

Supporting Information

Thiazolylalanine-Derived Catalysts for Enantioselective Intermolecular Aldehyde-Imine Cross-Couplings

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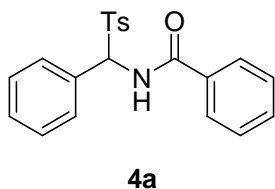
General Procedures. Proton NMR spectra were recorded on a Varian 500 MHz spectrometer. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00 ppm), or with the solvent reference relative to TMS employed as an internal standard (CDCl_3 , δ 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded on a 500 (125 MHz) spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl_3 , δ 77.0 ppm). All NMR spectra were acquired at ambient temperature. Infrared (IR) spectra were recorded on a ThermoNicolet Avatar 210 spectrometer, ν_{max} (cm^{-1}) and are partially reported. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60Å F254 precoated plates (0.25 mm thickness). TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with KMnO_4 , cerium ammonium molybdenate (CAM), or ninhydrin solutions. Flash column chromatography was performed using Silica Gel 60Å (32-63 micron). Optical rotations were recorded on a Rudolph Research Analytical Autopol IV Automatic polarimeter at the sodium D line (path length 50 mm). Melting point ranges were measured on a MelTemp® melting point apparatus and are uncorrected. High resolution mass spectra were acquired in the Mass Spectrometry facility at Boston

College (Chestnut Hill, MA). The method of ionization is indicated in parentheses. Chiral analytical normal phase HPLC was performed on a Hewlett-Packard 1100 Series chromatograph equipped with a diode array detector (214 nm and 254 nm) and compared to a racemic standard.

All reactions were carried out in a nitrogen atmosphere employing oven-dried glassware. All solvents were dried by passing through activated alumina. Thiazolylalanine was received as a donation from Synthetech Inc. (Albany, OR); all remaining amino acids and coupling reagents were purchased from Advanced ChemTech (Louisville, KY). All other chemicals were purchased from Aldrich Chemical Company (Milwaukee, WI); and solvents were purchased from Fisher Scientific.

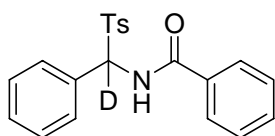
Representative Procedure for the Preparation of Tosyl Amides:¹

Tosyl amide substrates were prepared by the method of Reider et. al. and used as is without further purification. It is noteworthy that the tosyl amides employed here were not stable to silica gel chromatography and therefore no TLC information is provided with the exception of one tosyl amide substrate (**4f**):



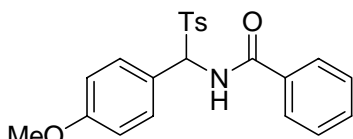
¹ Reider, P.J. et.al. J. Am. Chem. Soc. 2001, 123, 9696-9697.

***N*-[Phenyl-(toluene-4-sulfonyl)-methyl]-benzamide (4a):** ^1H NMR (CDCl_3 , 500 MHz) δ 7.75 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 7.3 Hz, 2H), 7.56-7.50 (m, 3H), 7.47-7.41 (m, 5H), 7.27 (d, J = 8.3 Hz, 1H), 7.14 (d, J = 10.3 Hz, 1H), 7.45 (d, J = 10.4, 1H), 2.41 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 166.1, 145.4, 133.7, 133.0, 132.3, 130.3, 129.9, 129.8, 129.2, 128.9, 128.8, 127.0, 72.3, 21.7; **IR** (film, cm^{-1}) 3605, 3534, 3197, 1661, 1617, 1401, 1210, 1167; **Exact Mass Calcd for** $[\text{C}_{21}\text{H}_{19}\text{NO}_3\text{S Na}]^+$ requires m/z = 388.0983, found m/z = 388.0981 (ESI).



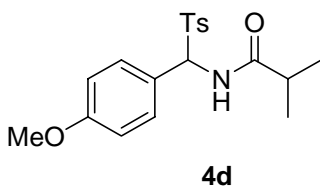
4a-D

***N*-[Phenyl-(toluene-4-sulfonyl)-methyl]-benzamide- ^2H (4a-D):** ^1H NMR (CDCl_3 , 500 MHz) δ 7.75 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 7.3 Hz, 2H), 7.56-7.50 (m, 3H), 7.47-7.41 (m, 5H), 7.27 (d, J = 8.3 Hz, 1H), 7.13 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 166.0, 145.4, 133.7, 133.0, 132.3, 130.2, 129.9, 129.8, 129.2, 128.9, 128.8, 127.0, 21.7; **IR** (film, cm^{-1}) 3583, 3377, 1650, 1505, 1476, 1313, 1151, 1137; **Exact Mass Calcd for** $[\text{C}_{21}^1\text{H}_{18}^2\text{HNO}_3\text{S Na}]^+$ requires m/z = 389.1046, found m/z = 389.1044 (ESI).

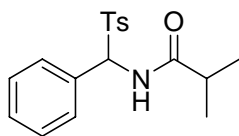


4b

***N*-[*(4*-Methoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-benzamide (4b):** ^1H NMR (CDCl_3 , 500 MHz) δ 7.75 (d, $J = 8.3$ Hz, 2H), 7.68 (d, $J = 8.6$ Hz, 2H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.47-7.42 (m, 4H), 7.27 (d, $J = 6.9$ Hz, 2H), 7.09 (d, $J = 10.3$ Hz, 1H), 6.94 (d, $J = 8.7$ Hz, 2H), 6.40 (d, $J = 10.3$ Hz, 1H), 3.82 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 160.9, 145.2, 133.8, 133.1, 132.3, 130.2, 129.8, 129.2, 128.8, 127.0, 122.0, 114.4, 71.9, 55.4, 21.7; **IR** (film, cm^{-1}) 3625, 3215, 1674, 1601, 1202; **Exact Mass Calcd for** $[\text{C}_{16}\text{H}_{17}\text{NO}_3(-\text{Ts}, +\text{OMe}) \text{Na}]^+$ requires $m/z = 294.1106$, found $m/z = 294.1111$ (ESI).

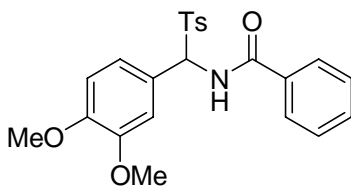


***N*-[*(4*-Methoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-isobutyramide (4d):** ^1H NMR (CDCl_3 , 500 MHz) δ 7.75 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 8.6$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 6.90 (d, $J = 8.6$ Hz, 2H), 6.75 (d, $J = 10.4$ Hz, 1H), 6.28 (d, $J = 10.4$ Hz, 1H), 3.82 (s, 3H), 2.43 (s, 3H), 2.33 (p, $J = 6.9$ Hz, 1H), 1.01 (d, $J = 6.9$ Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.6, 160.7, 145.1, 133.9, 130.3, 129.6, 129.3, 122.1, 114.2, 71.2, 55.3, 35.4, 21.7, 19.2, 19.2; **IR** (film, cm^{-1}) 3417, 2983, 1650, 1612, 1531, 1510, 1349, 1182; **Exact Mass Calcd for** $[\text{C}_{13}\text{H}_{19}\text{NO}_3(-\text{Ts}, +\text{OMe})+\text{Na}]^+$ requires $m/z = 260.1263$, found $m/z = 260.1260$ (ESI).



4e

***N*-[Phenyl-(toluene-4-sulfonyl)-methyl]-isobutyramide (4e):** ^1H NMR (CDCl_3 , 500 MHz) δ 7.75 (d, J = 8.2 Hz, 2H), 7.46-7.38 (m, 5H), 7.31 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 10.3 Hz, 1H), 6.31 (d, J = 10.4 Hz, 1H), 2.43 (s, 3H), 2.34 (p, J = 6.9 Hz, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 175.5, 145.2, 133.8, 130.3, 129.8, 129.7, 129.3, 128.9, 128.8, 71.6, 35.5, 21.7, 19.2, 19.2; **IR** (film, cm^{-1}) 3582, 3348, 2968, 1662, 1507, 1314, 1147, 1084; **Exact Mass Calcd for** $[\text{C}_{18}\text{H}_{21}\text{NO}_4\text{S}]^+$ requires m/z = 354.1140, found m/z = 354.1133 (ESI).

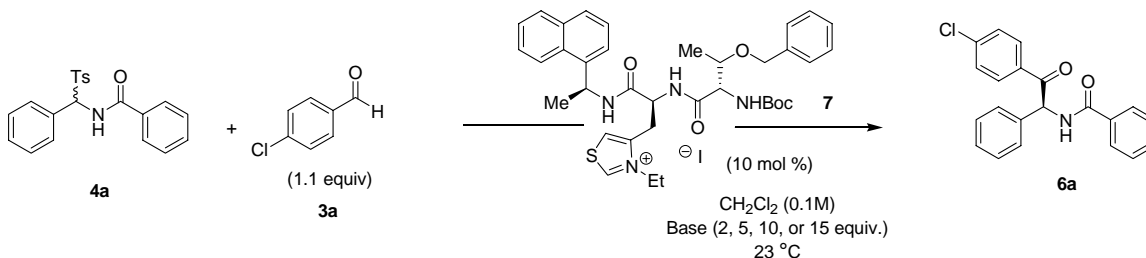


4f

***N*-[(3,4-Dimethoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-benzamide (4f):** ^1H NMR (CDCl_3 , 500 MHz) δ 7.75 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 7.3 Hz, 2H), 7.53-7.50 (m, 1H), 7.44-7.41 (m, 2H), 7.26 (d, J = 7.9 Hz, 2H), 7.10-7.08 (m, 2H), 7.00 (d, J = 2.1 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.39 (d, J = 10.2 Hz, 1H), 3.87 (d, J = 7.5 Hz, 6H), 2.40 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 166.1, 150.6, 149.4, 145.2, 134.1, 133.2, 132.3, 129.8, 129.3, 128.8, 127.1, 122.8, 121.6, 112.5, 111.5, 72.4, 56.1, 56.0, 21.6; **IR** (film, cm^{-1}) 3351, 2968, 1663, 1507, 1315, 1148; **TLC** R_f 0.25 (30% EtOAc/Hexanes); **Exact**

Mass Calcd for $[C_{17}H_{19}NO_4 (-Ts, +OMe)+Na]^+$ requires $m/z = 324.1212$, found $m/z = 324.1216$ (ESI).

General Procedure Employed During Base Optimization Studies:

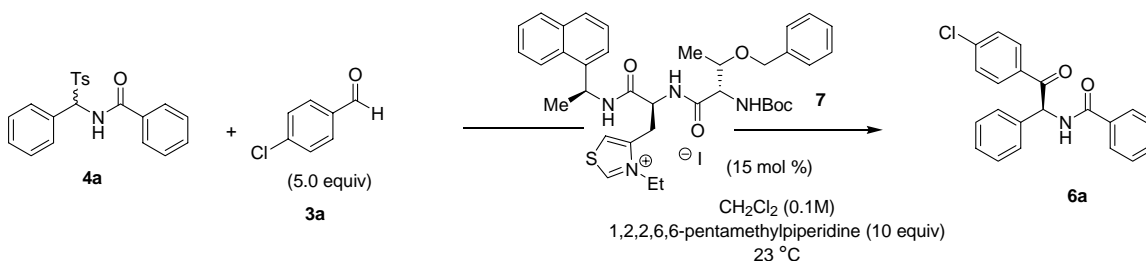


***N*-[2-(4-Chloro-phenyl)-2-oxo-1-phenyl-ethyl]-benzamide (6a):** Into a 10 mL round bottomed flask containing a stir bar was added *N*-[Phenyl-(toluene-4-sulfonyl)-methyl]-benzamide (23.7 mg, 0.0650 mmol) and 4-Chlorobenzaldehyde (10.0 mg, 0.325 mmol). The flask was sealed with a rubber septum and purged with dry nitrogen for 1 hour. A 650 μ L aliquot of catalyst² solution (0.00650 mmol in CH_2Cl_2) was added in one portion to the reaction mixture at 23 °C, followed by amine base (2, 5, 10, and 15 equiv in separate flasks) via syringe (note: Proton Sponge was added as a solid and the flask was quickly resealed). The resulting reaction mixture was allowed to stir at 23 °C for 1 h whereupon the reaction was diluted with 10 mL methylene chloride and washed with 10 mL 10% w/v citric acid_(aq) followed by extraction of the aqueous layer with methylene chloride (3 x 5 mL). The resulting organic layer was dried over anhydrous Na_2SO_4 and concentrated onto silica gel and immediately purified by silica gel chromatography 10% ethyl acetate:hexanes to yield *N*-[2-(4-Chloro-phenyl)-2-oxo-1-phenyl-ethyl]-benzamide

² Mennen, Steven M.; Blank, Jarred T.; Tran-Dubè, Michelle B.; Imbriglio, Jason E.; Miller, Scott J., *Chem. Comm.* Published online November 29, 2004.

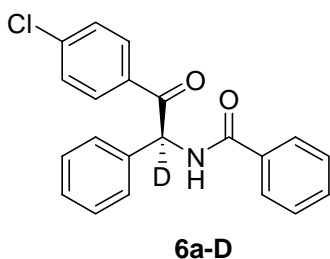
(note: Samples for chiral HPLC analysis were prepared in 15% 2-propanol:hexanes and solublized using a minimal amount of methylene chloride). **¹H NMR** (CDCl₃, 500 MHz) δ 7.95 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 7.0 Hz, 2H), 7.64 (d, J = 6.8 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.46-7.38 (m, 6H), 7.35-7.32 (m, 2H), 7.29-7.26 (m, 2H), 6.70 (d, J = 7.0 Hz, 1H); **¹³C NMR** (CDCl₃, 125 MHz) δ 194.7, 166.4, 140.4, 136.9, 133.8, 132.6, 131.8, 130.5, 129.4, 129.1, 128.6, 128.6, 128.3, 127.1, 59.0; **IR** (film, cm⁻¹) 3411, 3352, 3043, 2930, 1686, 1652, 1586, 1508, 1480, 1400, 1201; **TLC** R_f 0.45 (25% EtOAc:Hexanes); **Exact Mass Calcd for** [C₂₂H₁₆NO₂Cl Na]⁺ requires m/z = 372.0767, found m/z = 372.0760 (ESI); **HPLC** Chiralcel AD, 15% 2-propanol/hexanes, 1.0 mL/min, 20 °C, t_r = 25.6 min (major), t_r = 35.4 min (minor).

Representative Procedure for Aldehyde Acyl-Imine Cross-Coupling Reactions (Optimized Conditions):



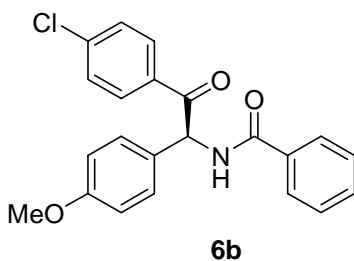
N-[2-(4-Chloro-phenyl)-2-oxo-1-phenyl-ethyl]-benzamide (6a): Into a 10 mL round bottomed flask containing a stir bar was added *N*-[Phenyl-(toluene-4-sulfonyl)-methyl]-benzamide (23.7 mg, 0.0650 mmol) and 4-Chlorobenzaldehyde (46.0 mg, 0.325 mmol). The flask was sealed with a rubber septum and purged with dry nitrogen for 1 hour. A 650 μ L aliquot of catalyst solution (0.00980 mmol in CH₂Cl₂) was added in one portion

to the reaction mixture at 23 °C, followed by addition of 1,2,2,6,6-pentamethylpiperidine (117 μ L, 0.650 mmol) via syringe. The resulting reaction mixture was allowed to stir at 23 °C for 1 h whereupon the reaction was diluted with 10 mL methylene chloride and washed with 10 mL 10% w/v citric acid_(aq) followed by extraction of the aqueous layer with methylene chloride (3 x 5 mL). The resulting organic layer was dried over anhydrous Na₂SO₄ and concentrated onto silica gel and immediately purified by silica gel chromatography 10% ethyl acetate:hexanes to yield *N*-[2-(4-Chloro-phenyl)-2-oxo-1-phenyl-ethyl]-benzamide (12.9 mg, 57% yield, 81% ee). The same procedure was repeated on larger scale and reacted for 2 h using *N*-[Phenyl-(toluene-4-sulfonyl)-methyl]-benzamide (95.0 mg, 0.260 mmol), 4-Chlorobenzaldehyde (181 mg, 1.30 mmol), catalyst (30.0 mg, 0.039 mmol), 1,2,2,6,6-pentamethylpiperidine (0.470 mL, 2.60 mmol), and methylene chloride (2.6 mL, 0.10 M) to yield (91.4 mg, 100% yield, 76% ee). The enantiopurity of the product was enhanced by crystallizing racemic material from ethyl acetate:hexanes and filtered to yield, in the mother liquor, (55.0 mg, 60% yield, >98% ee, $[\alpha]_D^{26.6} = +188.4^\circ$ (*c* 1.0 CHCl₃).



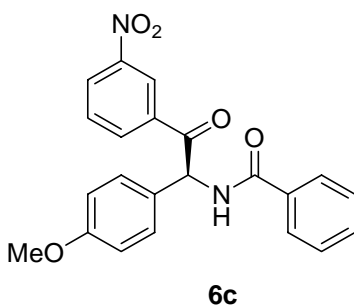
***N*-[2-(4-Chloro-phenyl)-2-oxo-1-phenyl-1-²H-ethyl]-benzamide (6a-D):** Same procedure as optimized conditions except *N*-[Phenyl-(toluene-4-sulfonyl)-methyl]-

benzamide-²H (23.8 mg, 0.0650 mmol) was employed as starting material, and the reaction stirred for 2 h to yield (19.6 mg, 86% yield, 85% ee). **¹H NMR** (CDCl₃, 500 MHz) δ 7.95 (d, *J* = 8.7 Hz, 2H), 7.84 (d, *J* = 7.0 Hz, 2H), 7.64 (s, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.46-7.38 (m, 6H), 7.35-7.32 (m, 2H), 7.29-7.26 (m, 2H); **¹³C NMR** (CDCl₃, 125 MHz) δ 194.7, 166.4, 140.4, 136.9, 133.8, 132.6, 131.8, 130.5, 129.4, 129.1, 128.6, 128.6, 128.3, 127.1; **IR** (film, cm⁻¹) 3414, 3330, 3055, 2941, 1686, 1651, 1586, 1508, 1478, 1282, 1259; **TLC** R_f 0.45 (25% EtOAc:Hexanes); **Exact Mass Calcd for** [C₂₁H₁₅²HNO₂Cl Na]⁺ requires *m/z* = 373.0830, found *m/z* = 373.0842 (ESI); **HPLC** Chiralcel AD, 15% 2-propanol/hexanes, 1.0 mL/min, 20 °C, t_r = 25.6 min (major), t_r = 35.4 min (minor).



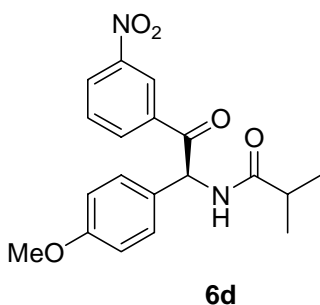
***N*-[2-(4-Chloro-phenyl)-1-(4-methoxy-phenyl)-2-oxo-ethyl]-benzamide (6b):** Same procedure as optimized conditions except *N*-[(4-Methoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-benzamide (25.7 mg, 0.0650 mmol) was employed as starting material. The reaction stirred for 2 h, and the product was purified using 15% ethyl acetate:hexanes as eluent to yield (22.1 mg, 90% yield, 87% ee). The same procedure was repeated on larger scale using *N*-[(4-Methoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-benzamide (341 mg, 0.860 mmol), 4-Chlorobenzaldehyde (602 mg, 4.30 mmol), catalyst (100 mg, 0.129

mmol), 1,2,2,6,6-pentamethylpiperidine (1.10 mL, 8.60 mmol), and methylene chloride (8.6 mL, 0.10 M) to yield (298 mg, 91% yield, 85% ee). The enantiopurity of the product was enhanced by crystallizing racemic material from ethyl acetate:hexanes and filtered to yield, in the mother liquor, (234 mg, 72% yield, 98% ee, $[\alpha]_D^{26.3} = +176.8^\circ$ (c 1.0 CHCl_3). **^1H NMR** (CDCl_3 , 500 MHz) δ 7.94 (d, $J = 8.6$ Hz, 2H), 7.85-7.82 (m, 2H), 7.61 (d, $J = 6.9$ Hz, 1H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.44-7.35 (m, 6H), 6.85 (d, $J = 8.7$ Hz, 2H), 6.64 (d, $J = 7.0$ Hz, 1H), 3.75 (s, 3H); **^{13}C NMR** (CDCl_3 , 125 MHz) δ 194.8, 166.3, 159.7, 140.3, 133.9, 132.7, 131.7, 130.5, 129.6, 129.1, 128.9, 128.5, 127.1, 114.8, 58.4, 55.2; **IR** (film, cm^{-1}) 3414, 3312, 3067, 2917, 1685, 1648, 1586, 1510, 1481, 1255; **TLC** R_f 0.30 (25% EtOAc:Hexanes); **Exact Mass Calcd for** $[\text{C}_{22}\text{H}_{18}\text{NO}_3\text{Cl Na}]^+$ requires $m/z = 402.0873$, found $m/z = 402.0871$ (ESI); **HPLC** Chiralcel AD, 15% 2-propanol/hexanes, 1.0 mL/min, 20 $^\circ\text{C}$, $t_r = 43.7$ min (major), $t_r = 68.5$ min (minor).



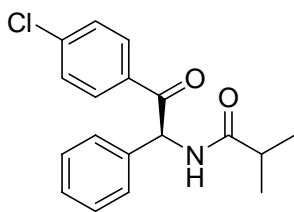
***N*-[1-(4-Methoxy-phenyl)-2-(3-nitro-phenyl)-2-oxo-ethyl]-benzamide (6c):** Same procedure as optimized conditions except *N*-[(4-Methoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-benzamide (25.7 mg, 0.0650 mmol) was employed as starting material, 3-Nitrobenzaldehyde (49.0 mg, 0.325 mmol) used in place of 4-Chlorobenzaldehyde. The

reaction stirred for 15 min, and the product was purified using 15%→30% ethyl acetate:hexanes as eluent to yield (17.9 mg, 71% yield, 83% ee). The same procedure was repeated on larger scale using *N*-[(4-Methoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-benzamide (103 mg, 0.260 mmol), 3-Nitrobenzaldehyde (196 mg, 1.30 mmol), catalyst (30.0 mg, 0.039 mmol), 1,2,2,6,6-pentamethylpiperidine (0.470 mL, 2.60 mmol), and methylene chloride (2.6 mL, 0.10 M) to yield (77.8 mg, 77% yield, 82% ee). **¹H NMR** (CDCl₃, 500 MHz) δ 8.84 (s, 1H), 8.37 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.45-7.39 (m, 4H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 6.8 Hz, 1H), 3.75 (s, 3H); **¹³C NMR** (CDCl₃, 125 MHz) δ 193.9, 166.5, 160.0, 148.4, 135.7, 134.4, 133.5, 131.9, 130.0, 129.7, 128.6, 127.8, 127.7, 127.1, 123.9, 115.0, 59.0, 55.2; **IR** (film, cm⁻¹) 3578, 2978, 1683, 1599, 1511, 1264, 1201; **TLC** R_f 0.50 (50% EtOAc:Hexanes); **Exact Mass Calcd for** [C₂₂H₁₈N₂O₅ Na]⁺ requires *m/z* = 413.1113, found *m/z* = 413.1107 (ESI); **HPLC** Chiralcel AD, 15% 2-propanol/hexanes, 1.0 mL/min, 20 °C, t_r = 65.6 min (major), t_r = 74.2 min (minor).



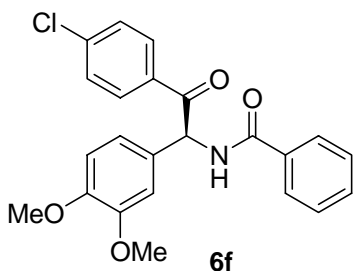
***N*-[1-(4-Methoxy-phenyl)-2-(3-nitro-phenyl)-2-oxo-ethyl]-isobutyramide (6d):** Same procedure as optimized conditions except *N*-[(4-Methoxy-phenyl)-(toluene-4-sulfonyl)-

methyl]-isobutyramide (23.5 mg, 0.0650 mmol) was employed as starting material, 3-Nitrobenzaldehyde (49.0 mg, 0.325 mmol) used in place of 4-Chlorobenzaldehyde. The reaction stirred for 15 min, and the product was purified using 15%→30% ethyl acetate:hexanes as eluent to yield (14.7 mg, 63% yield, 79% ee). The same procedure was repeated on larger scale using *N*-[(4-Methoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-isobutyramide (103 mg, 0.260 mmol), 3-Nitrobenzaldehyde (196 mg, 1.30 mmol), catalyst (30.0 mg, 0.039 mmol), 1,2,2,6,6-pentamethylpiperidine (0.470 mL, 2.60 mmol), and methylene chloride (2.6 mL, 0.10 M) to yield after recrystalizing the resulting product from ethyl acetate:hexanes (20.8 mg, 23% yield, needles, mp: 153-154 °C, >98% ee, $[\alpha]_D^{26.9} = +224.4^\circ$ (*c* 1.0 CHCl₃)). **¹H NMR** (CDCl₃, 500 MHz) δ 8.80 (s, 1H), 8.36-8.34 (m, 1H), 8.25 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.7, 2H), 6.72 (d, *J* = 6.6 Hz, 1H), 6.48 (d, *J* = 6.9 Hz, 1H), 3.76 (s, 3H), 2.46 (p, *J* = 6.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H); **¹³C NMR** (CDCl₃, 125MHz) δ 194.2, 176.3, 159.9, 148.4, 135.939, 134.3, 129.9, 129.5, 127.8, 127.7, 123.9, 115.0, 58.4, 55.3, 35.3, 19.4, 19.4; **IR** (film, cm⁻¹) 3312, 2965, 2947, 1698, 1654, 1611, 1532, 1511, 1349, 1257; **TLC** *R_f* 0.43 (50% EtOAc:Hexanes); **Exact Mass Calcd for** [C₁₉H₂₀N₂O₅ Na]⁺ requires *m/z* = 379.1270, found *m/z* = 379.1270 (ESI); **HPLC** Chiralcel AD, 15% 2-propanol/hexanes, 1.0 mL/min, 20 °C, *t_r* = 28.0 min (major), *t_r* = 18.0 min (minor).



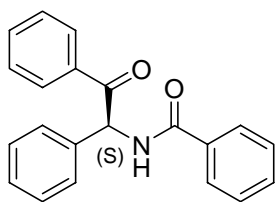
6e

***N*-[2-(4-Chloro-phenyl)-2-oxo-1-phenyl-ethyl]-isobutyramide (6e):** Same procedure as optimized conditions except *N*-[Phenyl-(toluene-4-sulfonyl)-methyl]-isobutyramide (85.9 mg, 0.260 mmol), 4-Chlorobenzaldehyde (182 mg, 1.30 mmol), catalyst (30.0 mg, 0.039 mmol), 1,2,2,6,6-pentamethylpiperidine (0.470 mL, 2.60 mmol), and methylene chloride (2.6 mL, 0.10 M) to yield (79.6 mg, 97% yield, 75% ee) after recrystallizing the resulting product from ethyl acetate:hexanes (39.1 mg, 48% yield, needles, mp: 144-145 °C, >98% ee, $[\alpha]_D^{25.7} = +283.7^\circ$ (*c* 1.0 CHCl₃)). **¹H NMR** (CDCl₃, 500 MHz) δ 7.90 (d, *J* = 8.7 Hz, 2H), 7.38-7.27 (m, 7H), 6.88 (d, *J* = 6.8 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 1H), 2.45 (p, *J* = 6.9 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H); **¹³C NMR** (CDCl₃, 125 MHz) δ 194.9, 176.1, 140.3, 137.0, 132.8, 130.4, 129.3, 129.1, 128.5, 128.1, 58.4, 35.4, 19.4; **IR** (film, cm⁻¹) 3301, 2961, 2924, 1653, 1588, 1496, 1398, 1253, 1219, 1093; **TLC** R_f 0.48 (30% EtOAc/Hexanes); **Exact Mass Calcd for** [C₁₈H₁₈ClNO₂ Na]⁺ requires *m/z* = 338.0924, found *m/z* = 338.0928 (ESI); **HPLC** Chiralcel AD, 15% isopropanol/hexane, 1.0 mL/min, 20 °C, t_r = 8.7 min (major), t_r = 11.4 min (minor).



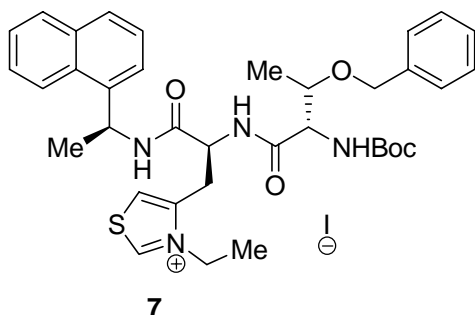
***N*-[2-(4-Chloro-phenyl)-1-(3,4-dimethoxy-phenyl)-2-oxo-ethyl]-benzamide (6f):**

Same procedure as optimized conditions except *N*-[(3,4-Dimethoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-benzamide (25.0 mg, 0.0588 mmol) was employed as starting material, and the reaction was run for 1 h to yield (19.3 mg, 80% yield, 81% ee). The same procedure was repeated on larger scale using *N*-[(3,4-Dimethoxy-phenyl)-(toluene-4-sulfonyl)-methyl]-benzamide (110.1 mg, 0.260 mmol), 4-Chlorobenzaldehyde (182 mg, 1.30 mmol), catalyst (30.0 mg, 0.039 mmol), 1,2,2,6,6-pentamethylpiperidine (0.470 mL, 2.60 mmol), and methylene chloride (2.6 mL, 0.10 M) to yield (102.6 mg, 97% yield, 70% ee). **¹H NMR** (CDCl₃, 500 MHz) δ 7.95 (d, *J* = 8.6 Hz, 2H), 7.83 (d, *J* = 7.1 Hz, 2H), 7.54 (d, *J* = 6.9 Hz, 1H), 7.51-7.48 (m, 1H), 7.45-7.38 (m, 4H), 6.98-6.96 (m, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 7.1 Hz, 1H), 3.83 (d, *J* = 16.5 Hz, 6H); **¹³C NMR** (CDCl₃, 125 MHz) δ 194.9, 166.5, 149.8, 149.5, 140.4, 134.0, 134.0, 131.7, 130.5, 129.4, 129.1, 128.6, 127.2, 121.1, 111.9, 111.5, 58.8, 56.1, 55.9, 29.7; **IR** (film, cm⁻¹) 3366, 2929, 1652, 1589, 1514, 1484, 1265, 1145, 1091, 1028; **TLC** *R_f* 0.21 (30% EtOAc/Hexanes); **Exact Mass Calcd for** [C₂₃H₂₀ClNO₄ Na]⁺ requires *m/z* = 432.0979, found *m/z* = 432.0980 (ESI); **HPLC** Chiralcel AD, 15% isopropanol/hexane, 1.0 mL/min, 20 °C, *t_r* = 37.5 min (major), *t_r* = 42.4 min (minor).



6g

(S)-N-(2-Oxo-1,2-diphenyl-ethyl)-benzamide (6g): Same procedure as optimized conditions benzaldehyde (33.0 μ l, 0.325 mmol) was used in place of 4-Chlorobenzaldehyde. The reaction stirred for 2 h, and the product was purified using 10% ethyl acetate:hexanes as eluent to yield (3.1 mg, 15% yield, 83% ee) The product was identical to literature characterization data and sign of optical rotation ($[\alpha]_D = +138.0^\circ$) confirms predominance of (S)-N-(2-Oxo-1,2-diphenyl-ethyl)-benzamide.³



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4-[2-(3-Benzoyloxy-2-tert-butoxycarbonylamino-butrylamino)-2-(1-naphthalen-1-yl-ethylcarbamoyl)-ethyl]-3-ethyl-thiazol-3-ium; iodide:⁴ ^1H NMR (CDCl_3 , 500 MHz) δ 10.03 (s, 1H), 8.27 (d, $J=8.5$ Hz, 1H), 8.14 (d, $J = 8.1$ Hz, 1H), 7.88 (d, $J=8.0$ Hz, 1H), 7.79 (m, 1H), 7.66 (d, $J=7.2$ Hz, 1H), 7.56 (t, $J = 7.2$ Hz), 7.52-7.46 (m, 3H), 7.36-7.27 (m, 3H), 6.75 (s, 1H), 6.00 (p, $J = 7.5$ Hz, 1H), 5.32 (bd, $J = 7.2$ Hz, 1H), 4.92 (d, $J = 6.4$

³ Maruoka, Keiji; et al, *J. Am. Chem. Soc.* **2002**, 124, 7640-7641.

⁴ See supplementary information for reference 2

Hz, 1H), 4.73 (p, $J = 7.3$ Hz, 1H), 4.64 (p, $J = 7.1$, 1H), 4.58 (d, $J = 11.7$ Hz, 1H), 4.45 (d, $J = 12.3$ Hz, 1H), 4.28 (dd, $J = 7.8, 3.0$ Hz, 1H), 4.14 (s, 1H), 3.27 ($J_{\text{abx}}, J_{\text{ax}}=6.0$, Hz, $J_{\text{bx}}=7.3$ Hz, $J_{\text{ab}}=15.4$ Hz, 2H), 1.67 (d, $J=6.8$ Hz, 3H), 1.52 (t, $J=7.3$ Hz, 3H), 1.47 (s, 9H), 1.12 (d, $J=5.5$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.8, 167.4, 158.1, 155.9, 145.3, 138.9, 137.9, 133.7, 130.8, 128.9, 128.4, 127.9, 127.7, 127.6, 126.5, 125.8, 124.4, 123.4, 122.4, 80.3, 74.5, 71.1, 58.5, 51.3, 49.8, 44.9, 30.0, 28.3, 20.9, 15.7, 15.2; **TLC** R_f 0.65 (15% MeOH: CH_2Cl_2); **Exact Mass Calcd for** $[\text{C}_{36}\text{H}_{45}\text{NO}_5\text{S}]^+$ requires $m/z = 645.111$, found $m/z = 645.3135$ (ESI); $[\alpha]_{\text{D}}^{26.3} = +5.4^\circ$ (*c* 1.0 CHCl_3).

