Zachary P. Demko, K. Barry Sharpless; *Organic Letters*

Experimental Section

All ^{1}H NMR spectra were taken on a Bruker AMX-400 spectrometer in d_6-DMSO with DMSO as a standard at 2.50 ppm. All ^{13}C NMR spectra taken on the same machine at 100 MHz in d_6-DMSO with DMSO as a standard at 39.50 ppm. All melting points were taken on a Thomas Hoover Uni-melt melting point apparatus, and are uncorrected. All enantiomeric excesses determined at 206 nm on a Chiracel ob or od column eluting with a mixture of *i*PrOH in hexanes at 0.50 mL/min. Reagents were used unpurified, and deionized water was used as solvent. Most tetrazole analogs of α-amino acids have been synthesized previously, but only **1**, **3**, **6**, and **7**, and **15** have been made with these particular protecting groups. Spectroscopic data from literature is given as a comparison where is has been reported.

General Procedure for the Transformation of Nitriles into Tetrazoles. To a 100 mL roundbottomed flask was added the α-amino nitrile (10 mmol), sodium azide (1.3 g, 20 mmol), zinc bromide (1.1 g, 5 mmol), 15 mL isopropanol, and 30 mL water. The reaction mixture is stirred at reflux for 16 hours. To the reaction is added 5 mL 3N HCl and 30 mL ethyl acetate is added, and stirring is continued until no solid is present. If necessary, additional ethyl acetate is added. The organic layer is isolated, and the aqueous layer extracted with 2x30 mL ethyl acetate. The combined organic layers are evaporated to yield the tetrazole as a solid. If necessary, the solid is triturated with hexanes, or 10% ethyl acetate in hexanes. In order to assess enantiomeric excess, the product is derivatized by adding an excess of Me_3SiCHN_2, stirring for 5 minutes, adding methanol (1 mL), and evaporating all solvent. The identity of the derivitized product is confirned by LCMS.

***N*-Carboxybenzyloxy alanine tetrazole (±) (1).** The reaction was run on 6.0 mmol scale. The product **1** (1.45 g; 98% yield) was a white solid and had m.p. 146°C, lit. m.p. 143-145°C; ^{1}H NMR 8.04 (d, 1H, J = 5.9 Hz), 7.39-7.12 (m, 5H), 5.09-5.00 (m, 3H), 1.49 (d, 3H, J = 7.1 Hz); ^{13}C NMR 158.6 (br), 155.68, 136.81, 128.42, 127.95, 147.92, 65.78, 19.37; HRMS (MALDI) calc'd for $C_{11}H_{14}N_5O_2$ (MH^+) 248.1142, found 248.1141.

***N*-Carboxybenzyloxy leucine tetrazole (±) (2).** The product **2** (2.68 g; 92% yield) was an off white solid and had m.p. 111°C; ^{1}H NMR 8.04 (d, 1H, J = 7.6 Hz), 7.39-7.16 (m, 5H), 5.10-4.97 (m, 3H), 1.87-1.69 (m, 2H), 1.65-1.56 (m, 1H), 0.91-0.87 (m, 6H); ^{13}C NMR 158.3 (br), 155.97, 136.86, 128.38, 127.91, 127.85, 65.79, 44.48, 41.83, 24.13, 22.60, 21.50; HRMS (MALDI) calc'd for $C_{14}H_{19}N_5O_2Na$ (MNa^+) 312.1431, found 312.1430.

***N*-Carboxybenzyloxy phenylalanine tetrazole (±) (3).** The product **3** (3.21 g; 99% yield) was a white solid and had m.p. 161-163°C, lit. m.p. 167-169°C; ^{1}H NMR 8.17 (d, 1H, J = 7.6 Hz), 7.34-7.02 (m, 10H), 5.21-5.17 (m, 1H), 5.02 (d, 2H, J = 12.3 Hz), 4.96 (d, 2H, J = 12.3 Hz), 3.33 (dd, 1H, J = 5.9, 13.8 Hz), 3.18 (dd, 1H, J = 9.7, 13.2 Hz); ^{13}C NMR 157.5 (br), 155.77, 137.13, 136.86, 129.28, 128.37, 128.30, 127.83, 127.61, 126.65, 65.57, 47.76, 38.56; HRMS (MALDI) calc'd for $C_{17}H_{17}N_5O_2Na$ (MNa^+) 346.1274, found 346.1273.

***N*-Carboxybenzyloxy-*O*-benzyl serine tetrazole (±) (4).** The product **4** (3.45 g; 97% yield) was a white solid and had m.p. 98-99°C; ^{1}H NMR 8.13 (d, 1H, J = 7.4 Hz), 7.43-7.13 (m, 10H), 5.25-5.18 (m, 1H), 5.10 (d, 1H, J = 12.0 Hz), 5.04 (d, 1H, J = 12.0 Hz), 4.52 (s, 2H), 3.93-3.80 (m, 2H); ^{13}C NMR 156.2 (br), 155.97, 137.89, 136.74, 128.37, 128.25, 127.91, 127.85, 127.52, 127.47, 72.13, 69.69, 65.81, 46.37; HRMS (MALDI) calc'd for $C_{18}H_{20}N_5O_3$ (MH^+) 354.1561, found 354.1563.

***N*-Carboxybenzyloxy methionine tetrazole (±) (5).** The product **5** (2.74 g; 90% yield) was a white solid and had m.p. 143-144°C; ^{1}H NMR 8.07 (d, 1H, J = 7.6 Hz), 7.39-7.15 (m, 5H), 5.10-4.99 (m, 3H), 2.54-2.48 (m, 2H), 2.20-2.06 (m, 2H), 2.03 (s, 3H); ^{13}C NMR 157.9 (br), 155.97, 136.78, 128.40, 127.94, 127.88, 65.85, 45.17, 32.40, 29.40, 14.58; HRMS (MALDI) calc'd for $C_{13}H_{18}N_5O_2S$ (MH^+) 308.1176, found 308.1177.

(*R*) *N*-Carboxybenzyloxy-*S*-benzyl cysteine tetrazole (6). The product **6** (3.44 g; 93% yield) was a white solid and had m.p. 129-132°C, lit. m.p. 138-140°C; ^{1}H NMR 8.17 (d, 1H, J = 8.2 Hz), 7.39-7.18 (m, 10H), 5.20-5.03 (m, 3H), 3.76 (s, 2H), 3.07 (dd, 1H, J = 6.2, 13.8 Hz), 2.91 (dd, 1H, J = 8.5, 13.8 Hz); ^{13}C NMR 157.0 (br), 155.91, 138.06, 136.75, 128.91, 128.46, 128.38, 127.93, 127.83, 126.97, 65.84, 46.02, 35.20, 33.90; HRMS (MALDI) calc'd for $C_{18}H_{19}N_5O_2SNa$ (MNa^+) 392.1152, found 392.1150; $[\alpha]_D^{20}$ (c=1, MeOH) -36.0, lit.: -36; enantiomeric excess was found to be 87% by HPLC: elution was with 15% *i*PrOH in hexanes on a Chircacel od column; retention time / area % : isomer A: (major) 60.4 min / 60.0 %, (minor) 54.3 min / 4.6 %; isomer B: (major) 50.3 min / 33.3 %, (minor) 56.0 min / 3.2 %.

(*S*) *N*-Carboxybenzyloxy proline tetrazole (7). The product **7** (2.48 g; 91% yield) was an oil, lit. m.p. 82-83°C; ^{1}H NMR (two rotamers) 7.39-7.20 (m, 4H), 7.00 (s, 1H), 5.30-5.26 (r1, m, 1H), 5.23-5.19 (r2, m, 1H), 5.10 (r1, d, 1H, J = 12.8 Hz), 5.04 (r1, d, 1H, J = 12.6 Hz), 4.99 (r2, d, 1H, J = 13.2 Hz), 4.94 (r2, d, 1H, J = 12.6 Hz), 3.63-3.55 (r1, m, 2H), 3.53-3.43 (r2, m, 2H), 2-42-2.22 (m, 1H), 1.98-1.81 (m, 3H); ^{13}C NMR 158.5 (br), 154.15, 153.56, 136.72, 136.59, 128.41, 128.21, 127.88, 127.65, 127.58, 126.93, 66.25, 66.00, 51.90, 51.57, 46.87, 46.33, 32.81, 31.70, 23.81, 22.90; HRMS (MALDI) calc'd for $C_{13}H_{15}N_5O_2Na$ (MNa^+) 296.1118, found 296.1117; $[\alpha]_D^{20}$ (c=1, MeOH) -56.0, lit.:

-66; enantiomeric excess was found to be 94% by HPLC: elution was with 15% *i*PrOH in hexanes on a Chircacel od column; retention time / area % : isomer A: (major) 32.7 min / 65.3 %, (minor) 38.5 min / 2.0 %; isomer B: (major) 28.17 min / 31.5 %, (minor) 30.0 min / 1.2 %.

(*S*) *N,N*-Dicarboxybenzyloxy lysine tetrazole (8). The reaction was run on 8.0 mmol scale. The product **8** (3.45 g; 98% yield) was a white solid and had m.p. 130-132°C; ^{1}H NMR 8.04 (d, 1H, J = 7.4 Hz), 7.48-7.21 (m, 11H), 5.11-5.01 (m, 4H) 4.96-4.89 (m, 1H), 2.96-3.02 (m, 2H), 1.98-1.79 (m, 2H), 1.49-1.22 (m, 4H); ^{13}C NMR 158.2 (br), 156.019, 156.02, 137.33, 136.85, 128.42, 128.40 (2), 127.95, 127.90, 127.80, 65.81, 65.23, 46.29, 40.08, 32.65, 28.96, 22.62; HRMS (MALDI) calc'd for $C_{22}H_{27}N_6O_2$ (MH^+) 439.2088, found 439.2085; $[\alpha]_D^{20}$ (c=1, MeOH) -21.7; enantiomeric excess was found to be 92% by HPLC: elution was with 15% *i*PrOH in hexanes on a Chircacel od column; retention time / area % : isomer A: (major) 23.4 min / 40.6 %, (minor) 12.0 min / 1.6 %; isomer B: unresolved 50.2 min / 57.7%.

***(R)*-*N*-Carboxybenzyloxy phenylglycine tetrazole (9).** The reaction was run on a 4.0 mmol scale. The product **9** (1.22 g; 98% yield) was a white solid and had m.p. 170-173°C; ^{1}H NMR 8.65 (d, 1H, J = 8.2 Hz), 7.44-7.28 (m, 10H), 6.23 (d, 1H, J = 7.9 Hz), 5.07 (s, 2H); ^{13}C NMR 158 (br), 155.71, 138.01, 136.68, 128.56, 128.35, 128.12, 127.90, 127.85, 127.62, 65.88, 50.19; HRMS (MALDI) calc'd for $C_{16}H_{16}N_5O_2$ (MH^+) 310.1298, found 310.1297; $[\alpha]_D^{20}$ (c=1, MeOH) -12.7; enantiomeric excess was found to be 39% by HPLC: elution was with 15% *i*PrOH in hexanes on a Chircacel od column; retention time / area % : isomer A: (major) 32.2 min / 69.7 %, (minor) 35.0 min / 30.3 %; isomer B: unresolved, 49.9 min.

***N*-Carboxybenzyloxy phenylglycine tetrazole (±) (10).** The product **10** (3.01 g; 97% yield) was a white solid and had m.p. 159-160°C; ^{1}H NMR 8.67 (d, 1H, J = 7.9 Hz), 7.43-7.30 (m, 10H),

6.25 (d, 1H, J = 8.2 Hz), 5.08 (s, 2H); ^{13}C NMR 157 (br), 155.75, 138.03, 136.71, 128.59, 128.38, 128.17, 127.95, 127.88, 127.67, 65.93, 50.22; HRMS (MALDI) calc'd for $C_{16}H_{16}N_5O_2$ (MH^+) 310.1298, found 310.1302.

***N*-Acetyl phenylglycine tetrazole (±) (11).** The reaction was run on 20 mmol scale. The product **11** (3.40 g; 78% yield) was a white solid and decomposed at 198-202°C; ^{1}H NMR 9.09 (d, 1H, J = 7.6 Hz), 7.41-7.31 (m, 5H), 6.42 (d, 1H, J = 7.6 Hz), 1.95 (s, 3H); ^{13}C NMR 169.46, 157.7 (br), 138.07, 128.78, 128.24, 127.74, 48.08, 22.48; HRMS (MALDI) calc'd for $C_{10}H_{12}N_5O$ (MH^+) 218.1036, found 218.1039.

***N-tert*-Butoxycarbonyl phenylglycine tetrazole (±) (12).** The reaction was run on 8.0 mmol scale. The product **12** (1.93 g; 88% yield) was a white solid and decomposed at 148-149°C; ^{1}H NMR 8.15 (br, 1H), 7.39-7.30 (m, 5H), 6.15 (d, 1H, J = 7.3 Hz), 1.39 (s, 9H); ^{13}C NMR 157.8 (br), 154.98, 138.32, 128.31, 128.00, 127.57, 78.82, 49.67, 28.12; HRMS (MALDI) calc'd for $C_{13}H_{17}N_5O_2Na$ (MNa^+) 298.1274, found 298.1275.

***N*-(4-Toluenesulfonyl) phenylglycine tetrazole (±) (13).** The reaction was run on 6.0 mmol scale. The product **13** was purified by column chromatography eluting with 500:500:1 ethyl acetate : hexanes : acetic acid to give a yellow solid (1.50 g; 76% yield) was a white solid and which decomposed at 155-159°C; ^{1}H NMR 9.06 (d, 1H, J = 7.6 Hz), 7.56 (d, 2H, J = 7.6 Hz), 7.29-7.11 (m, 7H), 5.85 (d, 1H, J = 7.6), 2.31 (s, 3H); ^{13}C NMR 157.7 (br), 142.74, 137.50, 136.95, 129.32, 128.56, 128.20, 127.41, 126.61, 52.34, 20.97; HRMS (MALDI) calc'd for $C_{15}H_{15}N_5O_2SNa$ (MNa^+) 352.0839, found 352.0841.

***N*-Carboxybenzyloxy-*N*-Benzyl phenylglycine tetrazole (±) (14).** The product **14** (3.60 g; 90% yield) was a white solid and had m.p. 115-117°C; ^{1}H NMR 8.84 (s, 1H), 7.40-7.16 (m, 13H), 6.97 (d, 2H, J = 6.4 Hz), 5.02 (s, 2H), 3.45 (d, 1H, J = 13.5 Hz), 3.19 (d, 1H, J = 13.5 Hz); ^{13}C NMR 157

(br), 154.42, 138.72, 136.36, 133.42, 130.69, 128.38, 128.23, 128.00, 127.84, 127.76, 127.43, 125.21, 118.74, 65.99, 59.97, 46.56; HRMS (MALDI) calc'd for $C_{23}H_{21}N_5O_2Na$ (MNa^+) 422.1587, found 422.1592.

***N*-Carboxybenzyloxy glycine tetrazole (15).** The product **15** (2.20 g; 95% yield) was an off white solid and had m.p. 163-165°C, lit. m.p. 170-172°C; ^{1}H NMR 8.03 (m, 1H), 7.40-7.22 (m, 5H), 5.07 (s, 2H), 4.54 (d, 2H, J = 5.8 Hz); ^{13}C NMR 156.43, 154.7 (br), 136.81, 128.44, 127.97, 127.95, 65.92, 34.51; HRMS (MALDI) calc'd for $C_{10}H_{12}N_5O_2$ (MH^+) 234.0985, found 234.0988.

***N*-Carboxybenzyloxy *tert*-leucine tetrazole (±) (16).** The product **16** (2.39 g; 83% yield) was an oil; ^{1}H NMR 8.26 (d, 1H, J = 9.1 Hz), 7.40-7.31 (m, 5H), 5.11 (s, 2H), 4.48 (d, 1H, J = 9.1 Hz), 0.99 (s, 9H); ^{13}C NMR 156.03, 136.50, 128.41, 128.03, 127.99, 118.51, 66.21, 52.33, 34.54, 25.41; HRMS (MALDI) calc'd for $C_{14}H_{19}N_5O_2Na$ ($M\backslash Na^+$) 312.1431, found 312.1432.

***N*-Carboxybenzyloxy dimethylglycine tetrazole (17).** The product **17** was purified by column chromatography eluting with 500:500:1 :: ethyl acetate : hexanes : acetic acid to give a clear oil (1.51 g; 58% yield); ^{1}H NMR 8.06 (s, 1H), 7.38-7.21 (m, 5H), 4.95 (d, 2H), 1.60 (s, 9H); ^{13}C NMR 157 (br), 154.68, 136.74, 128.34, 128.31, 127.85; HRMS (MALDI) calc'd for $C_{12}H_{16}N_5O_2$ (MH^+) 262.1298, found 262.1304.

***(R)*-*N*-Carboxybenzyloxy phenylglycinamide (18).** To a 250 mL roundbottomed flask was added *(R)*-*N*-Carboxybenzyloxy phenylglycine (3.71 g, 13.0 mmol), *t*-Butoxycarbonyl anhydride (3.15 g, 17.0 mmol), ammonium bicarbonate (1.30 g, 16.0 mmol), and acetonitrile (50 mL). The reaction flask was flushed with nitrogen, sealed, and pyridine (0.60 mL, 8 mmol) was slowly added. The reaction was stirred for 16 hours. To the reaction was added water (50 mL) and the volume was reduced under vacuum to approximately 50 mL. The solid was filtered, washed with water (3x50 mL), hexanes (3x50 mL) and redissolved in CH_2Cl_2 (200 mL). The solution was dried over $MgSO_4$, and

evaporated to yield **18** (3.12 g, 11.0 mmol, 84% yield) as white powder with m.p. 159-163°C; ^{1}H NMR 7.79 (d, 1H, J = 8.5 Hz), 7.59 (br, 1H), 7.45-7.40 (m, 2H), 7.39-7.24 (m, 8H), 7.14 (br, 1H), 5.17 (d, 1H, J = 8.5 Hz), 5.05 (d, 1H, J = 12.9 Hz), 5.01 (d, 1H, J = 12.9 Hz); ^{13}C NMR 171.65, 155.54, 138.79, 136.95, 128.29, 128.20, 127.74, 127.62, 127.50, 127.14, 65.49, 58.06; HRMS (MALDI) calc'd for $C_{16}H_{17}N_2O_3$ (MH^+) 285.1234, found 285.1234; enantiomeric excess was found to be 90%: elution was with 30% *i*PrOH in hexanes on a Chiracel ob column; retention time / area % : (major) 22.5 min / 95 %, (minor) 37.3 min / 5 %.

***(R)-N*-Carboxybenzyloxy phenylglycinonitrile (19).** To a 250 mL roundbottomed flask was added **18** (2.84 g, 10.0 mmol) and DMF (30 mL) and capped. The solution was chilled in an ice bath, and cyanuric chloride (1.2 g, 6.5 mmol) was added in one shot, the reaction was slowly let to warm to RT, and stirring was continued for eight hours. The reaction was quenched with water (50 mL) and the solution was extracted with ethyl acetate (100 mL). The organic layer was washed with water (5x50 mL), dried over $MgSO_4$, and evaporated. The solid was dissolved in a mixture of ethyl acetate (50 mL) and hexanes (100 mL), and run through a short plug of silica, followed by an equal amount of solvent of the same composition. The elute was evaporated to give **19** (2.66 g, 9.9 mmol, 99% yield) as white powder. The intial product was recrystallized to give enantiomerically pure **19** with m.p. 137°C; ^{1}H NMR 8.78 (d, 1H, J = 7.4 Hz), 7.50-7.30 (m, 10H), 6.01 (d, 1H, J = 8.5 Hz), 5.1 (s, 2H); ^{13}C NMR 155.37, 136.39, 134.42, 128.90, 128.88, 128.40, 128.04, 127.96, 126.93, 118.60, 66.29, 45.56; HRMS (MALDI) calc'd for $C_{16}H_{15}N_2O_2$ (MH^+) 267.1128, found 267.1130; enantiomeric excess of the crude product was found to be 90%: elution was with 15% *i*PrOH in hexanes on a Chircal ob column; retention time / area % : (major) 37.6 min / 95.15 %, (minor) 31.1 min / 4.85 %; enantiomeric excess of the recrystallized product was found to be >98%.