Ni(II) Bis(oxazoline)-Catalyzed Enantioselective Syn Aldol Reactions of *N*-Propionylthiazolidinethione in the Presence of Silyl Triflates

David A. Evans,* C. Wade Downey, and Jed L. Hubbs

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Supporting Information

General Information. Aldol reactions were carried out nitrogen atmosphere with a septum cap and magnetic stirring; no special precautions were taken to exclude water from the reaction vessel. Toluene and CH₂Cl₂ were purified by passage through a bed of activated alumina.¹ MeOH was distilled from Mg(OMe)₂. All other reaction solvents were used as received. Benzaldehyde, 2-naphthaldehyde, TESOTf, imidazole, Me(OMe)NH₂Cl, and AgOTf were used as received from Aldrich Chemical Co. Other aldehydes were distilled from suitable desiccants. NiCl₂ was used as received from Alfa/Aesar Chemical Co. 2,6-Lutidine was distilled from CaH₂ prior to use. TMSOTf was distilled prior to use. Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.² Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain, followed by heating. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T\text{ }^{\circ}\text{C}}$ (c = g/100 mL, solvent). Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ¹H-NMR spectra were recorded on a Varian Inova-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C-NMR spectra were recorded on a Varian Mercury 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.0 ppm). Low- and high-resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory.

General Procedure: Nickel-catalyzed direct aldol reaction of *N*-propionylthiazolidinethione with aldehydes To a 10-mL round-bottom flask in a glove box was added Ni(OTf)₂(*t*-BuBox) (0.10 mmol, 0.1 equiv). The flask was fitted with a septum cap and removed to ambient atmosphere. The nickel complex was dissolved in 50 μL CH₂Cl₂ and 200 μL toluene. After cooling to -78 °C, 2,6-lutidine (3.33 mmol, 3.33 equiv), *N*-propionylthiazolidinethione (1.0 mmol, 1 equiv), aldehyde (1.2 mmol, 1.2 equiv), and TMSOTf (1.25 mmol, 1.25 equiv) were added sequentially. The yellow reaction mixture was stirred 12-36 h until complete by TLC, then filtered directly through a plug of silica gel (5.0 cm x 5.0 cm) and eluted with Et₂O. The eluent was concentrated *in vacuo* and dissolved in THF (10 mL) and treated with 1.0 N HCl (2 mL). After stirring 1 h, the mixture was diluted with Et₂O (20 mL) and water (20 mL). The layers were separated and the organic layer was extracted sequentially with saturated NaHCO₃ (20 mL) and brine (20 mL). The organic layer was dried over Na₂SO₄ for 1 h, then filtered through a cotton plug and concentrated *in vacuo*. A sample was subjected to HPLC analysis to determine enantio- and diastereoselectivity. Flash chromatography (10-20% EtOAc/hexanes) afforded the pure major diastereomer, except where otherwise noted.

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

(2) Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

(2R,3R)-3-Hydroxy-2-methyl-3-phenyl-1-(2-thioxo(1,3-thiazolidin-3-yl))propan-1-one (3a). The title compound was prepared with 5 mol % catalyst according to the General Procedure and isolated by column chromatography (Et₂O/pentane) as an amorphous yellow solid (81% yield): $[\alpha]_D^{25} = -8.5^\circ$ ($c = 1.05$, CH₂Cl₂); IR (film) 3481, 2937, 1698, 1453, 1366, 1277, 1220, 1156, 1063, 1000, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.41-7.24 (m, 5H), 5.04 (d, 1H, $J = 5.4$ Hz), 4.87 (dq, 1H, $J = 5.4, 6.8$ Hz), 4.39-4.32 (m, 1H), 4.29-4.23 (m, 1H), 3.15-3.09 (m, 1H), 3.10-2.95 (m, 1H), 2.78 (bs, 1H), 1.25 (d, 3H, $J = 6.8$ Hz); ¹³C NMR (100 MHz, CDCl₃) δ 201.9, 178.7, 128.6, 128.0, 126.5, 75.0, 56.5, 46.7, 28.8, 11.8; HRMS (CI, NH₃): Exact mass calcd for C₁₃H₁₅O₂NS₂ [M+NH₄]⁺, 281.0782. Found 281.0772. Enantio- and diastereoselectivity determined by HPLC (Chiralcel ODH column, 10% *i*-PrOH/hexanes, 0.6 mL/min, 254 nm), anti₁ = 22.5 min, anti₂ = 38.3 min, syn_{major} = 27.1 min, syn_{minor} = 32.6 min; syn:anti = 94:6, ee = 97%.

(2R,3R)-3-Hydroxy-2-methyl-3-(4-methylphenyl)-1-(2-thioxo(1,3-thiazolidin-3-yl))propan-1-one (3b). The title compound was prepared according to the General Procedure and isolated by column chromatography (EtOAc/hexanes) as a crystalline yellow solid (80% yield): mp: 113-115 °C; $[\alpha]_D^{25} = -5.5^\circ$ ($c = 1.01$, CH₂Cl₂); IR (film) 3489, 2985, 1689, 1454, 1432, 1368, 1353, 1308, 1274, 1221, 1220, 1171, 1156, 1053, 1040, 1012, 958, 902, 875, 819, 713 cm⁻¹; ¹H NMR (500MHz) δ 7.27 (d, 2H, $J = 7.8$ Hz), 7.15 (d, 2H, $J = 7.8$ Hz), 5.00 (dd, 1H, $J = 5.4, 2.9$ Hz), 4.82-4.87 (m, 1H), 4.32-4.38 (m, 1H), 4.23-4.28 (m, 1H), 3.09-3.14 (m, 1H), 2.95-3.00 (m, 1H), 2.70 (dd, 1H, $J = 2.9, 1.5$ Hz), 2.36 (s, 3H), 1.25 (d, 3H, $J = 6.8$ Hz); ¹³C NMR (125 MHz) δ 201.5, 178.0, 138.4, 137.1, 128.7, 125.9, 74.7, 56.1, 46.5, 28.3, 20.9, 11.6; HRMS (CI, NH₃): Exact mass calcd for C₁₄H₂₁NO₂S₂ [M + NH₄]⁺, 313.1044. Found 313.1049. Enantio- and diastereoselectivity determined by HPLC (Chiracel AD column, 85:15 hexanes:isopropanol, 1.0 mL/min, 245 nm), syn_{major} = 22.9 min, syn_{minor} = 28.7 min, anti₁ = 32.3 min, anti₂ = 40.3 min; syn:anti = 93:7, ee = 95%. See below for X-ray crystallographic data.

(2R,3R)-3-(4-Chlorophenyl)-3-hydroxy-2-methyl-1-(2-thioxo(1,3-thiazolidin-3-yl))propan-1-one (3c). The title compound was prepared according to the General Procedure and isolated by column chromatography (EtOAc/hexanes) as a crystalline yellow solid (81% yield): mp: 109-112 °C; $[\alpha]_D^{25} +14.9^\circ$ ($c = 1.06$, CH₂Cl₂); IR (film) 3504, 2937, 1699, 1490, 1364, 1276, 1220, 1156, 1090, 1063, 1013 cm⁻¹; ¹H NMR (500MHz) δ 7.31-7.35 (m, 4H), 5.00 (dd, 1H, $J = 4.4, 2.9$ Hz), 4.86 (dq, 1H, $J = 6.8, 4.4$ Hz), 4.37-4.49 (m, 2H), 3.19-3.24 (m, 1H), 3.09-3.13 (m, 1H), 3.00 (d, 1H, $J = 2.9$ Hz), 1.17 (d, 3H, $J = 6.8$ Hz); ¹³C NMR (100 MHz) δ 201.7, 177.8, 139.8, 133.0, 128.1, 127.4, 73.4, 56.1, 45.9, 28.2, 11.1; HRMS (CI, NH₃): Exact mass calcd for C₁₃H₁₈ClN₂O₂S₂ [M + NH₄]⁺, 333.0498. Found 333.0494. Enantio- and diastereoselectivity determined by HPLC (Chiracel AD column, 85:15 hexanes:isopropanol, 1.0 mL/min, 245 nm), syn_{major} = 14.4 min, syn_{minor} = 29.9 min, anti₁ = 18.9 min, anti₂ = 20.4 min; syn:anti = 90:10, ee = 91%. See below for X-ray crystallographic data.

(2R,3R)-3-Hydroxy-2-methyl-3-naphthyl-1-(2-thioxo(1,3-thiazolidin-3-yl))propan-1-one (3d). The title compound was prepared according to the General Procedure and isolated by column chromatography (EtOAc/hexanes) as a crystalline yellow solid (73% yield): mp: 123-128 °C; $[\alpha]_D^{25} +169^\circ$ ($c = 1.04$, CH₂Cl₂); IR (film) 3478, 3068, 2934, 1682, 1353, 1273, 1220, 1174, 1159, 1062, 1032, 1008, 905, 873, 803, 781, 727 cm⁻¹. ¹H NMR (500MHz) δ 8.06 (d, 1H, $J = 8.3$ Hz), 7.87 (d, 1H, $J = 7.8$ Hz), 7.81 (d, 1H, $J = 7.8$ Hz), 7.71 (d, 1H, $J = 7.3$ Hz), 7.48-7.54 (m, 3H), 5.74 (d, 1H, $J = 4.9$ Hz), 5.12-5.17 (m, 1H), 4.23-4.29 (m, 1H), 3.96-4.01 (m, 1H), 3.15 (s, 1H), 2.98-3.03 (m, 1H), 2.72-2.77 (m, 1H), 1.31 (d, 3H, $J = 6.8$ Hz); ¹³C NMR (100 MHz) δ 201.0, 178.1, 136.3, 133.0, 129.6, 128.2, 127.8, 125.8, 125.2, 124.8, 124.3, 122.9, 71.6, 55.6, 45.0, 27.8, 11.9. HRMS (CI, NH₃): Exact mass calcd for C₁₇H₂₁N₂O₂S₂ [M + NH₄]⁺, 349.1045. Found 349.1052. Enantio- and diastereoselectivity determined by HPLC (Chiracel OD-H column, 80:20 hexanes:isopropanol, 0.8 mL/min, 245 nm), syn_{major} = 22.6 min, syn_{minor} = 20.6 min, anti₁ = 14.3 min, anti₂ = 43.4 min; syn:anti = 93:7, ee = 92%. See below for X-ray crystallographic data.

(2R,3R)-3-Hydroxy-2-methyl-3-(2-naphthyl)-1-(2-thioxo(1,3-thiazolidin-3-yl))propan-1-one (3e). The title compound was prepared with 5 mol % catalyst according to the General Procedure and isolated by column chromatography (Et₂O/pentane) as an amorphous yellow solid (82% yield): $[\alpha]_D^{25} = +33.9^\circ$ ($c = 1.01$, CH₂Cl₂); IR (film) 3454, 2699, 1352, 1277, 1219, 1154, 1061, 1000 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.87-7.81 (m, 4H), 7.53-7.45 (m, 3H), 5.21 (d, 1H, $J = 5.4$ Hz), 4.99 (dq, 1H, $J = 2.0$, 6.8 Hz), 4.36-4.29 (m, 1H), 4.23-4.17 (m, 1H), 3.03-2.97 (m, 1H), 2.96 (bs, 1H), 2.73-2.66 (m, 1H), 1.27 (d, 3H, $J = 6.8$ Hz); ¹³C NMR (100 MHz, CDCl₃) δ 202.0, 178.8, 139.0, 133.3, 133.2, 128.4, 128.3, 127.9, 126.5, 126.3, 125.4, 124.3, 75.1, 56.5, 46.6, 28.5, 11.8; HRMS (CI): Exact mass calcd for C₁₇H₁₇O₂NS₂ [M+NH₄]⁺, 349.1045. Found 349.1049. Enantio- and diastereoselectivity determined by HPLC (Chiralcel ODH column, 7.5% i-PrOH/hexanes, 1.0 mL/min, 254 nm), anti₁ = 34.7 min, anti₂ = 47.3 min, syn_{major} = 38.9 min, syn_{minor} = 70.3 min; syn:anti = 92:8, ee = 93%.

(2R,3R)-3-(2-Furyl)-3-hydroxy-2-methyl-1-(2-thioxo(1,3-thiazolidin-3-yl))propan-1-one (3f). The title compound was prepared with 5 mol % catalyst according to the General Procedure and isolated by column chromatography (Et₂O/pentane) as a yellow oil (82% yield): $[\alpha]_D^{25} = -53.1^\circ$ ($c = 1.01$, CH₂Cl₂); IR (film) 3448, 2936, 1696, 1356, 1277, 1221, 1159, 1064, 1005 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.25 (m, 1H), 6.35-6.33 (m, 1H), 6.30-6.27 (m, 1H), 5.05 (d, 1H, $J = 5.9$ Hz), 4.95 (m, 1H), 4.48-4.38 (m, 2H), 3.21 (ap t, 1H, $J = 6.8$ Hz), 3.20 (bs, 1H), 1.33 (d, 3H, $J = 6.8$ Hz); ¹³C NMR (100 MHz, CDCl₃) δ 201.8, 177.9, 154.4, 142.4, 110.5, 107.1, 69.5, 56.5, 44.6, 28.7, 12.4; HRMS (CI, NH₃): Exact mass calcd for C₁₁H₁₂O₃NS₂ [M+NH₄]⁺, 289.0681. Found 289.0681. Diastereoselectivity determined by ¹H NMR analysis of the unpurified, silylated reaction mixture. Enantioselectivity determined by HPLC of a diastereomerically pure sample (Chiralcel AD column, 30% i-PrOH/hexanes, 0.7 mL/min, 254 nm), syn_{major} = 12.0 min, syn_{minor} = 34.7 min; syn:anti = 88:12, ee = 95%.

(4E)(2R,3S)-3-Hydroxy-2-methyl-1-(2-thioxo(1,3-thiazolidin-3-yl))hex-4-en-1-one (3g). The title compound was prepared according to the General Procedure and isolated by column chromatography (Et₂O/pentane) as a crystalline yellow solid (46% yield): $[\alpha]_D^{25} = -6.0^\circ$ ($c = 0.98$, CH₂Cl₂); IR (film) 3440, 1697, 1367, 1283, 1215, 1170, 1062, 998 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.79-5.70 (m, 1H), 5.53-5.47 (m, 1H), 4.62 (dq, 1H, $J = 2.9$, 6.8 Hz), 4.54 (dt, 2H, $J = 2.9$, 7.8 Hz), 4.46 (bt, 1H, $J = 5.9$ Hz), 3.34-3.23 (m, 2H), 2.52 (bs, 1H), 1.72 (d, 3H, $J = 6.8$ Hz), 1.22 (d, 3H, $J = 6.8$ Hz); ¹³C NMR (100 MHz, CDCl₃) δ 202.0, 178.6, 130.5, 128.4, 73.4, 56.6, 44.6, 28.6, 18.0, 11.4; HRMS (CI, NH₃): Exact mass calcd for C₁₀H₁₅O₂NS₂ [M+NH₄]⁺, 263.0888. Found 263.0890. Diastereoselectivity determined by ¹H NMR analysis of the unpurified, silylated reaction mixture. Enantioselectivity determined by HPLC analysis of a diastereomerically pure sample (Chiralcel ODH column, 10% i-PrOH/hexanes, 1.0 mL/min, 254 nm), syn_{major} = 15.7 min, syn_{minor} = 18.7 min; syn:anti = 93:7, ee = 97%. See below for X-ray crystallographic data.

(4E)(2R,3S)-3-Hydroxy-2-methyl-5-phenyl-1-(2-thioxo(1,3-thiazolidin-3-yl))pent-4-en-1-one (3h). The title compound was prepared according to the General Procedure and isolated by column chromatography (EtOAc/hexanes) as a yellow oil (63% yield): $[\alpha]_D^{25} = -22.6^\circ$ ($c = 1.25$, CH₂Cl₂); IR (film) 3454, 2978, 2936, 1698, 1449, 1366, 1278, 1220, 1155, 1058, 1000, 968, 871, 753, 695 cm⁻¹; ¹H NMR (500MHz) δ 7.39-7.41 (m, 2H), 7.31-7.33 (m, 2H), 7.23-7.25 (m, 1H), 6.66 (dd, 1H, $J = 16.0$, 1.0 Hz), 6.21 (dd, 1H, $J = 15.6$, 5.9 Hz), 4.77 (qd, 1H, $J = 6.8$, 3.9 Hz), 4.69 (ap br s, 1H), 4.51-4.54 (m, 2H), 3.19-3.23 (m, 2H), 2.69 (d, 1H, $J = 2.4$ Hz), 1.28 (d, 3H, $J = 6.8$ Hz); ¹³C NMR (100 MHz) δ 201.8, 177.7, 136.2, 131.1, 128.7, 128.4, 127.6, 126.2, 73.3, 56.2, 44.6, 28.2, 11.3. HRMS (ES): Exact mass calcd for C₁₅H₁₇NO₂S₂ [M + H]⁺, 308.0779. Found 308.0774. The diastereomeric ratio was determined by HPLC with a Zorbax column (50:50 hexanes:ethyl acetate, 1 mL/min, 245 nm) $t_r = 6.6$ and 7.9 min; syn:anti = 88:12; Enantioselectivity determined by HPLC analysis of a diastereomerically pure sample (Chiralcel OD-H column, 90:10 hexanes:isopropanol, 1.0 mL/min, 245 nm), syn_{major} = 15.7 min, syn_{minor} = 18.4 min; ee = 93%.

(2R,3S)-3-Hydroxy-2-methyl-1-(2-thioxo(1,3-thiazolidin-3-yl))butan-1-one (3i). The title compound was prepared according to the General Procedure and isolated as a 97:3 mixture of diastereomers by column chromatography (EtOAc/hexanes) as a yellow oil (86%

yield): $[\alpha]_D^{25} -3.8^\circ$ ($c = 1.07$, CH_2Cl_2); IR (film) 3424, 2973, 2934, 1697, 1458, 1362, 1278, 1219, 1157, 1050, 1000, 908, 871 cm^{-1} ; ^1H NMR (500MHz) δ 4.51-4.59 (m, 3H), 4.18-4.21 (m, 1H), 3.27-3.32 (m, 2H), 2.70 (s, 1H), 1.23 (d, 3H, $J = 7.3$ Hz), 1.20 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz) δ 201.8, 178.5, 67.8, 56.2, 44.3, 28.1, 19.8, 10.2; HRMS (ES): Exact mass calcd for $\text{C}_8\text{H}_{13}\text{NO}_2\text{S}_2$ $[\text{M} + \text{H}]^+$, 220.0466. Found 220.0471. Enantio- and diastereoselectivity determined by HPLC (Chiracel OD-H column, 93:7 hexanes:isopropanol, 1.0 mL/min, 245 nm), syn = 24.0 min and 27.8 min; anti = 18.1 min and 19.7 min; syn:anti = 97:3, ee = 93%.

(2R,3S)-3-Hydroxy-2-methyl-1-(2-thioxo(1,3-thiazolidin-3-yl))pentan-1-one (3j). The title compound was prepared according to the General Procedure and isolated as a mixture of diastereomers by column chromatography (EtOAc/hexanes) as a yellow oil (84% yield): $[\alpha]_D^{25} +8.71^\circ$ ($c = 1.16$, CH_2Cl_2); IR (film) 3448, 2964, 2936, 2877, 1698, 1458, 1366, 1458, 1366, 1278, 1219, 1156, 1052, 1000, 975, 958, 920, 872, 745, 717 cm^{-1} ; ^1H NMR (500MHz) δ 4.62 (qd, 1H, $J = 6.8$, 2.4 Hz), 4.52-4.61 (m, 2H), 3.89-3.93 (m, 1H), 3.25-3.33 (m, 2H), 1.53-1.60 (m, 1H), 1.41-1.47 (m, 1H), 1.20 (d, 3H, $J = 7.3$), 0.96 (t, 3H, $J = 7.8$ Hz); ^{13}C NMR (100 MHz) δ 201.6, 178.6, 72.9, 56.2, 42.9, 28.0, 26.8, 10.1, 10.0; HRMS (ES): Exact mass calcd for $\text{C}_9\text{H}_{15}\text{NO}_2\text{S}_2$ $[\text{M} + \text{H}]^+$, 234.0622. Found 234.0625. Enantio- and diastereoselectivity determined by HPLC (Chiracel OD-H column, 90:10 hexanes:isopropanol, 1.0 mL/min, 245 nm), syn_{major} = 20.3 min, syn_{minor} = 15.5 min, anti = 10.1 min and 12.0 min; syn:anti = 97:3, ee = 90%.

(2R,3S)-3-Hydroxy-2,4-dimethyl-1-(2-thioxo(1,3-thiazolidin-3-yl))pentan-1-one (3k). The title compound was prepared according to the General Procedure and isolated as a mixture of diastereomers by column chromatography ($\text{Et}_2\text{O/pentane}$) as a yellow oil (70% yield): $[\alpha]_D^{25} = +12.8^\circ$ ($c = 0.68$, CH_2Cl_2); IR (film) 3476, 1700, 1352, 1277, 1219, 1154, 1062, 1000 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.81 (dq, 1H, $J = 2.4$, 6.8 Hz), 4.61-4.51 (m, 2H), 3.59 (dd, 1H, $J = 2.9$, 8.8 Hz), 3.35-3.24 (m, 2H), 2.71 (bs, 1H), 1.74-1.63 (m, 1H), 1.20 (d, 3H, $J = 6.8$ Hz), 1.03 (d, 3H, $J = 6.3$ Hz), 0.88 (d, 1H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 201.9, 179.8, 91.6, 77.1, 56.7, 41.4, 31.2, 28.4, 19.5, 19.1, 10.2; HRMS (CI): Exact mass calcd for $\text{C}_{10}\text{H}_{17}\text{O}_2\text{NS}_2$ $[\text{M} + \text{H}]^+$, 248.0779. Found 248.0787. Enantio- and diastereoselectivity determined by HPLC (Chiralcel ODH column, 10% i-PrOH/hexanes, 1.0 mL/min, 254 nm), anti₁ = 8.62 min, anti₂ = 11.0 min, syn_{major} = 12.7 min, syn_{minor} = 18.9 min; syn:anti = 98:2, ee = 90.

(2R,3R)-3-(Triethylsilyloxy)-2-methyl-3-phenyl-1-(2-thioxo(1,3-thiazolidin-3-yl))propan-1-one (4). To a 50-mL round-bottom flask in a glove box was added $[\text{Ni}((S,S)\text{-}t\text{-BuBox})](\text{OTf})_2$ (**2**) (0.499 mmol, 0.050 equiv). The flask was fitted with a septum cap and removed to ambient atmosphere. The nickel complex was dissolved in 2.5 mL CH_2Cl_2 and 10 mL toluene. After cooling to -78°C , 2,6-lutidine (33.5 mmol, 3.35 equiv), *N*-propionylthiazolidinethione (10.0 mmol, 1 equiv), aldehyde (12.0 mmol, 1.2 equiv), and TMSOTf (12.6 mmol, 1.26 equiv) were added sequentially. The yellow reaction mixture was stirred 36 h until complete by TLC, then filtered directly through a plug of silica gel (10.0 cm x 10.0 cm) and eluted with Et_2O . Flash chromatography ($\text{Et}_2\text{O/pentane}$) afforded a mixture of diastereomers as a yellow oil (96% yield): IR (film) 2955, 2877, 1704, 1455, 1362, 1278, 1220, 1162, 1090, 1069, 1002 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.25 (m, 5H), 4.71-4.62 (m, 2H), 4.05-3.97 (m, 1H), 3.85-3.80 (m, 1H), 2.84-2.79 (m, 1H), 2.59-2.52 (m, 1H), 1.38 (d, 3H, $J = 6.3$ Hz), 0.83 (t, 9H, $J = 7.8$ Hz), 0.54-0.41 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.5, 178.0, 143.5, 128.3, 128.0, 127.1, 78.5, 56.5, 49.8, 29.1, 14.0, 6.9, 5.0; HRMS (CI): Exact mass calcd for $\text{C}_{19}\text{H}_{29}\text{O}_2\text{NSiS}_2$ $[\text{M} + \text{H}]^+$, 396.1487. Found 396.1478. Enantio- and diastereoselectivity determined by HPLC analysis of desilylated product mixture (see compound **2a** for conditions), syn:anti = 94:6, ee = 94%.

(2R,3R)-3-(Triethylsilyloxy)-N-methoxy-2-methyl-N-methyl-3-phenylpropan-1-one (5). $[\text{Ni}((S,S)\text{-}t\text{-BuBox})](\text{OTf})_2$ (**2**) was weighed in a dry box, removed and placed under nitrogen. The yellow solid was dissolved in 1.25 mL of a 4:1 mixture of toluene in CH_2Cl_2 and cooled to -78°C . 2,6-Lutidine (388 mL, 3.33 mmol), *N*-propionylthiazolidinethione (140 mL, 1.00 mmol), benzaldehyde (109 mL, 1.20 mmol), and TESOTf (310 mL, 1.25 mmol) were added sequentially and the flask was placed in a -20°C bath and stirred for 14 h. Methylene chloride (1 mL), triethylamine (558 mL, 4.00 mmol), imidazole (408 mg, 6.00 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (278 mg, 3 mmol) were added and the reaction mixture was allowed to warm to room temperature and stir for 48 h. The solution was diluted with 100 mL of Et_2O and this solution was washed with 50 mL of 1 M NaHSO_4 , 2 X 50 mL 1 M NaOH , and 50 mL of brine. The solution was dried with

MgSO₄ and concentrated to give an oil that was purified by column chromatography (EtOAc/hexanes) to yield a yellow oil. $[\alpha]_D^{25} +2.5^\circ$ ($c = 1.09$, CH₂Cl₂); IR 2956, 2876, 1656, 1457, 1414, 1384, 1240, 1082, 1059, 996, 854, 731, 701 cm⁻¹; ¹H NMR (500MHz) δ 7.18-7.35 (m, 5H), 4.80 (d, 1H, $J = 8.8$ Hz), 3.26 (s, 3H), 3.19 (ap br s, 1H Hz), 2.94 (s, 3H), 1.30 (d, 3H, $J = 6.8$ Hz), 0.86 (t, 9H, $J = 7.8$ Hz), 0.44-0.56 (m, 6H Hz); ¹³C NMR (100 MHz) δ 175.3, 144.0, 127.7, 127.1, 126.6, 76.2, 61.0, 45.1, 31.6, 14.8, 6.5, 4.7.

Nickel(II) Bis(chloride) (2,2'-isopropylidenebis((4S)-4-tert-butyl-2-oxazoline)).

To a 100-mL flask was added NiCl₂ (3.50 mmol, 1 equiv) and (*S,S*)-*t*-BuBox (3.52 mmol, 1 equiv). The flask was charged with 75 mL CH₃CN and 1 mL water, then heated to reflux for 6 h. The purple mixture was cooled to room temperature and filtered through a glass frit. Solvent was removed in vacuo, and the purple solid was recrystallized from CH₂Cl₂ and hexanes (80% yield): See below for X-ray crystallographic data.

Nickel(II) Bis(trifluoromethanesulfonate) (2,2'-isopropylidenebis((4S)-4-tert-butyl-2-oxazoline) (2).

To a 100-mL flask was added NiCl₂((*S,S*)-*t*-BuBox) (1.89 mmol, 1 equiv) and AgOTf (4.13 mmol, 2.19 equiv). The flask was charged with 60 mL CH₂Cl₂ and stirred 18 h. The yellow mixture was filtered through a 0.45 μ filter and the solvent was removed under a stream of nitrogen. Residual solvent was removed by evacuation to provide a hygroscopic yellow powder (77% yield). A single crystal of the triflate-bridge dimer was grown by vapor diffusion of hexanes into CH₂Cl₂. See below for X-ray crystallographic data.

Nickel(II) Bis(aquo) bis(trifluoromethanesulfonate) (2,2'-isopropylidenebis((4S)-4-tert-butyl-2-oxazoline) (2•(H₂O)₂).

A sample of [Ni((*S,S*)-*t*-BuBox)](OTf)₂ (2) was hydrated by exposure to ambient atmosphere overnight, providing a yellow-green solid. A single crystal was grown by vapor diffusion of pentane into THF. See below for X-ray crystallographic data.

Stereochemical Proofs

Aldol adduct **3a** was transformed to its methyl ester by literature procedure,³ and the sign of its optical rotation compared to the literature value ($[\alpha]_D^{25} = +53.1^\circ$ ($c = 1.05$, CHCl₃)).⁴ Relative stereochemistry was determined according to the method of Heathcock.⁵

The stereochemistry of aldol adduct **3e** was assigned by analogy.

Aldol adduct **3f** was transformed to its methyl ester by literature procedure,⁶ and the sign of its optical rotation compared to the literature ($[\alpha]_D^{25} = +14.8^\circ$ ($c = 1.80$, CHCl₃)).⁷ Relative stereochemistry was determined according to the method of Heathcock.⁵

Aldol adduct **3h** transformed to its Weinreb amide by literature procedure,³ and the sign of its optical rotation compared to the literature value ($[\alpha]_D^{25} = -32.9^\circ$ ($c = 0.68$, CHCl₃)).⁸ Relative stereochemistry was determined according to the method of Heathcock.⁵

Aldol adduct **3i** was converted to its methyl ester using literature procedure.³ The ¹H NMR spectrum was identical to that reported.⁹ The absolute configuration was determined by Mosher ester analysis.¹⁰

(3) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894-902.

(4) Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61-64.

(5) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294-4299.

(6) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1903-1906.

(7) Martin, S. F.; Guinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588-5593.

(8) Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471-485.

(9) Trotter, N. S.; Takahashi, S.; Nakata, T. *Org. Lett.* **1999**, *1*, 957-959.

(10) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.

(R)-Mosher Ester for 3i. ^1H NMR (500MHz) δ 7.51-7.53 (m, 2H, ArH), 7.41-7.42 (m, 3H, ArH), 5.60 (qd, 1H, $J = 6.3, 3.9$, CHOR), 4.87 (qd, 1H, $J = 7.3, 3.9$, CHC=O), 4.51-4.56 (m, 1H, NCH₂), 4.43-4.49 (m, 1H, NCH₂), 3.55 (d, 3H, $J = 1.0$, OCH₃), 3.33-3.39 (m, 1H, C=SSCH₂), 3.15-3.20 (m, 1H, C=SSCH₂), 1.42 (d, 3H, $J = 6.4$, CH(OH)CH₃), 1.14 (d, 3H, $J = 6.8$, CH(C=O)CH₃).

(S)-Mosher Ester for 3i. ^1H NMR (500MHz) δ 7.51-7.52 (m, 2H, ArH), 7.40-7.42 (m, 3H, ArH), 5.60-5.65 (m, 1H, CHOR), 4.90-4.95 (qd, 1H, $J = 7.3, 3.9$, CHC=O), 4.42-4.48-4.56 (m, 2H, NCH₂), 3.55 (d, 3H, $J = 1.0$, OCH₃), 3.31-3.37 (m, 1H, C=SSCH₂), 3.14-3.19 (m, 1H, C=SSCH₂), 1.31 (d, 3H, $J = 6.4$, CH(OH)CH₃), 1.22 (d, 3H, $J = 6.8$, CH(C=O)CH₃).

Aldol adduct **3j** was transformed to its Weinreb amide by literature procedure,³ and the sign of its rotation compared to the literature value for its enantiomer ($[\alpha]_{\text{D}}^{25} = +17^\circ$ ($c = 2.0$, CHCl₃)).¹¹ Relative stereochemistry was determined by the method of Heathcock.⁵

Aldol adduct **3k** was transformed to its methyl ester by literature procedure,⁶ and the sign of its optical rotation compared to the literature value ($[\alpha]_{\text{D}}^{25} = +7.7^\circ$ ($c = 1.40$, CHCl₃)).¹² Relative stereochemistry was determined according to the method of Heathcock.⁵

Absolute and relative stereochemistry for aldol adducts **3b**, **3c**, **3d**, and **3g** was determined unequivocally by X-ray crystallography. The requisite CIF files have been submitted to the journal.

X-ray crystal structures of nickel complexes (requisite CIF files have been submitted to the journal):

X-ray structure of NiCl₂(*t*-BuBox).

X-ray structure of [Ni(OTf)₂(*t*-BuBox)]₂.

(11) Pilli, R. A.; de Andrade, C. K. Z.; Souto, C. R. O.; De Meijere, A. *J. Org. Chem.* **1998**, 63, 7811-7819.

(12) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, 103, 2127-2129.

X-ray structure of **Ni(OTf)₂(H₂O)₂(*t*-BuBox)**.