_2O (10 mL) at 0 °C. After 5 min, this mixture was diluted with saturated aqueous sodium potassium tartrate (50 mL) and Et_2O (50 mL) and allowed to stir for an additional 8 h. The organic layer was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography (20-100% EtOAc in hexanes) and concentrated *in vacuo* to afford 201 mg (0.568 mmol, 48% yield) of a pale yellow oil assigned as **S5**; $[\alpha]_D = -20.1$ (c = 1.00, $CHCl_3$). This substance was treated with methanesulfonyl chloride (0.057 mL, 0.74 mmol, 1.30 equiv), triethylamine (0.12 mL, 0.85 mmol, 1.5 equiv), and DMAP (10 mg) in THF (8 mL). After 2 h, the resulting suspension was carefully added to a stirring suspension of lithium aluminumhydride (108 mg, 2.84 mmol, 5.0 equiv) in THF (10 mL). After 6 h, this mixture was diluted with saturated aqueous sodium potassium tartrate (50 mL) and Et_2O (50 mL) and allowed to stir for an additional 3 h. The organic layer was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography (25% EtOAc in hexanes) to afford 99.9 mg of **S1** that was spectroscopically identical in all respects to **S1** generated above from (*R)*-3-(4-dimethylamino-2-methoxy-phenyl)-butyraldehyde. $[\alpha]_D$ (reference) = –13.3 (c = 1.12, $CHCl_3$); $[\alpha]_D$ (observed) = –11.6 (c = 0.999, $CHCl_3$).

(*S*)-3-(4-pyrolidin-1-yl-2-methoxy-phenyl)-3-phenyl-propanol (Table 1, entry 7). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one hydrochloride (28.2 mg, 0.100 mmol, 0.200 equiv), CH_2Cl_2 (0.50 ml), and 1-(3-methoxy-phenyl)-pyrrolidine (83.6 μl, 0.500 mmol, 1.00 equiv). The solution was cooled to –50 °C before addition of cinnamaldehyde (167 μL, 1.00 mmol, 2.00 equiv). After 36 h, the reaction mixture was added drop-wise to a stirring suspension of $NaBH_4$ (41 mg) in ethanol (0.75 mL). After five min, the reduction was quenched with saturated aqueous $NaHCO_3$ solution and diluted with CH_2Cl_2. The layers were separated and the organic was washed with saturated aqueous $NaHCO_3$ and brine solutions. The resulting solution was dried over sodium

sulfate and concentrated *in vacuo* and the residue was purified by silica gel chromatography. Gradient elution with 25-75% diethyl ether in hexanes afforded the product as a colorless oil in 82% yield (127.4 mg, 0.409 mmol); 84% ee. IR (film) 3356, 2941,2875, 2832, 1615, 1566, 1515, 1488, 1452, 1374, 1224, 1036, 699.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.23 (m, 4H, ArH), 7.18-7.11 (m, 1H, ArH), 6.96 (d, *J* = 8.8 Hz, 1H, ArH), 6.14 (dd, *J* = 2.2, 8.2 Hz, 1H, ArH), 6.09 (d, *J* = 2.2 Hz, 1H, ArH), 4.51 (dd, *J* = 6.6, 9.3 Hz, 1H, ArCH), 3.83 (s, 3H, OCH_3), 3.70-3.48 (m, 2H, C**H**$_2$OH), 3.32-3.23 (m, 4H, $N(CH_2)_2$), 2.37-2.23 (m, 1H, CHC**H**$_2$), 2.22-2.10 (m, 1H, CHC**H**$_2$), 2.01-1.94 (m, 4H, CH_2(**CH**$_2$)$_2$$CH_2$), 1.89 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 147.8, 145.8, 129.0, 128.3, 128.2, 125.8, 119.9, 104.5, 95.3, 61.7, 55.9, 48.0, 36.6, 38.2, 25.8. HRMS (CI) exact mass calcd for ($C_{20}H_{25}NO_2$) requires *m/z* 311.1885, found *m/z* 311.1880. $[\alpha]_D = -60.5$ (c = 1.07, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 15.1 min, *R* isomer t_r = 28.6 min.

(*S*)-3-(4-Chloro-phenyl)-3-(4-pyrolidin-1-yl-2-methoxy-phenyl)-propanol (Table 1, entry 8). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv), CH_2Cl_2 (0.50 ml), HCl (as a 4N solution in 1,4-dioxane, 25.0 μL, 0.100 mmol, 0.200 equiv) and 1-(3-methoxy-phenyl)-pyrrolidine (167 μl, 1.00 mmol, 2.00 equiv). The solution was cooled to –50 °C before addition of *p*-chloro-cinnamaldehyde as a solid (83.0 mg, 0.500 mmol, 1.00 equiv). After 80 h, the reaction mixture was added drop-wise to a stirring suspension of $NaBH_4$ (41 mg) in ethanol (0.75 mL). After five min, the reduction was quenched with saturated aqueous $NaHCO_3$ solution and diluted with CH_2Cl_2. The layers were separated and the organic was washed with saturated aqueous $NaHCO_3$ and brine solutions. The resulting solution was dried over sodium sulfate and concentrated *in vacuo* and the residue was purified by silica gel chromatography. Gradient elution with 25-75% diethyl ether in hexanes afforded the product as a colorless oil in 80% yield (137.8 mg, 0.399 mmol); 92% ee. IR (film) 3320, 2941, 2879, 2833, 1615, 1566, 1515, 1488, 1454, 1374, 1224, 1036, 1014, 808.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 4H, ArH), 6.93 (d, *J* = 8.3 Hz, 1H, ArH), 6.13 (dd, *J* = 2.1, 8.1 Hz, 1H, ArH), 6.07 (d, *J* = 2.1 Hz, 1H, ArH), 4.45 (dd, *J* = 6.6, 8.8 Hz, 1H, ArCH), 3.80 (s, 3H, OCH_3), 3.70-3.43 (m, 2H, C**H**$_2$OH), 3.32-3.20 (m, 4H, $N(CH_2)_2$), 2.32-2.03 (m, 2H, CHC**H**$_2$), 2.02-1.92 (m, 4H,

$CH_2(\mathbf{CH_2})_2CH_2$), 1.74 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 147.9, 144.4, 131.4, 129.5, 128.9, 128.7, 128.4, 127.8, 119.2, 104.4, 95.3, 61.4, 55.8, 48.0, 38.2, 38.0, 25.8. HRMS (CI) exact mass calcd for ($C_{20}H_{24}ClNO_2$) requires *m/z* 345.1496, found *m/z* 345.1490. $[\alpha]_D = -57.7$ (c = 1.90, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 12.4 min, *R* isomer t_r = 15.3 min.

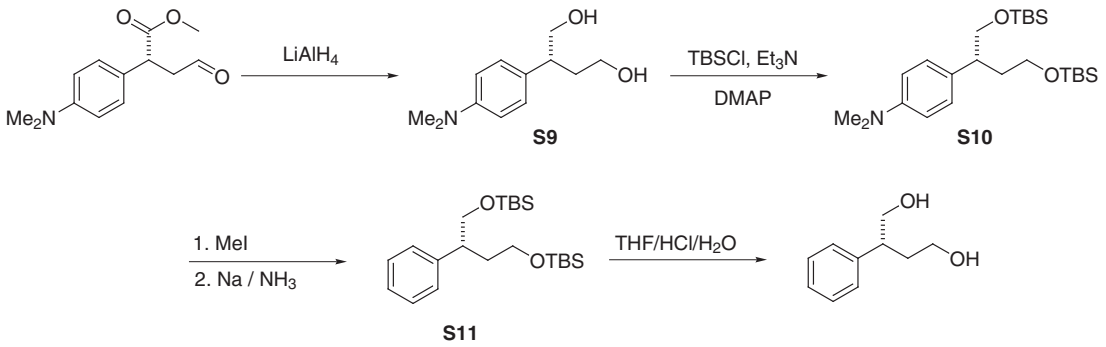
(*R*)-3-(4-nitro-phenyl)-3-(4-Dimethylamino-2-methoxy-phenyl)-propionaldehyde (Table 1, entry 9). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.100 equiv), *N,N*-dimethyl-*m*-anisidine hydrochloride (18.8 mg, 0.100 mmol, 0.100 equiv), CH_2Cl_2 (1.00 ml), and *N,N*-dimethyl-*m*-anisidine (425 μL, 2.90 mmol, 2.90 equiv). The solution was cooled to –10 °C before *p*-nitro-cinnamaldehyde (177 mg, 1.00 mmol, 1.00 equiv) was aded as a solid. After 48 h, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 10-50% EtOAc in hexanes followed by concentration in vacuo afforded the product as a bright orange oil in 87% yield (285 mg, 0.867 mmol); 92% ee. IR (film) 2938, 2894, 2837, 2726, 1722, 1614, 1516, 1345, 1241, 1120, 1033, 980.1, 858.6, 814.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H, CHO), 8.12 (td, *J* = 2.2, 9.3 Hz, 2H, ArH), 7.42 (td, *J* = 1.5, 9.3 Hz, 2H, ArH), 6.97 (d, *J* = 8.3 Hz, 1H, ArH), 6.30 (dd, *J* = 2.5, 8.8 Hz, 1H, ArH), 6.24 (d, *J* = 2.2 Hz, 1H, ArH), 4.98 (t, *J* = 7.8 Hz, 1H, ArCH), 3.79 (s, 3H, OCH_3), 3.21-3.09 (m, 2H, $C\mathbf{H_2}CO$), 2.96 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 157.8, 152.3, 151.4, 146.5, 128.9, 128.6, 123.8, 118.0, 104.8, 96.4, 55.4, 48.4, 40.8, 38.2. HRMS (CI) exact mass calcd for ($C_{18}H_{20}N_2O_4$) requires *m/z* 328.1423, found *m/z* 328.1422. $[\alpha]_D = -58.1$ (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction of the aldehyde) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *R* isomer t_r = 25.6 min, *S* isomer t_r = 29.5 min.

(*S*)-3-(4-Nitrophenyl)-3-(4-pyrolidin-1-yl-phenyl)-propionaldehyde (Table 1, entry 10). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv) CH_2Cl_2 (0.50 ml), HCl (as a 4N solution in 1,4-dioxane, 25 μL, 0.200 mmol, 0.200 equiv), and *p*-

nitrocinnamaldehyde (88.6 mg, 0.500 mmol, 1.00 equiv). The solution was cooled to –10 °C before addition of 1-phenylpyrrolidine (216 μL, 1.50 mmol, 3.00 equiv). After 48 h, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 25-50% EtOAc in hexanes followed by concentration in vacuo afforded the product as a bright orange oil in 82% yield (133 mg, 0.411 mmol); 90% ee. IR (film) 2968, 2894, 2835, 2728, 1723, 1614, 1520, 1375, 1345, 1182, 1110, 859.2, 804.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.4 Hz, 1H, CHO), 8.13 (d, *J* = 8.8 Hz, 2H, ArH), 7.38 (d, *J* = 8.8 Hz, 2H, ArH), 7.05 (d, *J* = 8.8 Hz, 2H, ArH), 6.50 (d, *J* = 8.8 Hz, 2H, ArH), 4.63 (t, *J* = 7.7 Hz, 1H, ArCH), 3.29-3.09 (m, 6H, C**H$_2$**CO, $N(CH_2)_2$), 2.03-1.94 (m, 4H, CH_2(**CH_2**)$_2$$CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 152.2, 147.1, 128.6, 127.9, 124.1, 112.1, 49., 47.9, 44.2, 25.8. HRMS (CI) exact mass calcd for ($C_{19}H_{20}N_2O_3$) requires *m/z* 324.1474, found *m/z* 324.1474. $[\alpha]_D$ = – 3.75 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding acetate (obtained by $NaBH_4$ reduction of aldehyde and subsequent acylation with Ac_2O) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 35.4 min, *R* isomer t_r = 47.0 min.

(*R*)-4-Oxo-2-(4-dimethylamino-phenyl)-butyric acid methyl ester (Table 2, entries 1 & 2). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.0500 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.5 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.0500 mmol, 0.100 equiv), and N,N-dimethylaniline (76 μL, 0.60 mmol, 1.2 equiv). The solution was stirred for 5.5 h at ambient temperature and then subjected directly to silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a colorless oil in 77% yield (90.0 mg, 0.383 mmol); 94% ee. The same reaction conducted at –10 °C was complete after 48h and purified in identical fashion to give the product in 86% yield (101 mg, 0.429 mmol) and 96% ee. IR (film) 2950, 2902, 2844, 2809, 2728, 1732, 1614, 1523, 1437, 1353, 1230, 1166, 947.3, 818.8, 777.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H, CHO), 7.14 (d, *J* = 7.1 Hz, 2H, ArH), 6.68 (d, *J* = 7.6 Hz, 2H, ArH), 4.03 (dd, *J* = 4.7, 9.9 Hz, 1H, ArCH), 3.66 (s, 3H, OCH_3), 3.35 (dd, *J* = 9.9, 18.7 Hz, 1H, C**H$_2$**CO), 2.93 (s, 6H, $N(CH_3)_2$), 2.77 (dd, *J* = 4.8, 18.3 Hz, 1H, C**H$_2$**CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 174.0, 150.1, 128.5, 125.2, 112.9, 52.7, 47.8, 44.2, 40.8. HRMS (CI) exact mass calcd for

($C_{13}H_{17}NO_3$) requires *m/z* 236.1286, found *m/z* 236.1285. $[\alpha]_D = -152.3$ (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 27.3 min, *R* isomer t_r = 29.4 min.



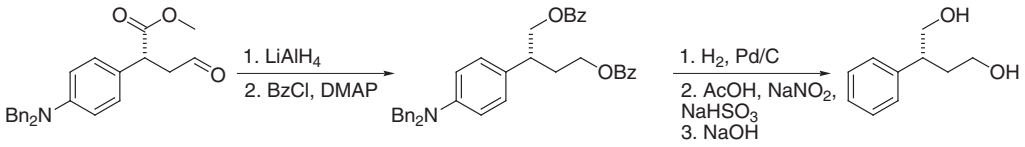
Determination of the absolute configuration (*R*)-4-oxo-2-(4-dimethylamino-phenyl)-butyric acid methyl ester by correlation to (*S*)-2-phenyl-butan-1,4,-diol. A solution of (*R*)-4-oxo-2-(4-dimethylamino-phenyl)-butyric acid methyl ester (1.78 g, 7.55 mmol, 1.00 equiv) in CH_2Cl_2 was added to a stirring suspension of lithium aluminum hydride (1.13 g, 29.8 mmol, 4.0 equiv) in Et_2O (45 mL). After 5 min, this mixture was diluted with saturated aqueous sodium potassium tartrate (100 mL) and Et_2O (100 mL) and allowed to stir for an additional 8 h. The organic layer was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was recrystallized from a hexanes, Et_2O and DCM to give 0.630 g (3.01 mmol, 40% yield) of a white solid assigned as **S9**; $[\alpha]_D = -23.1$ (c = 0.975, $CHCl_3$). This compound was then exposed to *tert*-butyldimethylsilyl chloride (907 mg, 6.02 mmol, 2.00 equiv), triethylamine (0.93 mL, 6.62 mmol, 2.2 equiv), and in CH_2Cl_2 (5.0 mL). After 5.5 h, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 1-10% EtOAc in hexanes followed by concentration *in vacuo* afforded **S10** as a faint-yellow oil in 49% yield (643 mg, 1.47 mmol); $[\alpha]_D = -23.1$ (c = 0.975, $CHCl_3$). This oil was dissolved in CH_3I (0.52 mL, 8.4 mmol, 5 equiv) and stirred for 10 h and subsequently concentrated *in vacuo* to provide a yellow microcrystaline solid in 97% yield (825 mg, 1.42 mmol). A portion of the ammonium salt (100 mg, 0.170 mmol, 1.00 equiv) was suspended in THF (20 mL) and added to a stirring solution of dissolved sodium (15.9 mg, 0.690 mmol, 4.00

equiv) in freshly condensed liquid ammonia (25 ml) at –78 °C. After 30 min, the reaction mixture was quenched with excess methanol, diluted with ether (20 mL) and allowed to warm to ambient temperature. The ethereal solution was washed with aqueous HCl (1N) and saturated NaCl and subsequently dried over Na_2SO_4. This residue was purified by silica gel chromatography to afford 61.1 mg of **S11** (0.155 mmol, 91% yield); $[\alpha]_D$ = –28.7 (c = 1.01, $CHCl_3$). This compound was treated with aqueous HCl (4N, 1.0 mL) and THF (1.0 mL) and stirred at ambient temperature for 16 h. Dilution of the reaction mixture with CH_2Cl_2 and saturated aqueous $NaHCO_3$ and subseqent separation, drying and concentration of the organic phase yielded a pale yellow oil. This compound was subjected to silica gel chromatography to afford 5.0 mg (30 μmol, 19% yield) of a substance that was spectroscopically identical in all respects to the known compound (*S*)-2-phenyl-butan-1,4,-diol.[6] $[\alpha]_D$ (literature) = –13 (c = 3.0 , $CHCl_3$); $[\alpha]_D$ (observed) = –29.8 (c = 0.50, $CHCl_3$).

(*R*)-4-Oxo-2-(4-dibenzylamino-phenyl)-butyric acid methyl ester (Table 2, entry 3). To an amber 2-dram vial under an argon atmosphere and equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.0500 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.5 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.0500 mmol, 0.100 equiv), and N,N-dibenzylaniline (273 mg, 1.00 mmol, 2.00 equiv). The solution was stirred for 24 h at ambient temperature and subjected directly to silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a colorless oil in 65% yield (126 mg, 0.325 mmol); 96% ee. IR (film) 3028, 2949, 2904, 2844, 2725, 1729, 1717, 1613, 1520, 1434, 1451, 1360, 1231, 1166, 956.2, 816.0, 733.7, 696.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H, CHO), 7.22-7.36 (m, 10H, ArH), 7.05 (d, *J* = 9.0 Hz, 2H, ArH), 6.68 (d, *J* = 8.7 Hz, 2H, ArH), 4.64 (s, 4H, $ArCH_2$), 4.01 (dd, *J* = 4.7, 9.9 Hz, 1H, ArCH), 3.66 (s, 3H, OCH_3), 3.33 (ddd, *J* = 0.9, 9.9, 18.7 Hz, 1H, C**H**$_2$CO), 2.76 (ddd, *J* = 0.8, 4.7, 18.4 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 173.9, 148.8, 135.5, 128.9, 128.7, 127.2, 126.8, 125.4, 112.8, 54.6, 52.7, 47.8, 44.1. HRMS (CI) exact mass calcd for ($C_{25}H_{25}NO_3$) requires *m/z* 387.1834, found *m/z* 387.1834. $[\alpha]_D$ = – 91.2 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and

[6] Krause, et al, *J. Organomet. Chem.* **1992**, *423*, 271-279.

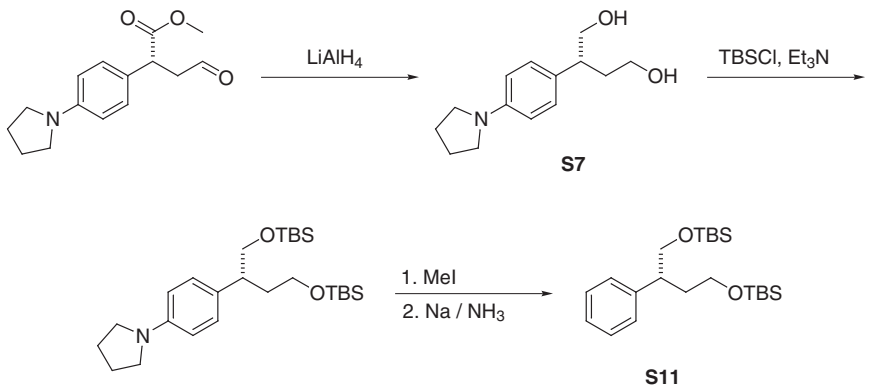
AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 25.5 min, *R* isomer t_r = 28.4 min.



Determination of the absolute configuration of (*R*)-4-oxo-2-(4-dibenzylamino-phenyl)-butyric acid methyl ester by correlation to (*S*)-2-phenyl-butan-1,4,-diol. A solution of (*R*)-4-oxo-2-(4-dibenzylamino-phenyl)-butyric acid methyl ester (848 mg, 2.19 mmol, 1.00 equiv) in CH_2Cl_2 (2.5 mL) was added to a stirring suspension of lithium aluminumhydride (332 mg, 8.76 mmol, 4.00 equiv) in Et_2O (15 mL). After 5 min, this mixture was diluted with saturated aqueous sodium potassium tartrate (100 mL) and Et_2O (100 mL) and allowed to stir for an additional 8 h. The organic layer was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. This residue was purified via silica gel chromatography (25-100% EtOAc in hexanes) to afford 418 mg of a white solid (1.16 mmol, 53% yield). This substance was exposed to benzoyl chloride (0.777 mL, 6.73 mmol, 2.2 equiv), triethylamine (0.944 mL, 6.73 mmol, 2.2 equiv), DMAP (50 mg) and CH_2Cl_2 (15.0 mL) fo 24 h at which point the reaction mixture was subjected directly to silica gel chromatography (10-50% EtOAc in hexanes) to afford 556 mg (0.976, 84% yield) of a pale yellow solid assigned as **S12**. A portion of this material (512 mg, 0.900 mmol, 1.00 equiv) was dissolved in EtOAc (8.0 mL) exposed to a suspension of 10% Pd on carbon (51.3 mg) in MeOH (20 mL) under H_2 atmosphere. After 22h, the reaction mixture was filtered through Celite and concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography to afford 323 mg (0.829 mmol, 94% yield) of a pale yellow solid; $[\alpha]_D$ = –29.9 (c = 1.92, $CHCl_3$). A solution of compound (30.8 mg, 79.1 μmol, 1.00 equiv) in ethanol (4.3 mL) and AcOH (0.64 mL) was treated with $NaNO_2$ (71.0 mg, 1.02 mmol, in 0.64 mL H_2O) and $NaHSO_3$ (107 mg, 1.02 mmol, in 0.64 mL H_2O). After 3 h, the solution was extracted with $CHCl_3$ and the extracts were collectively washed with H_2O and saturated aqueous NaCl and dried over Na_2SO_4. This solution was concentrated *in vacuo* and the resulting residue was treated with NaOH (100 mg, 2.50 mmol) and methanol (1.0 mL). After one hour, the reaction mixture was partitioned between

CH_2Cl_2 and H_2O, the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to silica gel chromatography (100% EtOAc) followed by concentration *in vacuo* to afford 4.1 mg (25 μmol, 31% yield from aniline) of a substance that was spectroscopically identical in all respects to the known compound (*S*)-2-phenyl-butan-1,4,-diol.[6] $[\alpha]_D$ (literature) = –13 (c = 3.0 , $CHCl_3$); $[\alpha]_D$ (observed) = –32.3 (c = 0.82, $CHCl_3$).

(*R*)-4-Oxo-2-(4-pyrrolidin-1-yl-phenyl)-butyric acid methyl ester (3) (Table 2, entries 4 & 5). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.0500 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.5 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.0500 mmol, 0.100 equiv), and 1-phenylpyrrolidine (144 μL, 1.00 mmol, 2.00 equiv). The solution was stirred for 20 min at ambient temperature and subjected directly to silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a white powder in 96% yield (126 mg, 0.480 mmol); 95% ee. IR (film) 2974, 2959, 2899, 2827, 2726, 1730, 1718, 1614, 1522, 1488, 1435, 1374, 1229, 1164, 1091, 814, 771, 531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 7.12 (d, *J* = 8.8 Hz, 2H, ArH), 6.51 (d, *J* = 8.8 Hz, 2H, ArH), 4.02 (dd, *J* = 4.7, 9.6 Hz, 1H, ArCH), 3.65 (s, 3H, OCH_3), 3.33 (dd, *J* = 9.9, 18.4 Hz, 1H, C**H**$_2$CO), 3.28-3.23 (m, 4H, $N(CH_2)_2$), 2.76 (dd, *J* = 5.0, 18.4 Hz, 1H, C**H**$_2$CO), 2.01-1.96 (m, 4H, CH_2(**C**$\mathbf{H_2}$)$_2$$CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 174.2, 147.6, 128.7, 124.1, 112.1, 52.5, 47.8, 47.7, 44.2, 25.7. HRMS (CI) exact mass calcd for ($C_{15}H_{19}NO_3$) requires *m/z* 261.1443, found *m/z* 262.1439. $[\alpha]_D$ = − 147.8 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 20.9 min, *R* isomer t_r = 24.4 min. The same reaction conducted at –20 °C was complete after 8h and purified in identical fashion to give the product as a white powder in 97% yield (127 mg, 0.487 mmol); 97% ee. On a 50-mmol scale using 2 mol% amine and 2 mol% HCl at ambient temperature, the reaction afforded the product in 93% yield (12.21 g, 46.7 mmol); 91% ee. A recrystallization of this product from ethyl acetate provided 10.56 g (86% yield) of material in 96% ee.



Determination of the absolute configuration of (*R*)-4-oxo-2-(4-pyrrolidin-1-yl-phenyl)-butyric acid methyl ester by correlation to (*S*)-2-phenyl-butan-1,4,-diol bis-*tert*-butyldimethylsilyl ether. A solution of (*R*)-4-oxo-2-(4-pyrrolidin-1-yl-phenyl)-butyric acid methyl ester (2.23 g, 8.53 mmol, 1.00 equiv) in THF (15 mL) was added carefully to a stirring suspension of lithium aluminum hydride (1.27 g, 33.5 mmol, 4.0 equiv) in Et_2O (45 mL). After 5 min, this mixture was diluted with saturated aqueous sodium potassium tartrate (100 mL) and Et_2O (100 mL) and allowed to stir for an additional 8 h. The organic layer was separated and the aqueous was extracted three times with CH_2Cl_2. The combined organics were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (100% EtOAc) to afford 1.97 g (8.37 mmol, 98% yield) of a white solid assigned as **S17**; $[\alpha]_D = -19.1$ (c = 1.03, $CHCl_3$). This compound was then exposed to *tert*-butyldimethylsilyl chloride (2.83 g, 18.8 mmol, 2.20 equiv), triethylamine (2.63 mL, 18.8 mmol, 2.2 equiv), and CH_2Cl_2 (20 mL). After 7.5 h, the reaction mixture was subjected directly to silica gel chromatography. Gradient elution with 10-20% EtOAc in hexanes followed by concentration *in vacuo* afforded 3.41 g (7.37 mmol, 86% yield) of a faint-yellow oil. A portion of this substance (1.17 g, 2.53 mmol, 1.00 equiv) was dissolved in CH_3I (0.47 mL, 7.6 mmol, 3.0 equiv) and stirred for 48 h and subsequently diluted with Et_2O and filtered to provide 1.484 g of a yellow solid. A portion of the ammonium salt (128 mg, 0.200 mmol, 1.00 equiv) was suspended in THF (20 mL) and added to a stirring solution of dissolved sodium (18.4 mg, 0.800 mmol, 4.00 equiv) in freshly condensed liquid ammonia (25 ml) at –78 °C. After 30 min, the reaction mixture was quenched with excess methanol, diluted with ether (20 mL) and allowed to warm to ambient temperature. The ethereal solution was washed with aqueous HCl (1N) and saturated NaCl and subsequently dried over Na_2SO_4. This residue was purified by

silica gel chromatography to afford 52.0 mg of **S11** (0.132 mmol, 61% yield) that was spectroscopically identical in all respects to the **S11** generated above from (*R*)-4-oxo-2-(4-dimethylamino-phenyl)-butyric acid methyl ester. $[\alpha]_D$ (reference) = –22.0 (c = 1.08 , $CHCl_3$); $[\alpha]_D$ (observered) = –22.8 (c = 0.92, $CHCl_3$).

(*R*)-4-Oxo-2-(6-pyrrolidin-1-yl-biphenyl-3-yl)-butyric acid methyl ester (Table 2, entry 6). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.0500 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.500 ml), HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.0500 mmol, 0.100 equiv), and 2-(pyrrolidin-1-yl)-biphenyl (223 mg, 1.00 mmol, 2.00 equiv). The solution was stirred for 12 h at ambient temperature and subjected directly to silica gel chromatography. Gradient elution with 10-40% EtOAc in hexanes afforded the product as a white powder in 94% yield (158.4 mg, 0.469 mmol); 99% ee. IR (film) 2949, 2871, 2820, 2721, 1734, 1719, 1606, 1505, 1482, 1354, 1329, 1229, 1164, 769.9, 701.1 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H, CHO), 7.44-7.24 (m, 5H, ArH), 7.13 (dd, *J* = 2.5, 8.5 Hz, 1H, ArH), 7.05 (d, *J* = 2.2 Hz, 1H, ArH), 6.82 (d, *J* = 8.2 Hz, 1H, ArH), 4.07 (dd, *J* = 4.7, 9.9 Hz, 1H, ArCH), 3.67 (s, 3H, OCH_3), 3.38 (dd, *J* = 9.9, 18.4 Hz, 1H, C**H**$_2$CO), 2.94 (m, 4H, N(CH_2)$_2$), 2.81 (dd, *J* = 4.7, 18.4 Hz, 1H, C**H**$_2$CO), 1.79-1.72 (m, 4H, CH_2(**CH_2**)$_2$$CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 173.9, 147.5, 142.9, 131.8, 130.3, 129.3, 128.1, 127.1, 126.7, 126.5, 114.9, 52.7, 51.3, 47.8, 44.3, 25.8. HRMS (CI) exact mass calcd for ($C_{21}H_{23}NO_3$) requires *m/z* 337.1679, found *m/z* 337.1678. $[\alpha]_D$ = − 110.1 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 13.9 min, *R* isomer t_r = 16.5 min.

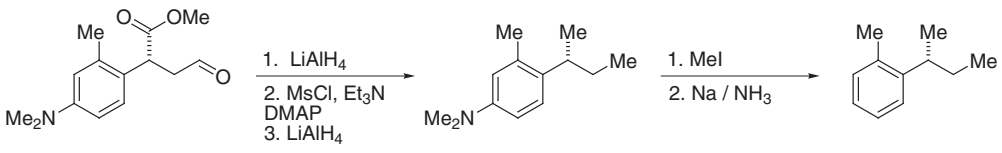
(*R*)-2-(1-Methyl-2,3-dihydro-1*H*-indol-5-yl)-4-oxobutyric acid methyl ester (Table 2, entries 7 & 8). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (12.3 mg, 0.050 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.500 ml), and HCl (as a 4N solution in 1,4-dioxane, 12.5 μL, 0.050 mmol, 0.100 equiv). The reaction vessel was cooled to –20 °C before the addition of 1-methylindoline (133 μL, 1.00 mmol, 2.00 equiv). The solution

was stirred for 8 h at –20 °C and then subjected directly to silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a colorless oil in 94% yield (116.6 mg, 0.471 mmol); 98% ee. IR (film) 2952, 2923, 2847, 2812, 2728, 1732, 1616, 1499, 1436, 1381, 1276, 1232, 1170, 1086, 1045, 988.7, 815.8, 585.2. cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H, CHO), 6.97 (s, 1H, ArH), 6.94 (d, *J* = 8.0 Hz, 1H, ArH), 6.39 (d, J = 8.0 Hz, 1H, ArH), 4.00 (dd, *J* = 4.7, 9.7 Hz, 1H, ArCH), 3.66 (s, 3H, OCH_3), 3.32 (ddd, *J* = 0.8, 9.9, 15.7 Hz, 1H, C**H**$_2$CO), 3.29 (t, *J* = 8.2 Hz, 2H, NCH_2), 2.91 (t, *J* = 8.2 Hz, 2H, $ArCH_2$), 2.75 (ddd, *J* = 0.6, 4.9, 18.3 Hz, 1H, C**H**$_2$CO), 2.73 (s, 3H, NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 174.2, 153.2, 131.4, 127.1, 126.7, 123.8, 107.3, 56.3, 52.6, 47.9, 44.5, 36.3, 28.8. . HRMS (CI) exact mass calcd for ($C_{14}H_{17}NO_3$) requires *m/z* 248.1286 for $[M+H]^+$, found *m/z* 248.1282. $[\alpha]_D$ = − 128.9 (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 13.9 min, *R* isomer t_r = 16.5 min. The same reaction conducted on 0.25–mmol scale at ambient temperature over 20 min and purified in identical fashion afforded the product in 93% yield (57.5 mg, 0.233 mmol) and 93% ee.

(*R*)-2-(4-Dimethylaminonaphthalen-1-yl)-4-oxobutyric acid methyl ester (Table 2, entry 9). To an amber 2-dram vial under an argon atmosphere and equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (6.1 mg, 0.025 mmol, 0.10 equiv), 4-oxobuteneoic acid methyl ester (28.5 mg, 0.250 mmol, 1.00 equiv), $CHCl_3$ (0.25 ml), HCl (as a 4N solution in 1,4-dioxane, 6.2 μL, 0.025 mmol, 0.10 equiv), and *N,N*-dimethyl-1-naphthylamine (82.0 μL, 0.500 mmol, 2.00 equiv). The solution was stirred for 36 h at ambient temperature and subjected directly to silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a colorless oil in 89% yield (63.8 mg, 0.224 mmol); 93% ee. IR (film) 2940, 2832, 2783, 2724, 1731, 1582, 1455, 1436, 1391, 1214, 1185, 1087, 1043, 767.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H, CHO), 8.29-8.34 (m, 1H, ArH), 7.99-8.04 (m, 1H, ArH), 748-7.58 (m, 2H, ArH), 7.28 (d, *J* = 8.0 Hz, 1H, ArH), 7.02 (d, *J* = 7.7 Hz, 2H, ArH), 4.91 (dd, *J* = 5.2, 9.9 Hz, 1H, ArCH), 3.68 (s, 3H, OCH_3), 3.54 (dd, *J* = 9.9, 18.7 Hz, 1H, C**H**$_2$CO), 2.89 (s, 6H, $N(CH_3)_2$), 2.86 (dd, *J* = 4.2, 18.6 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 174.1, 151.0, 132.3, 129.5, 128.5, 126.7, 125.5, 125.4, 125.3, 1234,

113.9, 52.8, 47.4, 45.5, 40.7. HRMS (CI) exact mass calcd for ($C_{17}H_{19}NO_3$) requires *m/z* 285.1365, found *m/z* 285.1365. $[\alpha]_D = -200.7$ (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 14.9 min, *R* isomer t_r = 16.9 min.

(*R*)- 2-(4-Dimethylamino-2-methylphenyl)-4-oxobutyric acid methyl ester (Table 2, entry 10). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), $CHCl_3$ (0.5 ml), HCl (as a 4N solution in 1,4-dioxane, 25.0 μL, 0.100 mmol, 0.200 equiv), and *N,N*-dimethyl-*m*-toluidine (145 μL, 1.00 mmol, 2.00 equiv). The solution was stirred for 10 h at –10 °C temperature and subjected directly to silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a colorless oil in 89% yield (112 mg, 0.447 mmol); 84% ee. IR (film) 2949, 2892, 2846, 2797, 2731, 1732, 1723, 1611, 1565, 1513, 1482, 1435, 1354, 1295, 1218, 1169, 1109, 1013, 968.6, 902.1, 840.9, 805.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H, CHO), 7.04 (dd, *J* = 2.4, 7.0 Hz, 1H, ArH), 6.55 (dd, *J* = 2.7, 7.5 Hz, 1H, ArH), 6.54 (s, 1H, ArH), 4.31 (dd, *J* = 5.4, 9.9 Hz, 1H, ArCH), 3.65 (s, 3H, OCH_3), 3.35 (ddd, *J* = 0.8, 9.9, 18.7 Hz, 1H, C**H**$_2$CO), 2.92 (s, 6H, $N(CH_3)_2$), 2.70 (dd, *J* = 0.6, 4.4, 18.4 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 174.3, 149.9, 136.8, 127.7, 124.1, 114.7, 110.9, 52.6, 47.4, 40.8, 40.1, 20.7. HRMS (CI) exact mass calcd for ($C_{14}H_{19}NO_3$) requires *m/z* 250.1443 for $[M+H]^+$, found *m/z* 250.1446. $[\alpha]_D = -129.8$ (c = 1.14, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 13.8 min, *R* isomer t_r = 15.4 min.



Determination of the absolute configuration of (*R*)-4-oxo-2-(4-dimethylamino-2-methylphenyl)-butyric acid methyl ester by correlation to (*R*)-*o*-*sec*-butyl-toluene. A solution of (*R*)-4-oxo-2-(4-dimethylamino-2-methylphenyl)-butyric acid methyl ester (499 mg, 2.00 mmol, 1.00 equiv) in CH_2Cl_2 (2.0 mL) was added carefully to a stirring suspension of lithium aluminumhydride (304 mg, 8.00 mmol, 4.00 equiv) in Et_2O (50 mL). After 5 min, this mixture was diluted with saturated aqueous sodium potassium tartrate (100 mL) and Et_2O (100 mL) and allowed to stir for an additional 8 h. The organic layer was separated and the aqueous was extracted three times with CH_2Cl_2. The combined organics were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography to afford 0.224 g (1.00 mmol, 50% yield) of a pale yellow oil. This substance was treated with methanesulfonyl chloride (0.232 mL, 3.00 mmol, 3.00 equiv), triethylamine (0.42 mL, 3.0 mmol, 3.0 equiv), and DMAP (24 mg) in CH_2Cl_2 (3 mL). After 2 h, the resulting solution was carefully added to a stirring suspension of lithium aluminumhydride (108 mg, 2.84 mmol, 5.0 equiv) in THF (10 mL) at 0 °C. The reaction was allowed to warm to ambient temperature and after 6 h, this mixture was diluted with saturated aqueous sodium potassium tartrate (50 mL) and Et_2O (50 mL) and allowed to stir for an additional 3 h. The organic layer was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in an excess of CH_3I (1.0 mL) and stirred for 4 h. The resulting mixture was then concentrated *in vacuo* and then dissolved in freshly condensed liquid ammonia (50 ml) at –78 °C and treated with sodium (72 mg, 3.0 mmol, 3.0 equiv). Three min later, the reaction mixture was quenched with excess methanol, diluted with ether (50 mL) and allowed to warm to ambient temperature. The resulting residue was purified via silica gel chromatography (1% Et_2O in CH_2Cl_2) to afford 16.1 mg of a colorless oil that was spectroscopically identical in all respects to the known compound.[7] $[\alpha]_D$ (literature) = + 28.6 (c = 1.0 , $CHCl_3$); $[\alpha]_D$ (observerd) = –12.3 (c = 0.760, $CHCl_3$), the opposite sign of the rotation indicating that we had produced the enantiomer of the known compound.

(*R*)-4-Oxo-2-(4-dimethylamino-2-methoxyphenyl)-butyric acid methyl ester (Table 2, entries 11 & 12). To an amber 2-dram vial equipped with a magnetic stir bar was added (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (6.13 mg, 0.0250 mmol, 0.100 equiv), 4-

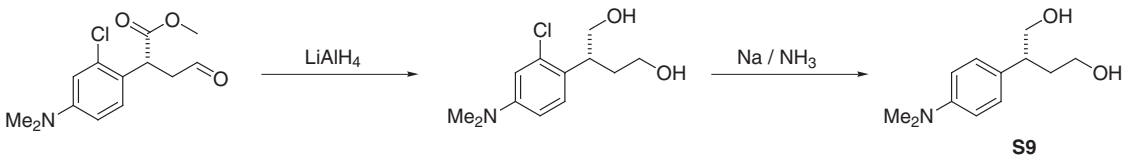
[7] Consiglio, et. al. *Tetrahedron* **1983**, 2699-2708.

oxobuteneoic acid methyl ester (28.5 mg, 0.250 mmol, 1.00 equiv), $CHCl_3$ (0.25 ml), HCl (as a 4N solution in 1,4-dioxane, 6.25 μL, 0.0250 mmol, 0.100 equiv), and 3-dimethylamino-anisole (44 μL, 0.30 mmol, 1.2 equiv). The solution was stirred for 5 min at ambient temperature and subjected directly to silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a colorless oil in 73% yield (48.2 mg, 0.182 mmol); 91% ee. IR (film) 2950, 2903, 2838, 2727, 1730, 1616, 1569, 1519, 1462, 1440, 1356, 1242, 1171, 1114, 1033, 979.4, 814.6, 642.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.1 Hz, 1H, CHO), 6.99 (d, *J* = 8.2 Hz, 1H, ArH), 6.27 (dd, J = 2.5, 8.5 Hz, 1H, ArH), 6.22 (d, *J* = 2.5 Hz, 1H, ArH), 4.38 (dd, *J* = 5.2, 9.1 Hz, 1H, ArCH), 3.81 (s, 3H, $ArOCH_3$), 3.66 (s, 3H, CO_2CH_3), 3.52 (ddd, *J* = 1.4, 9.1, 18.1 Hz, 1H, C**H**$_2$CO), 2.94 (s, 6H, $N(CH_3)_2$), 2.67 (ddd, *J* = 0.8, 4.9, 17.8 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 174.4, 157.5, 151.5, 129.3, 114.6, 104.9, 96.2, 55.6, 52.5, 46.7, 40.9, 39.2. HRMS (CI) exact mass calcd for ($C_{21}H_{23}NO_3$) requires *m/z* 266.1392 for $[M+H]^+$, found *m/z* 266.1387. $[\alpha]_D = -149.0$ (c = 1.0, $CHCl_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 26.0 min, *R* isomer t_r = 27.8 min. The same reaction conducted at –20 °C on 0.5–mmol scale was complete after 8h and purified in identical fashion to give the product in 90% yield (119 mg, 0.448 mmol) and 92% ee.

(*R*)-4-Oxo-2-(4-dimethylamino-2-methylthio-phenyl)-butyric acid methyl ester (Table 2, entry 13). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.100 equiv), 4-oxobuteneoic acid methyl ester (114.1 mg, 1.00 mmol, 1.00 equiv), $CHCl_3$ (1.00 ml), and HCl (as a 4N solution in 1,4-dioxane, 25.0 μL, 0.100 mmol, 0.100 equiv). The reaction vessel was cooled to –20 °C before the addition of 3-dimethylamino-thioanisole (334 mg, 2.00 mmol, 2.00 equiv). The solution was stirred for 20 h at –20 °C and then subjected directly to silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a colorless oil in 92% yield (258.6 mg, 0.920 mmol); 91% ee. IR (film) 2950, 2913, 2845, 2711, 1730, 1600, 1554, 1502, 1437, 1353, 1227, 1170, 958.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H, CHO), 7.02 (d, *J* = 8.5 Hz, 1H, ArH), 6.66 (d, *J* = 2.5 Hz, 1H, ArH), 6.53 (dd, J = 2.8, 8.8 Hz, 1H, ArH), 4.66 (dd, *J* = 4.4, 9.6 Hz, 1H, ArCH), 3.66 (s, 3H, OCH_3), 3.25 (ddd, *J* = 1.1, 9.6,

18.1 Hz, 1H, C**H**$_2$CO), 2.94 (s, 6H, N(CH$_3$)$_2$), 2.70 (ddd, *J* = 0.8, 4.7, 18.1 Hz, 1H, C**H**$_2$CO), 2.47 (s, 3H, SCH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 200.0, 173.8, 150.1, 137.3, 128.0, 124.7, 112.3, 110.8, 52.4, 47.1, 41.0, 40.5, 17.6. HRMS (CI) exact mass calcd for ($C_{14}H_{19}NO_3S$) requires *m/z* 281.1086, found *m/z* 281.1086. $[\alpha]_D = -130.1$ (c = 1.0, CHCl$_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by NaBH$_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 15.7 min, *R* isomer t_r = 17.4 min.

(*R*)-4-Oxo-2-(4-dimethylamino-2-chlorophenyl)-butyric acid methyl ester (Table 2. entries 14 & 15). To a 2-dram vial equipped with a magnetic stir bar was added (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (24.6 mg, 0.100 mmol, 0.200 equiv), 4-oxobuteneoic acid methyl ester (57.1 mg, 0.500 mmol, 1.00 equiv), CHCl$_3$ (0.500 ml), and HCl (as a 4N solution in 1,4-dioxane, 18.8 μL, 0.075 mmol, 0.150 equiv). The reaction vessel was cooled to –20 °C before the addition of 3-chloro-N,N-dimethylaniline (156 mg, 1.00 mmol, 2.00 equiv). The solution was stirred for 80 h at –20 °C and then subjected directly to silica gel chromatography. Gradient elution with 20-40% EtOAc in hexanes afforded the product as a colorless oil in 73% yield (98.7 mg, 0.366 mmol); 93% ee. IR (film) 2950, 2900, 2817, 2726, 1734, 1724, 1610, 1512, 1437, 1357, 1285, 1228, 1173, 129, 962.4, 818.5 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.77 (s, 1H, CHO), 7.06 (d, *J* = 8.8 Hz, 1H, ArH), 6.69 (d, *J* = 2.9 Hz, 1H, ArH), 6.56 (dd, J = 2.8, 8.8 Hz, 1H, ArH), 4.53 (dd, *J* = 4.7, 9.3 Hz, 1H, ArCH), 3.69 (s, 3H, OCH$_3$), 3.29 (ddd, *J* = 1.1, 9.6, 18.4 Hz, 1H, C**H**$_2$CO), 2.93 (s, 6H, N(CH$_3$)$_2$), 2.74 (ddd, *J* = 0.8, 4.9, 18.4 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, CDCl$_3$) δ 199.9, 173.6, 150.7, 134.4, 129.3, 122.6, 113.2, 111.5, 52.8, 46.7, 41.4, 40.6. HRMS (CI) exact mass calcd for ($C_{13}H_{16}ClNO_3$) requires *m/z* 269.0819, found *m/z* 269.0814. $[\alpha]_D = -156.4$ (c = 1.0, CHCl$_3$). The enantiomeric ratio of the product was determined by HPLC analysis of the corresponding alcohol (obtained by NaBH$_4$ reduction in ethanol at 0 °C) using a Chiracel AD and AD guard column (6.0% ethanol/hexanes, 1 mL/min); *S* isomer t_r = 23.3 min, *R* isomer t_r = 25.2 min. The same reaction conducted on 0.25–mmol scale at ambient temperature over 12 h and purified in identical fashion afforded the product in 66% yield (44.4 mg, 0.165 mmol) and 86% ee.



S9

Determination of the absolute configuration of (*R*)-4-oxo-2-(4-dimethylamino-2-chlorophenyl)-butyric acid methyl ester by correlation to (*S*)-2-(4'-dimethylamino-phenyl)-butan-1,4,-diol. A solution of (*R*)-4-oxo-2-(4-dimethylamino-2-chlorophenyl)-butyric acid methyl ester (270 mg, 1.00 mmol, 1.00 equiv) in CH_2Cl_2 (1.00 mL) was carefully added to a stirring suspension of lithium aluminumhydride (152 mg, 4.00 mmol, 4.00 equiv) in Et2O (5 mL). After 5 min, this mixture was diluted with saturated aqueous sodium potassium tartrate (100 mL) and Et_2O (100 mL) and allowed to stir for an additional 8 h. The organic layer was separated and the aqueous was extracted three times with CH_2Cl_2. The combined organics were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography to afford 0.149 g (0.611 mmol, 61% yield) of a white crystalline solid. A portion of this material (21.5 mg, 88.2 μmol, 1.00 equiv) was added to stirring solution of sodium (23 mg, 1.0 mmol, 11 equiv) in liquid ammonia (10 mL) at –50 °C. After an hour, the reaction was quenched with methanol and diluted with Et_2O and H_2O. The phases were separated and the organic was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography (100% EtOAc) to afford 11.1 mg (53.0 μmol, 60% yield) of a white solid that was spectroscopically identical in all respects to **S9** generated above from (*R*)-4-oxo-2-(4-dimethylamino-phenyl)-butyric acid methyl ester. $[\alpha]_D$ (reference) = –23.1 (c = 0.975 , $CHCl_3$); $[\alpha]_D$ (observered) = –20.5 (c = 0.555, $CHCl_3$).

(*S*)-3-(4-Dimethylamino-2-methoxy-phenyl)-3-phenyl-propanol. To a 50-mL round-bottom flask equipped with a magnetic stir bar was added (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (0.394 g, 1.60 mmol, 0.100 equiv), CH_2Cl_2 (16.0 mL), HCl (as a 4N solution in 1,4-dioxane, 0.400 mL, 1.60 mmol, 0.100 equiv), and *N,N*-dimethyl-*m*-anisidine (4.69 mL, 32.0 mmol, 2.00 equiv). The reaction vessel was cooled to 0 °C before the addition of cinnamaldehyde (2.06 ml, 16.0 mmol, 1.00 equiv). The solution was stirred for 12 h at 0 °C and then warmed to ambient temp and stirred for an additional 6h. At that time the reaction mixture

was added drop-wise to a stirring suspension of $NaBH_4$ (0.750 g, 0.198 mmol, 1.24 equiv) in ethanol. After 5 min, the reduction was quenched with saturated aqueous $NaHCO_3$ solution and diluted with CH_2Cl_2. The layers were separated and the organic was washed with saturated aqueous $NaHCO_3$ and brine solutions. The resulting solution was dried over sodium sulfate and concentrated *in vacuo* to give a pale yellow residue which was purified by silica gel chromatography. Gradient elution with 25-50% EtOAc in hexanes afforded the product as a colorless oil in 81% yield (3.70 g, 13.0 mmol); 74% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.12 (m, 5H, ArH), 6.99 (d, *J* = 8.2 Hz, 1H, ArH), 6.31 (dd, *J* = 2.7, 8.8 Hz, 1H, ArH), 6.27 (d, *J* = 2.2, Hz, 1H, ArH), 4.51 (dd, *J* = 6.6, 8.8 Hz, 1H, ArCH), 3.83 (s, 3H, OCH_3), 3.65-3.48 (m, 2H, C**H**$_2$OH), 2.93 (s, 6H, $N(CH_3)_2$), 2.38-2.12 (m, 2H, CHC**H**$_2$), 1.98 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 150.5, 145.5, 128.8, 128.4, 128.2, 125.9, 121.3, 105.5, 96.6, 61.6, 55.9, 41.1, 38.7, 38.2. The enantiomeric ratio of the product was determined by HPLC analysis using a Chiracel AD and AD guard column (10% ethanol/hexanes, 1 mL/min); *R* isomer t_r = 12.9 min, *S* isomer t_r = 18.1 min.

3-(4-Dimethylamino-2-methoxy-phenyl)-3-phenyl-propanol-*tert*-butyl-dimethylsilyl ether (4). 3-(4-Dimethylamino-2-methoxy-phenyl)-3-phenyl-propanol (0.250 g, 0.877 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3.0 mL) and treated sequentially with triethylamine (0.148 mL, 1.05 mmol, 1.20 equiv) and *tert*-butyldimethylsilyl chloride (0.159 g, 1.05 mmol, 1.20 equiv). The reaction was stirred overnight and then subjected directly to silica gel chromatography. Gradient elution with 10-20% EtOAc in hexanes afforded the product as a pale yellow oil in 75% yield (244 mg, 0.659 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 4H, ArH), 7.20-7.13 (m, 2H, ArH), 6.35 (dd, *J* = 2.7, 8.8 Hz, 1H, ArH), 6.29 (d, J = 2.4 1H, ArH), 4.48 (t, *J* = 8.2 Hz. 1H, ArCH), 3.81 (s, 3H, OCH_3), 3.63 (t, *J* = 7.1 Hz, 2H, CH_2O), 2.97 (s, 6H, $N(CH_3)_2$), 2.33-2.24 (m, 2H, CHC**H**$_2$), 0.95 (s, 9H, $C(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 150.5, 145.8, 128.3, 128.2, 125.7, 122.0, 105.1, 97.0, 62.1, 55.7, 41.2, 39.4, 38.5, 26.4, 18.8, -4.8. $[\alpha]_D = -15.4$ (c = 0.82, $CHCl_3$).

1-Methoxy-2-(3-*tert*-butyldimethylsiloxy-1-phenyl-propyl)-benzene (5). In a 25-mL pear-shaped flask equipped with a magnetic stir bar, **4a** (244 mg, 0.659 mmol, 1.00 equiv) was dissolved in iodomethane (0.41 ml, 6.6 mmol, 10 equiv). The neat reaction mixture was stirred

at ambient temperature for 8h at which time TLC analysis showed the starting material to be completely consumed. The iodomethane was removed *in vacuo* to furnish the quaternary ammonium iodide quantitatively (335 mg, 0.659 mmol) without need for further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.52 (d, *J* = 2.7 Hz, 1H, ArH), 7.34 (d, *J* = 8.8, 1H, ArH), 7.28-7.12 (m, 6H, ArH), 4.57 (t, *J* = 7.7 Hz, 1H, ArCH), 4.05 (s, 3H, OCH_3), 3.99 (s, 9H, $N(CH_3)_3$), 3.55-3.49 (m, 2H, CH_2O), 2.20 (q, *J* = 7.7 Hz, 2H, CHC**H$_2$**), 0.95 (s, 9H, $C(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 146.4, 143.0, 137.0, 128.9, 128.6, 128.3, 126.6, 110.0, 103.8, 61.2, 58.5, 58.0, 39.7, 37.6, 26.2, 18.6, -5.0. A portion of the quaternary ammonium salt (100 mg, 0.195 mmol, 1.00 equiv) was dissolved/suspended in tetrahydrofuran (3.0 mL) and added to a rapidly stirring solution of sodium (18.0 mg, 0.782 mmol, 4.0 equiv) in liquid ammonia (approx. 25 mL) at –78 °C. After 5 min, the cold reaction mixture was treated with benzylmethyl ether (0.2 mL) and the deep blue color was supplanted almost immediately by a bright orange. The mixture was then treated with isopropanol (2 mL) and stirred at –78 °C for another 5 min by which time all color had dissipated from the reaction. Diethyl ether (20 mL) and saturated aqueous ammonium chloride (10 mL) were added carefully and the reaction vessel was allowed to warm to room temperature. The organic phase was then dried over Na_2SO_4, concentrated and the residue purified by silica gel chromatography. Gradient elution with 2-10% EtOAc in hexanes provided the deaminated product in 96% yield (61.2 mg, 0.187 mmol). IR (film) 3027, 2954, 2929, 2856, 1601, 1492, 1462, 1438, 1244, 1100, 1051, 945.9, 834.8, 775.2, 751.9, 698.4 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.12 (m, 7H, ArH), 6.93 (dt, *J* = 1.1, 7.7 Hz, 1H, ArH), 6.84 (d, *J* = 8.7 Hz, 1H, ArH), 4.58 (t, *J* = 7.7 Hz, 1H, ArCH), 3.78 (s, 3H, OCH_3), 3.58 (t, *J* = 7.1 Hz, 1H, C**H$_2$**O), 2.27 (dq, *J* = 0.9, 6.6 Hz, 2H, CHC**H$_2$**), 0.90 (s, 9H, $C(CH_3)_3$), 0.00 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 144.9, 142.0, 133.3, 128.7, 128.5, 128.4, 128.3, 127.9, 127.3, 16.1, 126.0, 61.8, 55.7, 39.8, 38.3, 38.2, 26.3, 18.7, –4.9. HRMS (CI) exact mass calcd for ($C_{22}H_{32}O_2Si$) requires *m/z* 357.2250 for $[M+H]^+$, found *m/z* 357.2244. $[\alpha]_D = -15.7$ (c = 0.977, $CHCl_3$).