

**Chiral Proton Catalysis of Secondary Nitroalkane Additions to Azomethine:  
Synthesis of a Potent GlyT1 Inhibitor**

Tyler A. Davis, Michael W. Danneman, and Jeffrey N. Johnston\*

Department of Chemistry & Vanderbilt Institute of Chemical Biology  
Vanderbilt University  
2301 Vanderbilt Place, Nashville, TN 37235-1822

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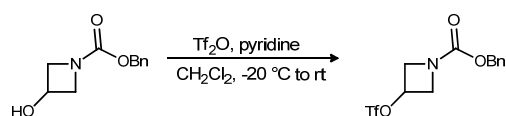
Experimental Section.....	2
Benzyl 3-(trifluoromethylsulfonyloxy)azetidine-1-carboxylate ( <b>S1</b> ).....	2
2,4-Dichloro- <i>N</i> -((1-((1-methyl-1 <i>H</i> -imidazol-4-yl) sulfonyl)azetidin-3-yl)(phenyl) methyl) benzamide ( <b>1</b> ).....	3
Summary of Structural Elucidation for Azetidine <b>1</b> .....	3
Benzyl 3-hydroxyazetidine-1-carboxylate ( <b>9</b> ).....	4
Benzyl 3-iodoazetidine-1-carboxylate ( <b>10</b> ).....	4
Benzyl 3-nitroazetidine-1-carboxylate ( <b>11</b> ).....	5
( <i>R</i> )-Benzyl 3-(( <i>tert</i> -butoxycarbonylamino)(phenyl)methyl)-3-nitroazetidine-1-carboxylate ( <b>12</b> ).....	5
( <i>S</i> )-Benzyl 3-((( <i>tert</i> -butoxycarbonyl)amino)(phenyl)methyl)azetidine-1-carboxylate ( <b>13</b> ).....	5
( <i>S</i> )- <i>tert</i> -Butyl (azetidin-3-yl(phenyl)methyl)carbamate ( <b>14</b> ).....	6
( <i>S</i> )- <i>tert</i> -Butyl((1-((1-methyl-1 <i>H</i> -imidazol-4-yl)sulfonyl)azetidin-3-yl)(phenyl)methyl) carbamate ( <b>16</b> ).....	6
( <i>S</i> )-(1-((1-Methyl-1 <i>H</i> -imidazol-4-yl)sulfonyl)azetidin-3-yl)(phenyl)methanamine ( <b>17</b> ).....	6

## Experimental Section

All reagents and solvents were commercial grade and purified prior to use when necessary. The following reagents were used as supplied by Sigma-Aldrich without further purification: 2-nitropropane,  $n\text{-Bu}_3\text{SnH}$ , benzyl chloroformate, and 2,4-dichlorobenzoyl chloride. Aldimines were prepared as reported in the literature.<sup>1,2</sup> (**7a**·HOTf and **7b**·HOTf were synthesized via the previously published general procedure.<sup>3</sup> Toluene was dried by passage through a column of activated alumina as described by Grubbs.<sup>4</sup> 3-Hydroxyazetidine hydrochloride was purchased from Oakwood Products Inc., triflic anhydride was purchased from Alfa Aesar, and sulfonyl chloride was purchased from Maybridge Chemical Co. Thin layer chromatography (TLC) was performed using glass-backed silica gel (250  $\mu\text{m}$ ) plates and flash chromatography utilized 230–400 mesh silica gel from Sorbent Technologies. UV light, and/or the use of potassium iodoplatinate and potassium permanganate solutions were used to visualize products.

Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker DRX-500 (500 MHz), Bruker AV-400 (400 MHz) or Bruker AV II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to  $\delta$  7.26 and  $\delta$  77.0 ( $\text{CDCl}_3$ ). IR spectra were recorded on a Thermo Nicolet IR100 spectrophotometer and are reported in wavenumbers ( $\text{cm}^{-1}$ ). Compounds were analyzed as neat films on a NaCl plate (transmission). Mass spectra were recorded on a Waters LCT spectrometer by use of the ionization method noted.

Absolute configurations of all compounds were assigned by analogy.<sup>3,5</sup>



**Benzyl 3-(trifluoromethylsulfonyloxy)azetidine-1-carboxylate (S1).** The following is modified from a literature procedure.<sup>6</sup> To a stirring solution of benzyl 3-hydroxyazetidine-1-carboxylate (1.000 g, 4.826 mmol), pyridine (778  $\mu\text{L}$ , 9.65 mmol), and  $\text{CH}_2\text{Cl}_2$  (24 mL) was added trifluoromethanesulfonic anhydride (974  $\mu\text{L}$ , 5.79 mmol) dropwise at  $-20\text{ }^\circ\text{C}$ . The reaction was allowed to gradually warm to room temperature while stirring. The reaction mixture was concentrated, and then dissolved in ethyl acetate. The organic solution was washed with water, satd aq  $\text{NaHCO}_3$ , and then brine before drying with  $\text{MgSO}_4$ . A golden oil was obtained (1.539 g, 94%).  $R_f = 0.30$  (20% EtOAc/hexanes); IR (film) 2958, 1718  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.30 (m, 5H), 5.47–5.40 (m, 1H), 5.11 (s, 2H), 4.41 (ddd,  $J = 11.2, 6.8, 0.8$  Hz, 2H), 4.25 (ddd,  $J = 10.8, 4.0, 0.8$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) ppm 155.9, 135.9, 128.5, 128.3, 128.1, 118.3 (q,  $J = 319.5$  Hz), 74.3, 67.3, 56.5; HRMS (EI): Exact mass calcd for  $\text{C}_{12}\text{H}_{12}\text{F}_3\text{NO}_5\text{S}$   $[\text{M}]^+$  339.0383, found 339.0389.

<sup>1</sup> Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238–1240.

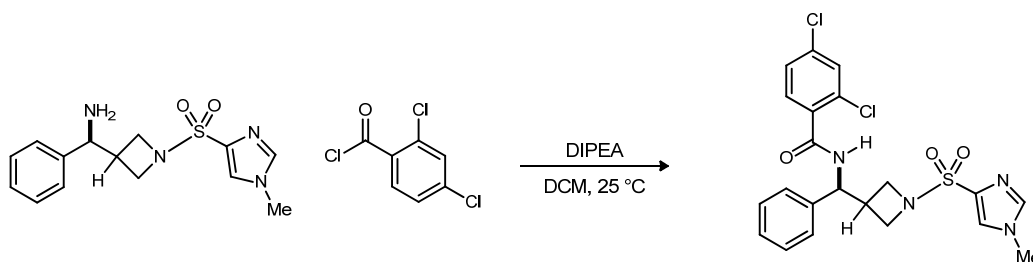
<sup>2</sup> Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398–15404.

<sup>3</sup> Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880–2882.

<sup>4</sup> Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

<sup>5</sup> Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419.

<sup>6</sup> Sureshan, K. M.; Ikeda, K.; Asano, N.; Watanabe, Y. *Tetrahedron* **2008**, *64*, 4072–4080.



### 2,4-Dichloro-*N*-((1-((1-methyl-1*H*-imidazol-4-yl) sulfonyl)azetidin-3-yl)(phenyl) methyl) benzamide (1).

To a flame dried flask equipped with a stir bar was added the amine (36.1 mg, 118  $\mu\text{mol}$ ) and dichloromethane (1 mL), immediately followed by addition of *N,N*-diisopropylethylamine (30.5 mg, 236  $\mu\text{mol}$ ) and the benzoyl chloride (42.1 mg, 201  $\mu\text{mol}$ ). The reaction was stirred at rt for 16 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with  $\text{NaHCO}_3$ , extracted with dichloromethane, dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo. Flash column chromatography of the residue ( $\text{SiO}_2$ , 0-10% methanol in dichloromethane) yielded the desired dichlorinated product as an off white viscous oil (15.3 mg, 27% over 2 steps). The major enantiomer was determined to be 87% ee by chiral HPLC analysis. Chiral HPLC analysis (Chiralpak AD, 65% isopropyl alcohol/hexanes, 1.2 mL/min,  $t_r(e_1, \text{major}) = 3.65$  min,  $t_r(e_2, \text{minor}) = 7.05$  min);  $[\alpha]_D^{20} -4.6$  ( $c$  0.41,  $\text{CHCl}_3$ );  $R_f = 0.40$  (5% MeOH/dichloromethane); IR (film) 3262, 3061, 2925, 2855, 1649  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 (s, 1H), 7.48 (d,  $J = 8.4$  Hz, 1H), 7.40 (d,  $J = 2.0$  Hz, 1H), 7.38 (s, 1H), 7.31 (m, 4H), 7.22 (d,  $J = 6.8$  Hz, 2H), 6.83 (br d,  $J = 8.4$  Hz, 1H), 5.06 (dd,  $J = 8.8, 8.8$  Hz, 1H), 4.07 (dd,  $J = 8.4, 8.4$  Hz, 1H), 3.96 (dd,  $J = 8.4, 8.4$  Hz, 1H), 3.95 (d,  $J = 7.2$  Hz, 2H), 3.79 (s, 3H), 3.03 (dddd,  $J = 8.8, 8.4, 8.4, 7.2, 7.2$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 165.3, 138.6, 136.9, 133.4, 131.5, 131.0, 129.9, 129.0, 128.2, 127.5, 126.5, 55.5, 54.0, 53.6, 34.2, 33.3; HRMS (ESI): Exact mass calcd for  $\text{C}_{21}\text{H}_{21}\text{Cl}_2\text{N}_4\text{O}_3\text{S}$   $[\text{M}+\text{H}]^+$  479.0679, found 479.0714. HSQC indicated that the methylene carbons of the azetidine ring are diastereotopic, as would be expected for the assigned structure.

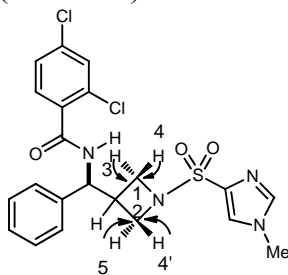
### Summary of Structural Elucidation for Azetidine 1.

#### Key Features

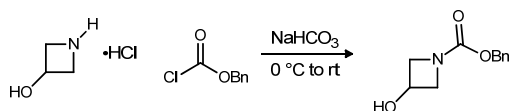
The structure was assigned as the desired azetidine using standard 1D and 2D NMR techniques.  $^1\text{H}$  NMR indicated the presence of a doublet of doublets integrating to 1H at 4.07 ppm, a doublet of doublets integrating to 1H at 3.96 ppm and a doublet integrating to 2H at 3.95. These 4 hydrogens account for both methylenes of the azetidine ring. The unorthodox splitting of the azetidine methylenes supported the proposal that the hydrogens on the methylenes of the azetidine ring were diastereotopic (all magnetically inequivalent).  $^1\text{H}$  NMR also indicated the presence of a doublet of doublets integrating to 1H at 5.06 ppm, assigned as the benzylic methine. A singlet integrating to 3H at 3.79 ppm was assigned as the methyl group of the methyl imidazole ring. A doublet of doublets of doublets of doublets of doublets integrating to 1H at 3.03 ppm was assigned as the methine of the azetidine ring. Also, the presence of 10H in the aromatic region further supports the desired azetidine structure.  $^{13}\text{C}$  NMR clearly indicates the presence of an amide at 165 ppm. Peaks at 54.0 ppm and 53.6 ppm indicates that the methylene carbons of the azetidine ring are diastereotopic. DEPT 135 experimentation further confirms this finding as the peaks at 54.0 ppm and 53.6 ppm are inverted indicating that they are methylene carbons.

Additional Features

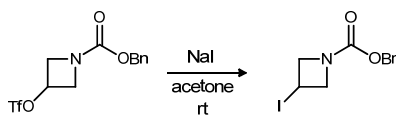
**Figure 1.** Key HSQC Correlations for **1** (600 MHz)



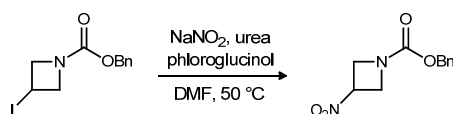
Further evidence supporting the structural assignment includes an HSQC (**Figure 1**), which clearly showed that the methylene hydrogens and carbons on the azetidine ring were diastereotopic via anticipated  $^1J_{\text{HC}}$  couplings. C1 (54.0 ppm) of the azetidine ring showed correlations to methylene hydrogens H3 (4.07 ppm) and H4 (3.95 ppm). C2 (53.6 ppm) of the azetidine ring also showed correlations to methylene hydrogens H5 (3.96 ppm) and H4' (3.95 ppm).



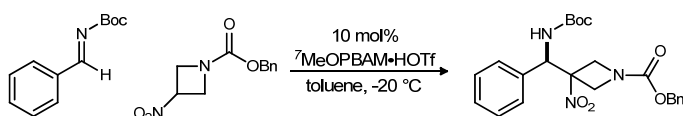
**Benzyl 3-hydroxyazetidine-1-carboxylate (9).** 3-Hydroxyazetidine hydrochloride (5.000 g, 45.64 mmol) was dissolved in 50 mL of deionized water. Sodium bicarbonate (17.43 g, 207.5 mmol) was added at room temperature. The stirring mixture was chilled to 0 °C, then benzyl chloroformate (7.078 g, 41.49 mmol) was added. The reaction mixture was allowed to warm gradually to room temperature overnight. The reaction mixture was diluted with water before extraction with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried with MgSO<sub>4</sub> and concentrated to a slightly golden oil (8.208 g, 95%).  $R_f = 0.14$  (50% EtOAc/hexanes); IR (film) 3405, 2951, 2881, 1683 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.40-7.28 (m, 5H), 5.08 (s, 2H), 4.58 (br s, 1H), 4.20 (dd,  $J = 10.0, 6.5$  Hz, 2H), 3.87 (dd,  $J = 10.0, 4.5$  Hz, 2H), 3.04 (d,  $J = 5.5$  Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) ppm 156.5, 136.5, 128.5, 128.1, 127.9, 66.8, 61.7, 59.1; HRMS (EI): Exact mass calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>3</sub> [M]<sup>+</sup> 207.0890, found 207.0884.



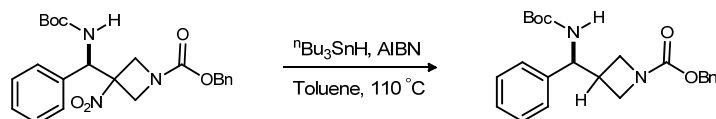
**Benzyl 3-iodoazetidine-1-carboxylate (10).** The triflate (142 mg, 419  $\mu$ mol) was dissolved in acetone (1 mL) in a vial equipped with a stir bar. Sodium iodide (126 mg, 838  $\mu$ mol) was then added and the reaction was stirred at room temperature for 2 h. The reaction was then filtered through silica with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was filtered to remove the precipitated solid which was washed with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were concentrated to a red oil (118 mg, 89%);  $R_f = 0.25$  (20% EtOAc/hexanes); IR (film) 2953, 2884, 1710 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.41-7.29 (m, 5H), 5.10 (s, 2H), 4.73 (dd,  $J = 9.2, 7.6$  Hz, 2H), 4.50 (tt,  $J = 7.6, 5.2$  Hz, 1H), 4.36 (dd,  $J = 10.4, 5.2$  Hz, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) ppm 155.7, 136.2, 128.5, 128.2, 128.0, 67.0, 61.6; HRMS (ESI): Exact mass calcd for C<sub>11</sub>H<sub>12</sub>INNaO<sub>2</sub> [M+Na]<sup>+</sup> 339.9811, found 339.9821.



**Benzyl 3-nitroazetidine-1-carboxylate (11).** To a solution of the iodide (457.3 mg, 1.442 mmol) in DMF (7.2 mL) was added urea (173.3 mg, 2.884 mmol), phloroglucinol (181.8 mg, 1.442 mmol), and sodium nitrite (497.6 mg, 7.211 mmol). The reaction was then heated to 50 °C and stirred for 19 h. The reaction mixture was poured onto water, extracted with ethyl acetate, and the combined organic layers were washed with water, dried over MgSO<sub>4</sub>, and concentrated. The resulting oil was purified by column chromatography (10-20% ethyl acetate in hexanes) to provide the nitro azetidine as a white solid (136.4 mg, 40%). Mp 90.0-92.0 °C;  $R_f$  = 0.35 (40% EtOAc/hexanes); IR (film) 2959, 1713, 1557 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.30 (m, 5H), 5.19-5.12 (m, 1H), 5.13 (s, 2H), 4.49 (dd,  $J$  = 10.4, 4.8 Hz, 2H), 4.42 (dd,  $J$  = 10.4, 8.0 Hz, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) ppm 155.8, 135.9, 128.5, 128.3, 128.1, 71.6, 67.3, 54.1; HRMS (EI): Exact mass calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub> [M]<sup>+</sup> 236.0792, found 236.0784.



**(R)-Benzyl 3-((tert-butoxycarbonylamino)(phenyl)methyl)-3-nitroazetidine-1-carboxylate (12).** Imine (20.5 mg, 100 μmol) and <sup>7</sup>MeOPBAM-HOTf (7.20 mg, 10.0 μmol) were dispensed into a flame dried vial with a stir bar. The two compounds were then stirred in toluene (100 μL) at room temperature until homogeneous. The reaction mixture was chilled to -20 °C before the nitroazetidine (23.6 mg, 100 μmol) was added. The reaction was stirred for 20 h, and then filtered through a pad of silica gel using CH<sub>2</sub>Cl<sub>2</sub> and EtOAc and concentrated. Flash column chromatography (SiO<sub>2</sub>, 12-20% ethyl acetate in hexanes) of the residue yielded the addition product as a colorless solid (41.2 mg, 93%); the major product was determined to be 92% ee by chiral HPLC analysis (Chiralcel IA, 10% <sup>1</sup>PrOH/hexanes, 1 mL/min,  $t_r$ (major) = 17.8 min,  $t_r$ (minor) = 15.4 min). Mp 134.0-136.0 °C;  $[\alpha]_D^{20}$  +6.82 ( $c$  1.10, CHCl<sub>3</sub>);  $R_f$  = 0.24 (20% EtOAc/hexanes); IR (film) 3325, 2978, 2932, 1714, 1549 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.40-7.30 (m, 8H), 7.20-7.10 (m, 2H), 5.76 (br s, 1H), 5.50 (d,  $J$  = 9.5 Hz, 1H), 5.11 (s, 2H), 4.57 (d,  $J$  = 10.5 Hz, 1H), 4.47 (d,  $J$  = 10.0 Hz, 1H), 4.42 (d,  $J$  = 10.5 Hz, 1H), 4.37 (d,  $J$  = 10.5 Hz, 1H), 1.44 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) ppm 155.9, 155.2, 135.8, 134.6, 129.1, 129.0, 128.5, 128.3, 128.1, 126.4, 85.9, 81.0, 67.4, 57.4, 56.7, 28.2; HRMS (ESI): Exact mass calcd for C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>NaO<sub>6</sub> [M+Na]<sup>+</sup> 464.1798, found 464.1776.

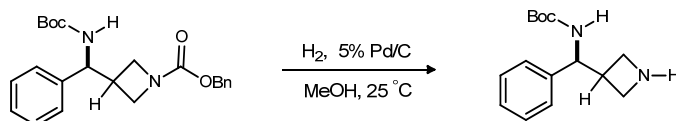


**(S)-Benzyl 3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)azetidine-1-carboxylate (13).** To a solution of the nitro azetidine (75.0 mg, 170 μmol) in toluene (2.1 mL) at room temperature was added <sup>n</sup>Bu<sub>3</sub>SnH (99.0 mg, 340 μmol). The resulting mixture was heated to 110 °C, immediately followed by the addition of azo bis(isobutyronitrile) (AIBN) (6.00 mg, 34.0 μmol). After the reaction mixture stirred for 1 h at 110 °C, additional AIBN (6.00 mg, 34.0 μmol) was added and the mixture was stirred at 110 °C for an additional 3 h. The reaction was cooled, concentrated, diluted with diethyl ether and washed with satd aq KF. The organic layer was dried (MgSO<sub>4</sub>), filtered through a Celite pad with diethyl ether and concentrated. Flash column chromatography of the residue (SiO<sub>2</sub>, 20-30% ethyl acetate in hexanes) yielded the desired azetidine as a white solid (45.0 mg, 67%).  $[\alpha]_D^{20}$  -26.7 ( $c$  0.69, CHCl<sub>3</sub>); mp 110-112 °C;  $R_f$  = 0.20 (25% EtOAc/hexanes); IR (film) 3328, 3032, 2973, 2886, 1705 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.31 (m, 8H), 7.21 (d,  $J$  = 7.2 Hz, 2H), 5.09 (s, 2H), 4.89 (br s, 1H), 4.82 (br s, 1H), 4.10 (dd,  $J$  = 8.4, 8.4 Hz, 1H), 3.98 (br dd,  $J$  = 5.6, 5.6 Hz, 1H), 3.91 (br

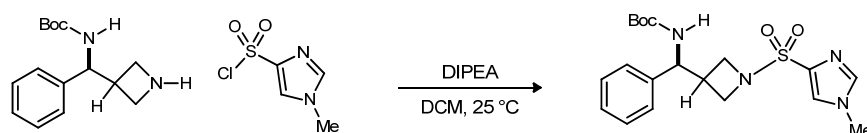
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Supporting Information

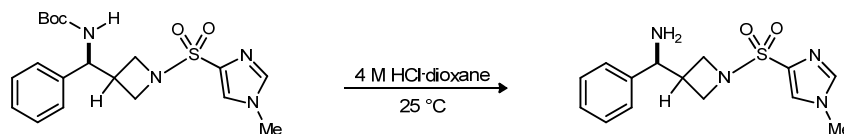
dd,  $J = 8.8, 8.8$  Hz, 1H), 3.69 (br dd,  $J = 6.0, 6.0$  Hz, 1H), 2.94 (br s, 1H), 1.41 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 156.3, 155.4, 140.1, 136.5, 128.7, 128.3, 127.9, 127.8, 126.5, 79.7, 66.5, 56.8, 51.6, 51.1, 34.1, 28.2; HRMS (ESI): Exact mass calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{NaO}_4$   $[\text{M}+\text{Na}]^+$  419.1898, found 419.1927.



**(S)-tert-Butyl ((1-(1-phenyl-2-(benzyloxycarbonylamino)ethyl)azetidin-3-yl)methyl)carbamate (14).** To a flame dried flask equipped with a stir bar was added the carbamate (50.0 mg, 126  $\mu\text{mol}$ ) followed by the addition of 5% Pd/C (27.0 mg). Methanol (1 mL) was then added and the resulting suspension was allowed to stir for 5 minutes. The flask and its contents were purged with  $\text{H}_2$  gas and stirred under a  $\text{H}_2$  atmosphere (balloon) at rt for 3 h. The reaction mixture was filtered through a Celite pad with methanol and dichloromethane and then concentrated in vacuo to afford the desired amine as a colorless oil. The unpurified material was used in the next step.



**(S)-tert-Butyl((1-(1-(1-methyl-1H-imidazol-4-yl)sulfonyl)azetidin-3-yl)(phenyl)methyl) carbamate (16).** To a flame dried flask equipped with a stir bar was added the azetidine (33.0 mg, 126  $\mu\text{mol}$ ) and dichloromethane (3 mL), immediately followed by addition of the sulfonyl chloride (27.0 mg, 151  $\mu\text{mol}$ ) and *N,N*-diisopropylethylamine (19.5 mg, 151  $\mu\text{mol}$ ). The reaction was stirred at rt for 16 h, diluted with water and extracted with ethyl acetate. The organic extracts were then washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated. Flash column chromatography of the residue ( $\text{SiO}_2$ , 0-10% methanol in dichloromethane) yielded the sulfonamide as an off white viscous oil (28.7 mg, 56% over 2 steps).  $[\alpha]_D^{20} -12.5$  ( $c$  0.77,  $\text{CHCl}_3$ );  $R_f = 0.4$  (5% MeOH/dichloromethane); IR (film) 3368, 3134, 2977, 1703, 1526  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (s, 1H), 7.51 (s, 1H), 7.25 (m, 3H), 7.12 (d,  $J = 7.2$  Hz, 2H), 5.21 (br d,  $J = 5.2$  Hz, 1H), 4.48 (dd,  $J = 8.8, 8.8$  Hz, 1H), 3.97 (dd,  $J = 8.4, 8.4$  Hz, 1H), 3.85 (dd,  $J = 8.4, 8.4$  Hz, 1H), 3.84 (d,  $J = 8.0$  Hz, 2H), 3.79 (s, 3H), 2.84 (dddd,  $J = 8.8, 8.4, 8.4, 8.0, 8.0$  Hz, 1H), 1.38 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ppm 155.3, 139.8, 139.6, 136.2, 128.7, 127.7, 126.2, 125.9, 79.6, 56.3, 53.9, 53.5, 34.1, 33.6, 28.2; HRMS (ESI): Exact mass calcd for  $\text{C}_{19}\text{H}_{26}\text{N}_4\text{NaO}_4\text{S}$   $[\text{M}+\text{Na}]^+$  429.1597, found 429.1565.



**(S)-1-((1-(1-Methyl-1H-imidazol-4-yl)sulfonyl)azetidin-3-yl)(phenyl)methanamine (17).** To a flame dried flask equipped with a stir bar was added the sulfonamide (48.0 mg, 118  $\mu\text{mol}$ ) and 4 M HCl·dioxane (220  $\mu\text{L}$ , 886  $\mu\text{mol}$ ). The resulting mixture was allowed to stir at rt for 16 h before it was diluted with dichloromethane and washed with  $\text{NaHCO}_3$ . The organic layer was then separated, dried ( $\text{MgSO}_4$ ), filtered, and concentrated to afford the desired amine as a cloudy oil. The unpurified material was used in the next step.