Double Diastereoselective Acetate Aldol Reactions with Chiral *N*-Acetyl Thiazolidinethione Reagents

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Supporting Information

Table of Contents:

S1	General Information
S2-S3	Synthesis of aldehyde 3
S4-S6	Synthesis of aldehyde 5
S6-S8	Synthesis of aldehyde 6
S8	General aldol procedure
S9-S12	Compound characterization of the products of Table 1
S13-S56	¹ H and ¹³ C NMR spectra for all new compounds

General Information. All air or moisture sensitive reactions were conducted in oven-dried glassware under a dry nitrogen atmosphere. Dichlorophenylborane (97%) was distilled then stored in a resealable container bearing a Teflon valve at -26 °C under a nitrogen atmosphere. (-)-Sparteine was distilled under high vacuum and stored under a nitrogen atmosphere at -26 °C. CH₂Cl₂, triethylamine, and 2,6-lutidine were distilled from CaH₂ under nitrogen. THF was distilled from Na benzophenone ketyl under nitrogen. All other starting materials were used as received. Aldehyde **4** was synthesized by the procedure of Curran.¹ Flash chromatography of the thiazolidinethione aldol adducts was performed on neutral silica gel (Mallinckrodt Silicar Silica Gel 150, 60-200 mesh (75-250 micron)) following the procedure of Still.² All other flash chromatography was performed using 60 Å silica gel (32-63 micron). Flash chromatography of the thiazolidinethione 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 as indicated in CDCl₃ and were referenced to residual CHCl₃ at 7.24 ppm. ¹³C NMR spectra were obtained at 100MHz in CDCl₃ and were referenced to the center line of solvent at 77.23ppm. Infrared spectra were recorded as thin films on NaCl plates. Optical rotations were determined on a digital polarimeter at 27 °C (room temperature). Exact mass was calculated on M+Na for electrospray ionization, or on the parent for electron impact ionization as indicated.

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- (1) Minguez, J. M.; Kim, S.-Y.; Giuliano, K. A.; Balachandran, R.; Madiraju, C.; Day, B. W.; Curran, D. P. *Bioorg. Med. Chem.* **2003**, *11*, 3335.
(2) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Aldehyde **3** was synthesized from known compound **S1**³ by the sequence shown in Scheme S1 below.

Scheme S1

Diol S2. To a cooled (0 °C) yellow solution of compound **S1** (1.05g, 3.46 mmol, 1.00 eq) in ethanol (10 mL) was added NaBH₄ (392 mg, 10.38 mmol, 3.00eq) in three portions over two minutes. The reaction was warmed to room temperature and stirred until the yellow solution became colorless. The reaction was then quenched by the addition of saturated NH₄Cl (10 mL) and stirred for 5 min. The mixture was diluted with CH₂Cl₂ (10 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (20 mL x2), and the combined organic phases were dried over MgSO₄ and concentrated at reduced pressure using a rotary evaporator. The residue was dissolved in methanol (5 mL) to convert any borate esters to trimethylborate and concentrated at reduced pressure. This procedure was repeated two more times to ensure distillation of all the trimethyl borate, and the product was then purified by flash chromatography (1:1 hexanes:ethyl acetate) to provide diol **S2** (420 mg, 3.177 mmol, 92 %) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 3.95-3.76 (m, 3H), 2.81 (br, s, OH), 2.66 (br, s, OH), 1.76-1.58 (m, 3H), 1.44 (m, 1H), 1.23 (m, 1H), 0.89 (d, 6H, J=6.60 Hz). ¹³C NMR (400 MHz, CDCl₃): δ 70.5, 62.0, 47.2, 38.9, 24.6, 23.5, 22.4. IR (cm⁻¹): 3375, 2955, 2924. [α]_D = 10.6 (c 0.075, EtOAc). HRMS m/z calc'd for C₇H₁₆O₂: 132.1150; found:132.1145.

PMB acetal S3. To a cooled (0 °C) solution of diol **S2** (400 mg, 3.025 mmol, 1.0 eq) in CH₂Cl₂ (5 mL) was added *p*-anisaldehyde dimethyl acetal (0.773mL, 4.538 mmol, 1.5 eq) by syringe. PPTS (152 mg, 0.605 mmol, 0.2 eq) was then added in one portion and the solution

(3) Zhang, Y; Phillips, A. J.; Sammakia, T. *Org Lett.* **2004**, 6, 23.

stirred for 1 h at 0 °C. The reaction was then filtered through a short plug of silica with a layer of celite on top using ether as the eluent, and concentrated at reduced pressure using a rotary evaporator. Flash chromatography (25:1 hexanes:ethyl acetate) provided analytically pure **S3** as a colorless oil (704 mg, 2.813 mmol, 93%).

^1H NMR (400 MHz, CDCl_3): δ 7.39 (m, 2H), 6.86 (m, 2H), 5.45 (s, 1H), 4.24 (m, 1H), 3.95 (m, 1H), 3.87 (m, 1H), 3.78 (s, 3H), 1.86 (m, 1H), 1.77 (m, 1H), 1.63 (m, 1H), 1.46 (m, 1H), 1.30 (m, 1H), 0.93 (d, 3H, $J=6.60$ Hz), 0.91 (d, 3H, $J=6.60$ Hz). ^{13}C NMR (400 MHz, CDCl_3): 159.9, 131.7, 127.7, 101.1, 75.6, 67.3, 55.5, 45.3, 31.9, 24.1, 23.3, 22.6. IR (cm^{-1}): 2951, 2917, 1612, 1518. $[\alpha]_{\text{D}} = 56.7$ (c 0.250, EtOAc). HRMS m/z calc'd for $\text{C}_{15}\text{H}_{22}\text{O}_3\text{Na}^+$: 273.1461; found: 273.1463.

Alcohol S4. To a cooled (0 °C) solution of **S3** (650 mg, 2.596 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) was added DIBAL-H (3.89 mL, 1.00 M in hexanes, 3.894 mmol, 1.5 equiv) dropwise. The resulting solution was stirred for 10 min at 0 °C then allowed to warm to room temperature and stirred for 4 h. The reaction was then quenched by careful addition of saturated potassium sodium tartrate (8 mL) and stirred vigorously for 2 h. The aqueous phase was saturated with NaCl, separated, then extracted with 1:1 CH_2Cl_2 :Et₂O (10 mL, 3x). The combined organic phases were dried over MgSO_4 and concentrated at reduced pressure using a rotary evaporator. Flash chromatography (4:1 hexanes:ethyl acetate) provided alcohol **S4** (563 mg, 2.23 mmol, 86 %) as a colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 7.25 (m, 2H), 6.88 (m, 2H), 4.49 (A of AB, $J=11.00$ Hz), 4.42 (B of AB, $J=11.00$ Hz), 3.78 (m, 1H), 3.78 (s, 3H), 3.67 (m, 2H), 2.49 (d, OH, $J=5.22$ Hz), 1.85 (m, 1H), 1.68 (m, 2H), 1.64 (m, 1H), 1.28 (m, 1H), 0.88 (d, 3H, $J=6.40$ Hz), 0.86 (d, 3H, $J=6.40$ Hz). ^{13}C NMR (400 MHz, CDCl_3): 159.4, 130.7, 129.7, 114.1, 70.7, 60.9, 55.5, 43.2, 36.1, 24.9, 23.3, 23.0. IR (cm^{-1}): 3414, 2951, 2918, 1612, 1510. $[\alpha]_{\text{D}} = -2.71$ (c 0.025, EtOAc). HRMS m/z calc'd for $\text{C}_{15}\text{H}_{24}\text{O}_3\text{Na}^+$: 275.1617; found: 275.1605.

Aldehyde 3. To a cooled (0 °C) solution of alcohol **S4** (500 mg, 1.98 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane⁴ (1.008 g, 2.38 mmol, 1.2 eq). The resulting solution was allowed to warm to room temperature and stirred for 2 h. The reaction was then concentrated at reduced pressure to a volume of 3 mL and directly subjected to purification by flash chromatography (20:1 hexanes : ethylacetate) to provide aldehyde **3** (450 mg, 91 %) as a colorless oil.

(4) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277, Ireland, RE; Liu, L. *J. Org. Chem.* **1993** *58*, 2899, Boeckman, R. K.; Shao, P.; Mullins, J. J. In *Organic Syntheses*; Wiley & Sons: New York, 2004; Collect. Vol. X, p 696.

^1H NMR (400 MHz, CDCl_3): δ 9.80 (t, 1H, J = 2.20 Hz), 7.24 (m, 2H), 6.87 (m, 2H), 4.48 (d, A of AB, J =11.2 Hz), 4.46 (d, A of AB, J =11.2 Hz), 4.00 (m, 1H), 3.80 (s, 3H), 2.61 (m, 2H), 1.73 (m, 1H), 1.63 (m, 1H), 1.30 (m, 1H), 0.89 (d, 3H, J =3.95 Hz), 0.88 (d, 3H, J =3.95 Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 202.1, 159.5, 130.5, 129.7, 114.0, 72.6, 71.1, 55.5, 48.8, 44.2, 24.8, 23.2, 22.7, 22.6, 14.3. IR (cm^{-1}): 2959, 2919, 1724, 1612, 1511. $[\alpha]_{\text{D}} = 26.9$ (c 0.150, EtOAc). HRMS m/z calc'd for $\text{C}_{15}\text{H}_{22}\text{O}_3\text{Na}^+$: 273.1461; found: 273.1459.

Aldehyde **5** was synthesized from known compound **S5**^{5,6} by the sequence shown in Scheme S2 below.

Scheme S2

Aldol adduct S6. To a cooled ($0\text{ }^\circ\text{C}$) solution of thiazolidinethione **S5** (652 mg, 3.00 mmol, 1.0 eq) in CH_2Cl_2 (8 mL) was added TiCl_4 (1.0 M solution in CH_2Cl_2 , 3.15 mL, 3.15 mmol, 1.05 eq) dropwise. The resulting bronze colored solution was stirred for 5 min, then (-)-sparteine (1.28 mL, 6.00 mmol, 2.0 eq) was added dropwise. Upon addition of the sparteine, the reaction immediately turned a deep red color. The reaction was stirred at $0\text{ }^\circ\text{C}$ for 20 min and then cooled to $-78\text{ }^\circ\text{C}$, at which point 3-methyl-butyaldehyde (0.487 mL, 4.50 mmol, 1.5 eq) was added dropwise. The reaction was stirred for 1 h at $-78\text{ }^\circ\text{C}$, then warmed to $0\text{ }^\circ\text{C}$ over a period of about 20 minutes. The reaction was then quenched with a half-saturated NH_4Cl solution (10 mL) and warmed to room temperature. The CH_2Cl_2 layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 . The combined organic extracts were dried over MgSO_4 , filtered, and concentrated at reduced pressure by rotary evaporation to yield a pale orange oil. Analysis of this material by ^1H NMR indicated a 30:1 diastereomeric ratio. The product was purified by flash chromatography on neutral silica gel (15:1 hexanes:ethyl acetate, see general information for details regarding the use of neutral silica gel) to yield the alcohol **S6** (850 mg, 2.80 mmol, 93 %) as a yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 5.17 (ddd, 1H, J =1.20, 6.40, 7.80 Hz), 4.38 (dq, 1H, J =2.56, 6.95 Hz), 3.97 (m, 1H), 3.50 (A of ABX, 1H, J =7.80, 11.50 Hz), 3.01 (B of ABX, 1H,

(5) Nagao, Y.; Kumagai, T.; Nagase, Y.; Tamai, S.; Inoue, Y.; Shiro, M. *J. Org. Chem.* **1992**, *57*, 4232.

(6) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775.

$J=1.20, 11.50$ Hz), 2.88 (d, OH, $J=3.00$ Hz), 2.30 (m, 1H), 1.75 (m, 1H), 1.48 (m, 1H), 1.24 (d, 3H, $J=6.80$ Hz), 1.08 (m, 1H), 1.04 (d, 3H, $J=6.80$ Hz), 0.94 (d, 3H, $J=7.80$ Hz), 0.89 (d, 3H, $J=6.70$ Hz), 0.88 (d, 3H, $J=6.70$ Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 202.9, 179.0, 71.7, 69.9, 43.3, 43.2, 31.0, 30.7, 24.7, 23.7, 22.2, 19.2, 18.1, 11.3. IR (cm^{-1}): 3437, 2959, 1685. $[\alpha]_{\text{D}} = 395$ (c 1.65, EtOAc). HRMS m/z calc'd for $\text{C}_{14}\text{H}_{25}\text{NO}_2\text{S}_2\text{Na}^+$: 326.1219; found: 326.1224.

TES ether S7. To a solution of alcohol **S6** (800 mg, 2.64 mmol, 1.0 eq) and imidazole (269 mg, 3.95 mmol, 1.5 eq) in dichloromethane (3 mL) was added triethylsilyl triflate (0.775 mL, 3.43 mmol, 1.3 eq) at 0 °C. The resulting solution was warmed to room temperature and stirred for 1 h, then quenched with a saturated solution of NaHCO_3 . The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over MgSO_4 , filtered, then concentrated at reduced pressure. Flash chromatography on neutral silica gel (30:1 hexanes:ethyl acetate, see general information for details regarding the use of neutral silica gel) provided **S7** (973 mg, 2.345 mmol, 89 %) as a yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 4.99 (ddd, 1H, $J=0.90, 6.13, 8.00$ Hz), 4.55 (m, 1H), 4.00 (m, 1H), 3.43 (A of ABX, 1H, $J=7.78, 11.50$ Hz), 3.00 (B of ABX, 1H, $J=0.90, 11.50$ Hz), 2.38 (m, 1H), 1.60 (m, 1H), 1.40 (m, 1H), 1.25 (m, 1H), 1.17 (d, 3H, $J=6.80$ Hz), 1.04 (d, 3H, $J=6.80$ Hz), 0.94 (t, 9H, $J=8.00$ Hz), 0.92 (d, 3H, $J=6.80$ Hz), 0.88 (d, 3H, $J=6.70$ Hz), 0.86 (d, 3H, $J=6.70$ Hz), 0.58 (q, 6H, $J=8.20$ Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 202.9, 176.6, 72.8, 72.5, 45.2, 42.8, 31.2, 30.9, 24.6, 24.1, 22.7, 19.3, 18.1, 13.2, 7.3, 5.5. IR (cm^{-1}): 2955, 2873, 1689. $[\alpha]_{\text{D}} = 362$ (c 0.65, EtOAc). HRMS m/z calc'd for $\text{C}_{20}\text{H}_{39}\text{NO}_2\text{S}_2\text{SiNa}^+$: 440.2084; found: 440.2084.

Alcohol S8. To a cooled (0 °C) yellow solution of compound **S7** (900 mg, 2.17 mmol, 1.00 eq) in ethanol (8 mL) was added NaBH_4 (246 mg, 6.51 mmol, 3.00eq) in three portions over 2 minutes. The reaction was warmed to room temperature and stirred until the yellow solution became colorless (about 30 minutes). The reaction was then quenched by the addition of saturated NH_4Cl (10 mL) and stirred for 5 min. CH_2Cl_2 (10 mL) was then added, and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL x2), and the combined organic phases were dried over MgSO_4 and concentrated at reduced pressure using a rotary evaporator. The residue was dissolved in methanol (5 mL) to convert any borate esters to trimethylborate and concentrated at reduced pressure. This procedure was repeated two more times to ensure distillation of all the trimethyl borate, and the product was then purified by flash chromatography (8:1 hexanes:ethyl acetate) to provide alcohol **S8** (537 mg, 2.062 mmol, 95 %) as a colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 3.83 (m, 1H), 3.62 (m, 1H), 3.46 (m, 1H), 2.99 (br, s, OH), 1.88 (m, 1H), 1.59 (m, 1H), 1.33 (m, 1H), 1.23 (m, 1H), 0.91 (t, 9H, $J=8.10$ Hz), 0.86 (d,

3H, J=6.70 Hz), 0.82 (d, 3H, J=6.70 Hz), 0.74 (d, 3H, J=7.00 Hz), 0.56 (q, 6H, J=8.10 Hz). ^{13}C NMR (400 MHz, CDCl_3): 74.0, 66.2, 41.9, 39.7, 24.5, 23.4, 22.6, 11.8, 7.0, 5.3. IR (cm^{-1}): 3355, 2955, 2874, 1456. $[\alpha]_{\text{D}} = -12.5$ (c 0.900, EtOAc). HRMS m/z calc'd for $\text{C}_{14}\text{H}_{32}\text{O}_2\text{Si}^+$: 260.2166; found: 260.2176.

Aldehyde 5. To a cooled (0 °C) solution of alcohol **S8** (400 mg, 1.54 mmol, 1.0 eq) in CH_2Cl_2 (8 mL) was added Dess-Martin periodinane (782 mg, 1.84 mmol, 1.2 eq). The resulting solution was warmed to room temperature and stirred for 2 h. The reaction was then concentrated at reduced pressure to a volume of about 3 mL and directly subjected to purification by flash chromatography (25:1 hexanes : ethylacetate) to provide aldehyde **5** (365 mg, 1.41 mmol, 92 %) as a colorless oil.

^1H NMR (400 MHz, CDCl_3): 9.76 (d, 1H, J= 0.92 Hz), 4.18 (m, 1H), 2.40 (m, 1H), 1.60 (m, 1H), 1.31 (m, 2H), 1.02 (d, 3H, J=6.96 Hz), 0.90 (d, 3H, J=6.50 Hz), 0.89 (t, 9H, J=7.80 Hz), 0.88 (d, 3H, J=6.50 Hz), 0.56 (q, 6H, J=7.80 Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 205.8, 70.5, 51.6, 43.9, 24.8, 23.0, 22.9, 7.7, 7.1, 5.3. IR (cm^{-1}): 2959, 2877, 1728, 1460. $[\alpha]_{\text{D}} = 47.3$ (c 0.550, EtOAc). HRMS m/z calc'd for $\text{C}_{14}\text{H}_{30}\text{O}_2\text{SiNa}^+$: 281.1907; found: 281.1900.

Aldehyde **6** was synthesized from known compound **S9** by the sequence shown in Scheme S3 below.

Scheme S3

Dicyclohexylborontriflate (6.600 mmol in 5 mL CH_2Cl_2 , 2.2 eq) was added dropwise to a -78 °C solution of **S9**⁷ (1.440 g, 3.000 mmol, 1.0 eq) and Et_3N (1.004 mL, 7.200 mmol, 2.4 eq) in CH_2Cl_2 (15 mL). After 2 hours, 3-methyl-butyraldehyde (0.487 mL, 4.500 mmol, 1.5 eq) was added dropwise, and the reaction was stirred for an additional hour at -78 °C, then warmed to room temperature, and stirred for 1 hour. The reaction was quenched by the addition of pH7 buffer (5mL), MeOH (10 mL), and hydrogen peroxide (5 ml of a 30% solution). The resulting

(7) Abiko, A. *Organic Syntheses* **2002**, 79, 109-115.

mixture was vigorously stirred overnight then diluted with water (20 mL), and CH₂Cl₂ (40 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (40 mL x3). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄, filtered and concentrated at reduced pressure. The product was determined to be a 30:1 mixture of diastereomers by ¹H NMR analysis of the crude reaction mixture. Flash chromatography (6:1 hexanes:ethyl acetate) provided alcohol **S10** (1.562 g, 2.76 mmol, 92 %) as a white foam.

¹H NMR (400 MHz, CDCl₃): δ 7.30-7.16 (m, 8H), 6.87 (m, 4H), 5.83 (d, 1H, J=4.40 Hz), 4.76 (A of AB, J=16.50 Hz), 4.54 (B of AB, J=16.50 Hz), 4.13 (m, 1H), 3.68 (m, 1H), 2.49 (s, 6H), 2.47 (br, s, OH), 2.45 (m, 1H), 2.28 (s, 3H), 1.83 (m, 1H), 1.37 (m, 1H), 1.18 (m, 1H), 1.18 (d, 3H, J=7.05 Hz), 1.16 (d, 3H, J=7.23 Hz), 0.89 (d, 3H, J=6.70 Hz), 0.88 (d, 3H, J=6.70 Hz). ¹³C NMR (400 MHz, CDCl₃): δ 174.9, 142.8, 140.5, 138.6, 138.3, 133.5, 132.3, 128.6, 128.5, 128.2, 127.9, 127.4, 126.2, 91.0, 78.4, 71.5, 56.9, 48.5, 46.2, 43.9, 24.6, 24.0, 23.1, 21.7, 21.1, 14.4, 13.8. IR (cm⁻¹): 3402, 1632, 1491. [α]_D = 63.7 (c 0.500, EtOAc). HRMS m/z calc'd for C₃₃H₄₃O₅SiNa⁺: 588.2754; found: 588.2756.

To a solution of alcohol **S10** (1.400 g, 2.47 mmol, 1.0 eq) and 2,6-lutidine (0.858 mL, 7.42 mmol, 3.0 eq) in dichloromethane (2 mL) was added TESOTf (1.120 mL, 4.948 mmol, 2.0 eq) at 0 °C. The reaction was warmed to room temperature and stirred for 20 h, then quenched with saturated NaHCO₃. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with 1M HCl, saturated NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated at reduced pressure. Flash chromatography (8:1 hexanes:ethyl acetate) provided ester **S11** (1.480 g, 2.177 mmol, 88 %) as a white foam.

¹H NMR (400 MHz, CDCl₃): δ 7.38 (m, 2H), 7.31 (m, 2H), 7.28 (m, 2H), 7.16 (m, 2H), 6.88 (m, 4H), 5.79 (d, 1H, J=5.20 Hz), 4.81 (A of AB, J=16.30 Hz), 4.56 (B of AB, J=16.30 Hz), 4.13 (m, 1H), 4.06 (m, 1H), 2.55 (m, 1H), 2.47 (s, 6H), 2.32 (s, 3H), 1.62 (m, 1H), 1.34 (m, 1H), 1.22 (d, 3H, J=6.92 Hz), 1.11 (d, 3H, J=7.14 Hz), 0.98 (t, 9H, J=8.00 Hz), 0.93 (m, 1H), 0.82 (d, 3H, J=6.60 Hz), 0.73 (d, 3H, J=6.60 Hz), 0.62 (q, 6H, J=8.00 Hz). ¹³C NMR (400 MHz, CDCl₃): 172.3, 142.7, 140.5, 138.6, 138.4, 133.3, 132.3, 128.6, 128.4, 128.1, 128.0, 127.4, 126.7, 78.1, 71.5, 56.8, 48.3, 46.3, 42.3, 24.3, 23.8, 23.1, 22.0, 21.1, 14.2, 10.7, 7.1, 5.2. IR (cm⁻¹): 2951, 2874, 1732, 1448. [α]_D = 28.6 (c 0.700, EtOAc). HRMS m/z calc'd for C₃₉H₅₇NO₅SSiNa⁺: 702.3619; found: 702.3633.

To a cooled (-78 °C) solution of ester **S11** (1.400 g, 2.058 mmol, 1.0 equiv) in Et₂O (20 mL) was added DIBAL-H (5.15 mL, 1.00 M in hexanes, 5.15 mmol, 2.5 equiv) dropwise. The resulting solution was allowed to warm to room temperature and stirred for 20 min. The reaction was then quenched by careful addition of saturated potassium sodium tartrate (15 mL) and

allowed to warm to room temperature and stir for 30 min. The reaction was then cooled to the temperature described in Table 1, and the aldehyde (0.192 mmol, 1.0 eq.) in 0.8 mL CH₂Cl₂ was added dropwise via cannula over a period of about 5 min. The flask containing the aldehyde was rinsed with 0.8 mL CH₂Cl₂, which was also added to the reaction via cannula. For entries 1-4 of Table 1, the reaction was stirred for 6 h at -78 °C, and then slowly warmed to 0 °C over a period of about 3 h by allowing the dry ice to evaporate. As the temperature approached 0 °C, the reaction was placed in an ice bath and stirred for 30 min. As for entries 5-10 of Table 1, the reaction was stirred for 3 h at 0 °C. The reaction was then quenched by the addition of hexanes (3 mL) and H₂O₂ (30%, 1 mL), and stirred rapidly for 10 min at room temperature. (Note that rapid stirring is required at this step. If the rate of stirring is too slow, incomplete oxidation of the borane occurs, and boron species remain in the product.) The solution was diluted with hexanes and CH₂Cl₂ (4:1, 80 mL), and the layers were separated. The organic layer was further washed with distilled water and brine, dried over anhydrous MgSO₄, filtered, and concentrated at reduced pressure to provide an orange oil. Analysis of this material by ¹H NMR provided the d.r. values given in Table 1. The products were purified by flash chromatography using neutral silica gel (1:1 hexanes / CH₂Cl₂ to 1:4 hexanes / CH₂Cl₂ depending on substrate, see general information for details regarding the use of neutral silica gel) to provide the aldol adducts as clear yellow oils. *Note that N-acyl thiazolidinethiones are sensitive to hydrolysis, and that this work-up has been optimized to minimize hydrolysis, and should be followed carefully in order to obtain high yields and reproducible results.*

Compound characterization of the products of Table 1

Table 1, entry 1:

¹H NMR (500 MHz, CDCl₃): δ 7.25 (m, 2H), 6.86 (m, 2H), 5.33 (X of ABX, 1H, J=0.73, 8.33 Hz), 4.48 (A of AB, J=11.08 Hz), 4.40 (B of AB, J=11.08 Hz), 4.20 (m, 1H), 3.79 (s, 3H), 3.66 (m, 1H), 3.61 (d, OH, J=3.02 Hz), 3.55 (A of ABX, 1H, J=3.33, 11.80 Hz), 3.48 (A of ABX, 1H, J=8.33, 17.49 Hz), 3.32 (B of ABX, 1H, J=3.84, 17.49 Hz), 3.10 (B of ABX, 1H, J=0.73, 11.80 Hz), 1.83 (m, 1H), 1.68 (m, 2H), 1.55 (m, 1H), 1.33 (m, 1H), 1.00 (s, 9H), 0.90 (d, 3H, J=3.94 Hz), 0.89 (d, 3H, J=3.94 Hz). ¹³C NMR (400 MHz, CDCl₃): δ 205.2, 172.6, 159.4, 130.8, 129.8, 114.0, 75.9, 72.3, 70.3, 66.8, 55.5, 45.6, 43.6, 41.0, 38.2, 30.7, 27.1, 24.9, 23.2, 23.1. IR (cm⁻¹): 3452, 1685, 1607, 1507, 1460. [α]_D = 269 (c 1.26, EtOH). HRMS m/z calc'd for C₂₄H₃₇NO₄S₂Na⁺: 490.2056; found: 490.2075.

Table 1, entry 2:

^1H NMR (500 MHz, CDCl_3): δ 7.26 (m, 2H), 6.86 (m, 2H), 5.31 (X of ABX, 1H, $J=1.28$, 8.06 Hz), 4.51 (A of AB, $J=10.90$ Hz), 4.47 (B of AB, $J=10.90$ Hz), 4.34 (m, 1H), 3.80 (s, 3H), 3.77 (m, 1H), 3.49 (A of ABX, 1H, $J=9.17$, 17.31 Hz), 3.48 (d, OH, $J=3.10$ Hz), 3.43 (A of ABX, 1H, $J=8.06$, 11.53 Hz), 3.39 (B of ABX, 1H, $J=1.28$, 11.53 Hz), 3.30 (B of ABX, 1H, $J=3.39$, 17.31 Hz), 1.73 (m, 2H), 1.57 (m, 2H), 1.31 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 0.95 (t, 9H, $J=7.80$ Hz), 0.91 (d, 3H, $J=6.50$ Hz), 0.89 (d, 3H, $J=6.50$ Hz), 0.61 (q, 6H, $J=7.80$ Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 205.7, 172.8, 159.3, 134.0, 129.7, 114.0, 74.6, 72.5, 71.3, 65.6, 55.5, 45.6, 43.8, 41.2, 30.3, 28.3, 26.5, 24.9, 23.2, 23.1, 7.3, 6.8. IR (cm^{-1}): 3495, 1693, 1612, 1511, 1460. $[\alpha]_{\text{D}} = -226$ (c 1.27, EtOH). HRMS m/z calc'd for $\text{C}_{29}\text{H}_{49}\text{NO}_5\text{S}_2\text{SiNa}^+$: 606.2713; found: 606.2707.

Table 1, entry 3:

^1H NMR (500 MHz, CDCl_3): δ 5.35 (X of ABX, 1H, $J=0.73$, 8.33 Hz), 4.24 (m, 1H), 3.64 (d, 2H, $J=5.68$ Hz), 3.56 (A of ABX, 1H, $J=7.42$, 17.13 Hz), 3.52 (A of ABX, 1H, $J=8.33$, 11.81 Hz), 3.35 (d, OH, $J=4.31$ Hz), 3.29 (B of ABX, 1H, $J=2.84$, 17.13 Hz), 3.10 (B of ABX, 1H, $J=0.73$, 11.81 Hz), 1.75 (m, 1H), 1.03 (s, 9H), 0.93 (d, 3H, $J=6.69$ Hz), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (400 MHz, CDCl_3): δ 205.3, 173.1, 72.5, 69.7, 66.6, 43.0, 40.0, 38.2, 30.7, 27.0, 26.1, 18.5, 11.2, -5.2, -5.3. IR (cm^{-1}): 3503, 1689. $[\alpha]_{\text{D}} = 309$ (c 0.63, EtOH). HRMS m/z calc'd for $\text{C}_{19}\text{H}_{37}\text{NO}_3\text{S}_2\text{SiNa}^+$: 442.1876; found: 442.1870.

Table 1, entry 4:

^1H NMR (500 MHz, CDCl_3): δ 5.32 (X of ABX, 1H, $J=1.28$, 8.05 Hz), 4.05 (m, 1H), 3.72 (d, 2H, $J=4.67$ Hz), 3.71 (d, OH, $J=4.94$ Hz), 3.64 (A of ABX, 1H, $J=2.50$, 16.76 Hz), 3.54 (B of ABX, 1H, $J=9.33$, 16.76 Hz), 3.46 (A of ABX, 1H, $J=8.05$, 11.53 Hz), 3.41 (B of ABX, 1H, $J=1.28$, 11.53 Hz), 1.81 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 0.94 (t, 9H, $J=8.00$ Hz), 0.93 (d, 3H, $J=6.95$ Hz), 0.89 (s, 9H), 0.61 (q, 6H, $J=8.00$ Hz), 0.06 (s, 6H). ^{13}C NMR (400 MHz, CDCl_3): δ 206.0, 173.1, 76.9, 72.7, 71.6, 66.4, 43.0, 40.4, 30.3, 28.4, 26.5, 26.1, 18.5, 13.7, 7.3, 6.8, -5.2, -5.3. IR (cm^{-1}): 3472, 1685. $[\alpha]_{\text{D}} = -216$ (c 0.52, EtOH). HRMS m/z calc'd for $\text{C}_{24}\text{H}_{49}\text{NO}_4\text{S}_2\text{Si}_2\text{Na}^+$: 558.2533; found: 558.2514.

Table 1, entry 5:

^1H NMR (500 MHz, CDCl_3): δ 5.35 (X of ABX, 1H, $J=0.74$, 8.43 Hz), 4.23 (m, 1H), 3.93 (m, 1H), 3.57 (A of ABX, 1H, $J=8.52$, 17.67 Hz), 3.52 (A of ABX, 1H, $J=8.43$, 11.72 Hz),

3.42 (B of ABX, 1H, $J=4.03$, 17.67 Hz), 3.39 (d, OH, $J=3.02$ Hz), 3.10 (B of ABX, 1H, $J=0.74$, 11.72 Hz), 1.63 (m, 1H), 1.52 (m, 2H), 1.27 (m, 1H), 1.04 (s, 9H), 0.95 (t, 9H, $J=8.05$ Hz), 0.94 (d, 3H, $J=6.96$ Hz), 0.88 (d, 3H, $J=3.11$ Hz), 0.86 (d, 3H, $J=3.11$ Hz), 0.60 (q, 6H, $J=8.05$ Hz). ^{13}C NMR (400 MHz, CDCl_3): 205.1, 172.6, 74.6, 72.5, 71.1, 43.8, 43.7, 41.1, 38.2, 30.7, 27.1, 25.0, 23.8, 22.6, 7.8, 7.3, 5.7. IR (cm^{-1}): 3440, 1697. $[\alpha]_{\text{D}} = 235$ (c 0.60, EtOH). HRMS m/z calc'd for $\text{C}_{23}\text{H}_{45}\text{NO}_3\text{S}_2\text{SiNa}^+$: 498.2502; found: 498.2488.

Table 1, entry 6:

^1H NMR (500 MHz, CDCl_3): δ 5.35 (X of ABX, 1H, $J=1.28$, 8.05 Hz), 4.06 (m, 1H), 4.04 (m, 1H), 3.96 (d, OH, $J=3.67$ Hz), 3.51 (A of ABX, 1H, $J=3.02$, 16.94 Hz), 3.47 (A of ABX, 1H, $J=7.96$, 11.35 Hz), 3.43 (B of ABX, 1H, $J=8.97$, 16.94 Hz), 3.41 (B of ABX, 1H, $J=1.28$, 11.35 Hz), 1.70 (m, 1H), 1.60 (m, 1H), 1.40 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H), 0.96 (t, 9H, $J=8.05$ Hz), 0.94 (t, 9H, $J=7.78$ Hz), 0.90 (d, 3H, $J=6.59$ Hz), 0.88 (d, 3H, $J=6.59$ Hz), 0.80 (d, 3H, $J=7.05$ Hz), 0.62 (q, 6H, $J=7.78$ Hz), 0.60 (q, 6H, $J=8.05$ Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 205.7, 173.0, 77.0, 72.8, 72.4, 70.6, 44.3, 43.0, 42.4, 30.3, 28.6, 26.6, 24.9, 23.3, 23.2, 11.5, 7.5, 7.3, 7.0, 5.5. IR (cm^{-1}): 3425, 1678. $[\alpha]_{\text{D}} = -216$ (c 0.98, EtOH). HRMS m/z calc'd for $\text{C}_{28}\text{H}_{57}\text{NO}_4\text{S}_2\text{Si}_2\text{Na}^+$: 614.3159; found: 614.3154.

Table 1, entry 7:

^1H NMR (500 MHz, CDCl_3): δ 5.34 (X of ABX, 1H, $J=0.64$, 8.34 Hz), 4.09 (m, 1H), 3.89 (m, 1H), 3.54 (A of ABX, 1H, $J=8.34$, 11.81 Hz), 3.46 (m, 2H), 3.36 (d, OH, $J=4.67$ Hz), 3.12 (B of ABX, 1H, $J=0.64$, 11.81 Hz), 1.82 (m, 1H), 1.72 (m, 1H), 1.32 (m, 1H), 1.20 (m, 1H), 1.04 (s, 9H), 0.96 (t, 9H, $J=7.80$ Hz), 0.90 (d, 3H, $J=4.31$ Hz), 0.88 (d, 3H, $J=4.31$ Hz), 0.87 (d, 3H, $J=7.33$ Hz), 0.61 (q, 6H, $J=7.80$ Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 205.3, 173.6, 72.4, 71.3, 70.0, 44.3, 43.4, 41.7, 38.2, 30.8, 27.2, 24.6, 24.1, 22.4, 11.2, 7.3, 5.5. IR (cm^{-1}): 3500, 1681. $[\alpha]_{\text{D}} = 263$ (c 0.63, EtOH). HRMS m/z calc'd for $\text{C}_{23}\text{H}_{45}\text{NO}_3\text{S}_2\text{SiNa}^+$: 498.2502; found: 498.2519.

Table 1, entry 8:

^1H NMR (500 MHz, CDCl_3): δ 5.34 (X of ABX, 1H, $J=1.19$, 8.15 Hz), 4.52 (m, 1H), 3.83 (m, 1H), 3.81 (br s, OH), 3.49 (A of ABX, 1H, $J=8.61$, 16.70 Hz), 3.46 (A of ABX, 1H, $J=8.15$, 11.44 Hz), 3.39 (B of ABX, 1H, $J=1.28$, 16.70 Hz), 3.36 (B of ABX, 1H, $J=1.28$, 11.44 Hz), 1.60

(m, 3H), 1.39 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 1.05 (d, 3H, $J=7.05$ Hz), 0.96 (t, 9H, $J=8.06$ Hz), 0.93 (t, 9H, $J=8.00$ Hz), 0.91 (d, 3H, $J=6.50$ Hz), 0.87 (d, 3H, $J=6.50$ Hz), 0.62 (q, 6H, $J=8.00$ Hz), 0.60 (q, 6H, $J=8.06$ Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 205.5, 171.9, 76.9, 76.6, 72.8, 72.4, 67.3, 44.3, 43.8, 39.5, 30.2, 28.5, 26.6, 25.0, 23.9, 22.5, 11.8, 7.4, 7.3, 6.9, 5.4. IR (cm^{-1}): 3476, 1689. $[\alpha]_{\text{D}} = -210$ (c 0.64, EtOH). HRMS m/z calc'd for $\text{C}_{28}\text{H}_{57}\text{NO}_4\text{S}_2\text{Si}_2\text{Na}^+$: 614.3159; found: 614.3152.

Table 1, entry 9:

^1H NMR (500 MHz, CDCl_3): δ 5.33 (X of ABX, 1H, $J=8.13$ Hz), 4.09 (m, 1H), 4.05 (m, 1H), 3.95 (m, 2H), 3.57 (A of ABX, 1H, $J=9.23$, 17.58 Hz), 3.54 (A of ABX, 1H, $J=8.13$, 11.76 Hz), 3.47 (B of ABX, 1H, $J=2.75$, 17.58 Hz), 3.29 (d, OH, $J=4.61$ Hz), 3.11 (B of ABX, 1H, $J=11.76$ Hz), 1.39 (s, 3H), 1.33 (s, 3H), 1.02 (s, 9H). ^{13}C NMR (400 MHz, CDCl_3): δ 205.3, 172.9, 109.8, 77.8, 72.3, 70.0, 67.1, 41.2, 38.1, 30.8, 30.7, 27.2, 26.9, 25.8, 25.4. IR (cm^{-1}): 3452, 1682. $[\alpha]_{\text{D}} = 289$ (c 1., EtOH). HRMS m/z calc'd for $\text{C}_{15}\text{H}_{25}\text{NO}_4\text{S}_2\text{Na}^+$: 370.1117; found: 370.1128.

Table 1, entry 10:

^1H NMR (500 MHz, CDCl_3): δ 5.33 (X of ABX, 1H, $J=8.02$ Hz), 4.20 (m, 1H), 4.15 (m, 1H), 4.05 (m, 1H), 3.91 (m, 1H), 3.72 (A of ABX, 1H, $J=9.45$, 16.92 Hz), 3.51 (A of ABX, 1H, $J=8.24$, 11.54 Hz), 3.44 (B of ABX, 1H, $J=11.54$ Hz), 3.32 (B of ABX, 1H, $J=3.30$, 16.92 Hz), 3.29 (d, OH, $J=6.15$ Hz), 1.47 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.97 (t, 9H, $J=7.91$ Hz), 0.64 (q, 6H, $J=7.91$ Hz). ^{13}C NMR (400 MHz, CDCl_3): δ 206.0, 172.2, 109.9, 77.7, 72.6, 68.9, 65.6, 41.1, 30.3, 28.3, 26.6, 26.5, 25.4, 7.3, 6.8. IR (cm^{-1}): 3445, 1689. $[\alpha]_{\text{D}} = -282$ (c 2.57, EtOH). HRMS m/z calc'd for $\text{C}_{20}\text{H}_{37}\text{NO}_5\text{S}_2\text{SiNa}^+$: 486.1775; found: 486.1796.

Relax. delay 1.500 sec
Pulse 28.2 degrees
Acq. time 3.000 sec
Width 6000.6 Hz
16 repetitions

OBSERVE H1, 400.1547355

DATA PROCESSING
Line broadening 0.1 Hz
FT size 131072
Total time 1 minute

Solvent: CDCl₃
Ambient temperature
File: ycz-7-078-1h

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Data Acquired: Apr 11 2005

S12

Relax. delay 1.500 sec
Pulse 28.2 degrees
Acq. time 3.000 sec
Width 6000.6 Hz
8 repetitions

OBSERVE H1, 400.1547356

DATA PROCESSING
Line broadening 0.1 Hz
FT size 131072
Total time 1 minute

Solvent: CDCl₃
Ambient temperature
File: ycz-6-110-2h

6

Table 1, entry 1

Table 1, entry 1

Table 1, entry 2

Table 1, entry 3

Table 1, entry 3

Table 1, entry 4

Table 1, entry 5

Table 1, entry 6

Data Acquired: Dec 8 2004

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Table 1, entry 7

Table 1, entry 8

Table 1, entry 8

Table 1, entry 9

Table 1, entry 9

Table 1, entry 10