Highly Selective Asymmetric Acetate Aldol Reactions of an *N*-Acetyl Thiazolidinethione Reagent

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Supporting Information

General Information. All non-aqueous reactions were conducted in oven-dried glassware, under a dry nitrogen atmosphere. Dichlorophenylborane (97%) was purchased from Aldrich and stored in a resealable container bearing a teflon valve at $-26\text{ }^{\circ}\text{C}$ under a nitrogen atmosphere, and was used without further purification. (-)-Sparteine was distilled and stored under a nitrogen atmosphere at $-26\text{ }^{\circ}\text{C}$ until used. All aldehydes were distilled from MgSO_4 and stored at $-26\text{ }^{\circ}\text{C}$ under a nitrogen atmosphere. CH_2Cl_2 was distilled from CaH_2 under nitrogen. THF was distilled from Na benzophenone ketyl under nitrogen. All other starting materials were used as received. Flash chromatography of the aldol adducts was performed on neutral silica gel (Mallinckrodt Silicar Silica Gel 150, 60-200 mesh (75-250 micron)) following the procedure of Still.¹ All other flash chromatography was performed using Sorbent Technologies 60 Å silica gel (32-63mm). Flash chromatography of the aldol adducts on this silica or other "ordinary" silica gel (i.e., silica gel with a pH other than 7.0) led to partial cleavage of the thiazolidinethione auxiliary. ^1H NMR spectra were recorded at 500MHz or 400MHz, using CDCl_3 (internal reference 7.24 ppm) or C_6D_6 (internal reference 7.16 ppm) as solvent. ^{13}C NMR spectra were obtained at 100MHz using CDCl_3 (internal reference 77.23ppm) or C_6D_6 (internal reference 128.39 ppm) as solvent. Infrared spectra were recorded as thin films on NaCl plates. Melting points were determined in capillaries and are uncorrected. Optical rotations were determined on a JASCO 1030 polarimeter at $28\text{ }^{\circ}\text{C}$. Combustion analyses were performed by NuMega Resonance Labs, Inc. of San Diego, CA. Exact mass was calculated on $\text{M}+\text{Na}$ using electrospray ionization.

(4*S*)-*tert*-Butyl-thiazolidine-2-thione:

Reduction of *L*-*tert*-leucine:² A 500-mL three-necked round-bottom flask was equipped with a magnetic stirbar, a reflux condenser, and a pressure equalizing addition funnel. The flask was charged with sodium borohydride (4.33 g, 114 mmol) and THF (100 mL). *L*-*tert*-leucine (5.00 g, 38mmol) was added in one portion. The remaining neck of the flask was sealed with a septum, connected to a nitrogen line, and the flask was cooled to $0\text{ }^{\circ}\text{C}$ in an ice bath. A solution of iodine in THF (11.61 g, 45.7 mmol, in 30 mL) was added dropwise via addition funnel over 30 min, resulting in the vigorous evolution of hydrogen. After addition of the iodine was complete and gas evolution had ceased, the flask was heated to reflux for 18 h, and then cooled to room temperature, and methanol was added cautiously until the mixture became clear. After stirring 30 min, the solvent was removed by rotary evaporation, leaving a white paste which was dissolved by addition aqueous KOH (20% by weight, 80 mL). The solution was stirred for 4 h and extracted with methylene chloride (3 x 125 mL). The organic extracts were dried over MgSO_4 and concentrated in vacuo, affording *L*-*tert*-leucinol as a white semisolid, which was used directly in the next reaction.

The *L*-*tert*-leucinol produced from the above reaction was dissolved in aqueous potassium hydroxide (5 M, 200 mL), then CS_2 (304 mmol, 18.3 mL, 8 equiv) was added. An efficient reflux condenser was attached to the flask, and the reaction mixture was heated to reflux for 72 h. After cooling to room temperature, the reaction mixture was extracted with dichloromethane (3 x 200 mL). The

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, .2923

² Prepared by the method of Meyers, see: McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.

combined organic layers were dried over anhydrous MgSO_4 filtered, then concentrated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexanes : CH_2Cl_2 then CH_2Cl_2) to provide (4*S*)-*tert*-butyl-thiazolidine-2-thione as a white crystalline solid (4.01 g, 60% over two steps).³

^1H NMR (500 MHz, CDCl_3): δ 7.60 (br s, 1H), 4.00 (dt, 1H, $J=1.10, 8.68, 9.30$ Hz), 3.41 (dd, 1H, $J=8.68, 11.20$ Hz), 3.37 (dd, 1H, $J=9.30, 11.20$ Hz), 0.98 (s, 9H). ^{13}C NMR (400 MHz, CDCl_3): δ 201.8, 73.6, 34.7, 34.6, 26.1. m.p. = 140 ~ 141 °C. $[\alpha]_D = -56.5$ (c 0.32, CHCl_3). HRMS m/z calc'd for $\text{C}_7\text{H}_{13}\text{NS}_2\text{Na}^+$: 198.0381; found: 198.0372.

1-[(4*S*)-*tert*-Butyl-2-thioxo-thiazolidin-3-yl]-ethanone (3)

(4*S*)-*tert*-Butyl-thiazolidine-2-thione (4.01 g, 22.9 mmol) was dissolved in THF (100 mL) and cooled to -78 °C. *n*-BuLi (15.74 mL, 25.19 mmol, 1.6 M in hexane) was then added dropwise, and the reaction was stirred at -78 °C for 30 min. Acetyl chloride (1.79 mL, 25.19 mmol) was then added dropwise, and the reaction was stirred at -78 °C for 1 hour, and then warmed to room temperature and stirred for 30 min. The reaction was quenched by the addition of aqueous NH_4Cl (saturated solution, 20 mL). The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over anhydrous MgSO_4 , filtered and then concentrated at reduced pressure to a yellow oil. Purification by flash chromatography (3:1 hexanes: CH_2Cl_2 then 1:1 hexanes: CH_2Cl_2) gave 1-[(4*S*)-*tert*-butyl-2-thioxo-thiazolidin-3-yl]-ethanone (3) as a clear, yellow oil (4.73 g, 95%).

^1H NMR (500 MHz, CDCl_3): δ 5.30 (dd, 1H, $J=0.66, 8.50$ Hz), 3.51 (dd, 1H, $J=8.50, 11.86$ Hz), 3.08 (dd, 1H, $J=0.66, 11.86$ Hz), 2.76 (s, 3H), 0.98 (s, 9H). ^{13}C NMR (400 MHz CDCl_3): δ 205.5, 170.5, 72.1, 38.1, 30.6, 27.0. IR (cm^{-1}): 3415, 1691, 1082. $[\alpha]_D = +558.9$ (c 0.23, CHCl_3). Anal. Calcd for $\text{C}_9\text{H}_{15}\text{NOS}_2$: C, 49.73; H, 6.96; N, 6.44, Found: C, 50.10; H, 7.13; N, 6.66.

Typical aldol procedure:

To a 10 mL round-bottom flask at room temperature was added N-acetyl thiazolidinethione (120 mg, 0.552 mmol, 1.30 eq) and CH_2Cl_2 (1.5 mL). PhBCl_2 (neat, 73.5 μL , 0.552 mmol, 1.30 eq) was then added dropwise to give an orange colored solution. After stirring for 10 min, (-)-sparteine (neat, 0.254 mL, 1.104 mmol, 2.6 eq.) was added dropwise. Upon addition of the sparteine, the reaction immediately turned yellow and cloudy and then after about 1 min, it turned clear again. The reaction was stirred at room temperature for 30 min, and then was cooled to -78 °C. The aldehyde (neat, 0.423 mmol, 1.0 eq.) was then slowly added dropwise, and the reaction was stirred for 5 h at -78 °C. The solution was then slowly warmed to room temperature over a period of about 2 h by allowing the dry ice to evaporate, and was stirred at room temperature for 30 min. The reaction was quenched by the addition of hexanes (3 mL) and H_2O_2 (30%, 1.5 mL), and then stirred for 3 min at room temperature. The solution was diluted with hexanes and CH_2Cl_2 (4:1, 100mL), and the layers were separated. The organic layer was further washed with distilled water and brine, dried over anhydrous MgSO_4 , filtered, and concentrated at reduced pressure to an orange oil. Analysis of this material by ^1H NMR provided the d.r. values given in Table 1. The products were purified using flash chromatography (neutralized silica gel (see general information for details), 5:1 hexanes : CH_2Cl_2 to 1:5 hexanes : CH_2Cl_2 depending on substrate) to provide the aldol adducts as clear yellow oils. *This work-up procedure is optimized to minimize hydrolysis of the thiazolidinethione from the product, and should be followed carefully in order to obtain high yields and reproducible results.*

³ The synthesis of this compound requires harsher conditions than described in the literature for the synthesis of other thiazolidinethiones due to the steric hinderance imposed by the bulky *tert*-butyl group. For the synthesis of other thiazolidinethiones, see: Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604.

1-[(4*S*)-*tert*-Butyl-2-thioxo-thiazolidin-3-yl]-(3*R*)-hydroxy-5-phenyl-pentan-1-one (Table 1, entry 1):

^1H NMR (500 MHz, C_6D_6): δ 7.20-7.06 (m, 5H), 4.98 (d, 1H, $J=8.25$ Hz), 4.01 (m, 1H), 3.52 (dd, 1H, $J=9.67, 17.47$ Hz), 3.30 (d, OH, $J=4.40$ Hz), 3.14 (dd, 1H, $J=2.86, 17.47$ Hz), 2.85 (m, 1H), 2.71 (m, 1H), 2.52 (dd, 1H, $J=8.25, 11.87$ Hz), 2.05 (d, 1H, $J=11.87$ Hz), 1.81 (m, 1H), 1.60 (m, 1H), 0.73 (s, 9H). ^{13}C NMR (400 MHz, C_6D_6): δ 205.0, 172.8, 142.3, 128.8, 128.5, 125.9, 71.8, 67.4, 45.5, 38.6, 37.7, 32.1, 29.7, 26.5. IR (cm^{-1}): 3436, 1683, 1470, 1160. $[\alpha]_{\text{D}} = +348.2$ (c 0.25, CHCl_3). HRMS m/z calc'd for $\text{C}_{18}\text{H}_{25}\text{NO}_2\text{S}_2\text{Na}^+$: 374.1218; found: 374.1210. Anal. Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2\text{S}_2$: C, 61.50; H, 7.17; N, 3.98, S, 18.24; Found: C, 61.23; H, 7.23; N, 4.13, S, 17.85.

1-[(4*S*)-*tert*-Butyl-2-thioxo-thiazolidin-3-yl]-(3*S*)-hydroxy-4-methyl-pentan-1-one (Table 1, entry 2):

^1H NMR (500 MHz, CDCl_3): δ 5.35 (dd, 1H, $J=0.74, 8.30$ Hz), 3.80 (m, 1H), 3.54 (dd, 1H, $J=8.30, 11.82$ Hz), 3.50 (dd, 1H, $J=10.16, 17.12$ Hz), 3.30 (dd, 1H, $J=2.38, 17.12$ Hz), 3.23 (br s, OH), 3.10 (dd, 1H, $J=0.74, 11.82$ Hz), 1.75 (m, 1H), 1.02 (s, 9H), 0.97 (d, 3H, $J=6.80$ Hz), 0.92 (d, 3H, $J=6.80$ Hz). ^{13}C NMR (400 MHz, C_6D_6): δ 205.8, 173.8, 73.5, 72.4, 43.2, 38.2, 34.2, 30.2, 27.0, 19.2, 18.2. IR (cm^{-1}): 3509, 1687, 1155. $[\alpha]_{\text{D}} = +304.8$ (c 0.51, CHCl_3). HRMS m/z calc'd for $\text{C}_{13}\text{H}_{23}\text{NO}_2\text{S}_2\text{Na}^+$: 312.1062; found: 312.1068.

1-[(4*S*)-*tert*-Butyl-2-thioxo-thiazolidin-3-yl]-(3*R*)-hydroxy-heptan-1-one (Table 1, entry 3):

^1H NMR (500 MHz, C_6D_6): δ 5.04 (dd, 1H, $J=0.50, 8.35$ Hz), 4.06 (m, 1H), 3.56 (dd, 1H, $J=9.45, 17.14$ Hz), 3.25 (dd, 1H, $J=2.85, 17.14$ Hz), 3.21 (d, OH, $J=4.17$ Hz), 2.54 (dd, 1H, $J=8.35, 11.86$ Hz), 2.06 (dd, 1H, $J=0.50, 11.86$ Hz), 1.52 (m, 2H), 1.30 (m, 2H), 1.25 (m, 2H), 0.87 (t, 3H, $J=7.25$ Hz), 0.74 (s, 9H). ^{13}C NMR (400 MHz, C_6D_6): δ 205.6, 173.5, 72.4, 68.9, 46.1, 38.2, 37.2, 30.2, 28.5, 27.0, 23.4, 14.6. IR (cm^{-1}): 3456, 1695, 1160. $[\alpha]_{\text{D}} = +387.0$ (c 0.27, CHCl_3). HRMS m/z calc'd for $\text{C}_{14}\text{H}_{25}\text{NO}_2\text{S}_2\text{Na}^+$: 326.1218; found: 326.1215. Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_2\text{S}_2$: C, 55.41; H, 8.30; N, 4.62; S, 21.13; Found: C, 55.47; H, 8.27; N, 4.79; S, 20.79.

1-[(4*S*)-*tert*-Butyl-2-thioxo-thiazolidin-3-yl]-(3*R*)-hydroxy-5-methyl-hexan-1-one (Table 1, entry 4):

^1H NMR (500 MHz, C_6D_6): δ 5.04 (d, 1H, $J=8.10$ Hz), 4.65 (m, 1H), 3.53 (dd, 1H, $J=9.23, 17.14$ Hz), 3.23 (dd, 1H, $J=2.64, 17.14$ Hz), 3.24 (br s, OH), 2.60 (dd, 1H, $J=8.10, 11.86$ Hz), 2.10 (d, 1H, $J=11.86$ Hz), 1.95 (m, 1H), 1.52 (m, 1H), 1.09 (m, 1H), 0.91 (d, 3H, $J=2.41\text{Hz}$), 0.89 (d, 3H, $J=2.41\text{Hz}$), 0.75 (s, 9H). ^{13}C NMR (400 MHz, C_6D_6): δ 205.1, 172.9, 72.0, 66.5, 46.1, 37.7, 29.8, 26.5, 24.6, 23.6, 22.1. IR (cm^{-1}): 3448, 1683, 1152. $[\alpha]_{\text{D}} = +500.7$ (c 0.29, CHCl_3). HRMS m/z calc'd for $\text{C}_{14}\text{H}_{25}\text{NO}_2\text{S}_2\text{Na}^+$: 326.1218; found: 326.1201.

4-Benzyloxy-1-[(4S)-tert-Butyl-2-thioxo-thiazolidin-3-yl]-(3S)-hydroxy-butan-1-one (Table 1, entry 5):

^1H NMR (500 MHz, CDCl_3): δ 7.40-7.29 (m, 5H), 5.35 (d, 1H, $J=7.91$ Hz), 4.60 (dd, 2H, $J=12.09, 15.38$), 4.31 (m, 1H), 3.62 (dd, 1H, $J=9.01, 18.00$ Hz), 3.55 (dd, 1H, $J=7.91, 11.75$ Hz), 3.54 (br s, OH), 3.26 (dd, 1H, $J=7.50, 18.00$ Hz), 3.13 (d, 1H, $J=11.75$ Hz), 1.06 (s, 9H). ^{13}C NMR (400 MHz, CDCl_3): δ 205.2, 172.5, 138.1, 128.6, 127.9, 73.5, 73.1, 72.3, 67.6, 42.2, 38.1, 30.7, 27.0. IR (cm^{-1}): 3436, 1687, 1470, 1160. $[\alpha]_{\text{D}} = +574.5$ (c 0.10, CHCl_3). HRMS m/z calc'd for $\text{C}_{18}\text{H}_{25}\text{NO}_3\text{S}_2\text{Na}^+$: 390.1168; found: 390.1185.

5-(tert-Butyl-dimethyl-silanyloxy)-1-[(4S)-tert-butyl-2-thioxo-thiazolidin-3-yl]-(3R)-hydroxy-pentan-1-one (Table 1, entry 6):

^1H NMR (500 MHz, CDCl_3): δ 5.33 (d, 1H, $J=8.35$ Hz), 4.25 (m, 1H), 3.80 (m, 2H), 3.53 (dd, 1H, $J=3.75, 8.00$ Hz), 3.52 (br s, OH), 3.49 (dd, 1H, $J=8.35, 11.60$ Hz), 3.36 (dd, 1H, $J=3.75, 17.49$ Hz), 3.09 (d, 1H, $J=11.60$ Hz), 1.72 (m, 2H), 1.02 (s, 9H), 0.87 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (400 MHz, CDCl_3): δ 205.2, 172.7, 72.3, 66.9, 61.0, 45.5, 38.8, 38.1, 30.7, 27.0, 26.1, 18.4. $[\alpha]_{\text{D}} = +541.2$ (c 0.20, CHCl_3). HRMS m/z calc'd for $\text{C}_{18}\text{H}_{35}\text{NO}_3\text{S}_2\text{SiNa}^+$: 428.1719; found: 428.1693. Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_2\text{S}_2$: C, 53.29; H, 8.70; N, 3.45; S, 15.81, Found: C, 53.21; H, 8.63; N, 3.64. S, 15.56.

1-[(4S)-tert-Butyl-2-thioxo-thiazolidin-3-yl]-(3S)-hydroxy-3-phenyl-propan-1-one (Table 1, entry 7):

^1H NMR (500 MHz, CDCl_3): δ 7.41-7.05 (m, 5H), 5.19 (m, 1H), 4.98 (dd, 1H, $J=0.55, 8.35$), 3.97 (dd, 1H, $J=9.23, 17.14$ Hz), 3.58 (dd, 1H, $J=3.30, 17.14$ Hz), 3.50 (d, OH, $J=4.61$ Hz), 2.44 (dd, 1H, $J=8.35, 11.87$ Hz), 2.01 (dd, 1H, $J=0.55, 11.87$ Hz), 0.72 (s, 9H). ^{13}C NMR (400 MHz, C_6D_6): δ 205.5, 172.7, 144.0, 129.1, 128.1, 126.7, 72.4, 71.2, 47.5, 38.2, 30.2, 27.0, 26.9. IR (cm^{-1}): 3448, 1679, 1478, 1143. $[\alpha]_D = +550.6$ (c 0.10, CHCl_3). HRMS m/z calc'd for $\text{C}_{16}\text{H}_{21}\text{NO}_2\text{S}_2\text{Na}^+$: 346.0905; found: 346.0904.

1-[(4*S*)-*tert*-Butyl-2-thioxo-thiazolidin-3-yl]-(3*S*)-hydroxy-5-phenyl-pent-4-en-1-one (Table 1, entry 8):

^1H NMR (500 MHz, C_6D_6): δ 7.25-7.02 (m, 5H), 6.73 (d, 1H, $J=15.82$ Hz), 6.22 (dd, 1H, $J=5.50, 15.82$), 5.01 (d, 1H, $J=8.35$ Hz), 4.77 (m, 1H), 3.81 (dd, 1H, $J=8.79, 17.14$ Hz), 3.40 (dd, 1H, $J=3.73, 17.14$ Hz), 3.25 (d, OH, $J=5.05$ Hz), 2.50 (dd, 1H, $J=8.35, 11.86$ Hz), 2.02 (d, 1H, $J=11.86$ Hz), 0.74 (s, 9H). ^{13}C NMR (400 MHz, C_6D_6): δ 205.6, 172.5, 137.6, 131.5, 131.0, 129.1, 128.2, 127.3, 72.5, 69.7, 45.8, 38.2, 30.3, 27.1. IR (cm^{-1}): 3391, 1732, 1695, 1491, 1164. $[\alpha]_D = +361.0$ (c 0.25, CHCl_3). HRMS m/z calc'd for $\text{C}_{18}\text{H}_{23}\text{NO}_2\text{S}_2\text{Na}^+$: 372.1062; found: 372.1042.