JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
J. Am. Chem. Soc., 1996, 118(24), 5814-5815, DOI:10.1021/ja960712i

J5815-1

C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Aldol Additions of Silylketene Acetals to Benzyloxyacetaldehyde

David A. Evans,* Jerry A. Murry, and Marisa C. Kozlowski

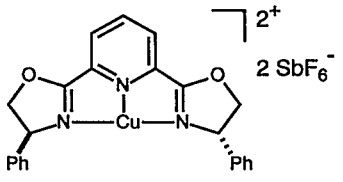
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138.

Supporting Information

General Information. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Solvents and reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] $CuCl_2$ and $AgSbF_6$ were purchased from the Cerac Chemical company, stored in an inert atmosphere dry box and used without further purification. 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 aqueous ceric ammonium molybdate solution followed by heating. Melting points were measured with a Büchi SMP-20 melting point apparatus equipped with an Omega Model 450 AET thermocouple and are uncorrected. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^T$ (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 Bruker AM-400 (400 MHz) spectrometer and are reported in ppm from internal tetramethylsilane. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration; proton assignments). Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AM-400 (100 MHz) spectrometer and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 77.0 ppm). High resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory. Gas chromatography was performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a split-mode capillary injection system and flame ionization detector using a DB 1701 capillary column (30 m x 0.25 mm). Gas chromatography with mass spectral detection was carried out on a Hewlett-Packard 5890 Series II Gas chromatograph equipped with a Hewlett-Packard 5971 Mass Selective Detector using a DB-1701 capillary column (30 m x 0.25 mm) employing chemical ionization with methane/helium gases. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1090 Series HPLC with a diode array detector or on a Hewlett-Packard 1050 Series HPLC equipped with a variable wavelength detector using a Chiralcel OD-H column (0.46 cm x 25 cm) from Daicel.

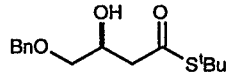
Bis(*tert*-butyloxazoline) **1** and bis(phenyloxazolinyl)pyridine **2** and the corresponding Cu(II) complexes **1a,b 2a,b** were prepared as previously described.[2] Benzyloxyacetaldehyde was prepared by the method of Garner.[3] All of the silyl ketene acetals were prepared by treating the corresponding ester with LDA and quenching the resulting enolate with TMSCl following literature procedures.[4]

Preparation of a 0.0125 M Solution of (*S*,*S*)-Bis(phenyloxazolinyl)pyridineCu(II)-hexafluoroantimonate 2b. To a 20 mL round bottom flask containing a magnetic stirring bar was added (*S*,*S*) bis(phenyloxazolinyl)pyridine (46.0 mg, 0.125 mmol), $CuCl_2$ (17.0 mg, 0.125 mmol) and $AgSbF_6$ (86.0 mg, 0.25 mmol). The flask was fitted with a serum cap and charged with dichloromethane (10 mL). The resulting suspension was stirred rapidly for 4 h and filtered through a plug of cotton to remove the precipitated AgCl. The resulting clear blue liquid was used as a 0.0125 M solution. This solution could be kept at room temperature for one week without any loss of activity or precipitation.

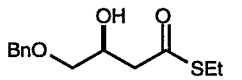


General Procedure for the Catalyzed Addition of Silyl Ketene Acetals to Benzyloxyacetaldehyde. To a 5 mL round bottom flask equipped with a magnetic stirring bar and fitted with a septum was added 200 μL (2.5 μmol, 0.5 mol%) of a 0.0125 M solution of **2b**. After cooling to -78 °C, benzyloxyacetaldehyde (74.8 mg, 0.50 mmol, 70.0 μL, d = 1.069) was added followed by a silyl ketene acetal (0.60 mmol). The resulting solution was stirred at -78 °C until the aldehyde was completely consumed, as determined by TLC (30 % ethyl acetate/hexanes). The reaction mixture was then filtered through a 1.5 x 8 cm plug of silica gel with Et_2O (50 mL). Concentration of the ether solution gave a

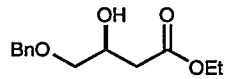
clear oil which was dissolved in THF (10 ml) and 1N HCl (2 mL). After standing at room temperature for 15 min, this solution was poured into a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). After mixing, the aqueous layer was discarded and the ether layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $MgSO_4$, filtered and concentrated to provide the hydroxy esters.



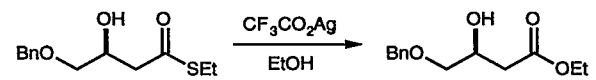
Preparation of (-)-*S*-*tert*-Butyl 4-Benzyloxy-3-hydroxybutanethioate 4a. Prepared according to the general procedure using silyl ketene acetal **3a** (122 mg, 0.60 mmol, 153 μL) to provide pure **4a** in 100% yield (141 mg, 0.50 mmol, 100%). The analytical data obtained from this material (^1H NMR, ^{13}C NMR, IR, and HRMS) were identical to that previously reported.[5] $[\alpha]_D^{rt}$ -10.9° (c 3.0, CH_2Cl_2); $[\alpha]_D^{26}$ (Lit.) +10.0° (c 1.0, $CHCl_3$) 96% ee (*R*). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (94.2:0.8:5.0 hexanes:isopropanol:ethyl acetate), 1.0 mL/min; (*R*) enantiomer t_r = 16.3 min.; (*S*) enantiomer t_r = 17.9 min.; 99% ee.



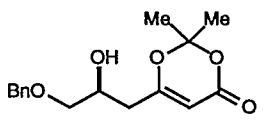
Preparation of (-)-*S*-Ethyl 4-Benzyloxy-3-hydroxybutanethioate 4b. Prepared according to the general procedure employing thioethyl silyl ketene acetal **3b** (106 mg, 0.60 mmol, 132 μL) to provide pure **4b** in 95% yield (121 mg, 0.048 mmol). The analytical data obtained from this material (^1H NMR, ^{13}C NMR, and HRMS) were identical to that previously reported.[5] $[\alpha]_D^{rt}$ -10.6° (c 4.2, CH_2Cl_2); $[\alpha]_D^{26}$ (Lit.) +11.4° (c 1.0, $CHCl_3$) 94% ee (*R*). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexanes:isopropanol), 1.0 mL/min; (*S*) enantiomer t_r = 31.6 min.; (*R*) enantiomer t_r = 35.7 min.; 98% ee.



Preparation of (-)-*S*-Ethyl 4-Benzyloxy-3-hydroxybutanoate 4c. The silyl ether was prepared according to the general procedure employing the silyl ketene acetal derived from ethyl acetate **3c** (96 mg, 0.6 mmol, 114 μL). Deprotection of the TMS ether using 1N HCl caused decomposition to the retroaldol product; thus, a fluoride induced deprotection was used. The crude oil from the reaction was dissolved in THF (5 mL) and cooled to 0 °C. TBAF (1.0 M in THF, 0.6 mmol, 0.6 mL) was added dropwise. After 15 min the solution was diluted with Et_2O (10 mL) and saturated $NaHCO_3$ (10 mL) and poured into a separatory funnel. After mixing, the aqueous layer was discarded and the organic layer washed with brine (10 mL) and dried over $MgSO_4$. Filtration and concentration gave the pure hydroxy ethyl ester in 99% yield (117 mg, 0.49 mmol). R_f 0.27 (30% ethyl acetate/hexanes); $[\alpha]_D^{rt}$ -8.8° (c 2.1, CH_2Cl_2); IR (CH_2Cl_2) 3579, 3061, 2905, 1728, 1184, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H, Ph**H**), 4.56 (s, 2H, PhC**H**$_2$), 4.24 (dq, *J* = 4.6, 6.1 Hz, 1H, CH_2**C**H**O**H**C**H_2), 4.15 (q, *J* = 7.1 Hz, 2H, CO_2**C**H_2CH$_3$), 3.51 (dd, *J* = 4.5, 9.6 Hz, 1H, BnOC**H**H**C**H**O**H**C**H_2), 3.47 (dd, *J* = 6.0, 9.6 Hz, 1H, BnOCH**H**C**H**O**H**C**H_2), 2.96 (br s, 1H, O**H**), 2.54 (d, *J* = 6.3 Hz, 2H, CHOHC**H**$_2$CO$_2$Et), 1.25 (t, *J* = 7.3 Hz, 3H, CO_2CH_2C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.8, 128.3, 127.7, 127.6, 73.2, 73.0, 67.1, 60.6, 38.2, 14.0; HRMS (EI) exact mass calcd for $C_{13}H_{18}O_4^+$ requires *m/z* 238.1205, found *m/z* 238.1206. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (94.2:0.8:5.0 hexanes:isopropanol:ethyl acetate), 1.0 mL/min; (*S*) enantiomer t_r = 24.8 min.; (*R*) enantiomer t_r = 29.3 min.; 98% ee.

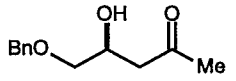


Determination of the Absolute Configuration of 4c by Correlation with 4b. The absolute stereochemistry of ethyl ester **4c** was determined by comparison to the product from treatment of ethyl thioester **4b** with silver trifluoroacetate in ethanol.[6] Thioethyl ester **4b** (98 mg, 0.35 mmol) was treated with silver trifluoroacetate (155 mg, 0.70 mmol) in anhydrous ethanol for 1 d. The solvent was removed and the resultant oil was chromatographed (30% ethyl acetate/hexane) to yield pure ethyl ester **4c** (72 mg, 0.30 mmol, 87%) as a clear oil. This material was identical in all respects (^1H NMR, ^{13}C NMR, IR, HRMS) to the material obtained from the aldol addition of benzyloxyacetaldehyde with silyl ketene acetal **3c**. $[\alpha]_D^{rt}$ -8.5° (c 2.6, CH_2Cl_2).

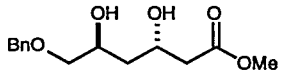


Preparation of (-)-*S*-2-hydroxy-3-benzyloxy-propyl-2,2-dimethyl-1,3-dioxin-4-one 4d. Prepared according to the general procedure except that 2mL of the 0.0125 M (0.025mmol, 5 mol%) standard solution were used. Employing the trimethylsilyl ketene acetal derived from 2,2,6 trimethyl-1,3-dioxene-4-one[7] (126 mg, 0.60 mmol) provided the pure hydroxy ethyl ester **4d** (165 mg, 0.564 mmole) in 94% yield. R_f 0.20 (50% ethyl acetate/hexanes); $[\alpha]_D^{rt}$ -15.1, $[\alpha]_{546}^{rt}$ -14.9 (c 1.3, $CHCl_3$); IR (neat) 3438, 3089, 2914, 2863, 1718, 1634, 1454, 1393 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H, Ph**H**), 5.31 (s, 1H, C(O)=C**H**CO), 4.56 (s, 2H,

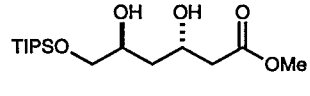
$PhCH_2O$), 4.10 (m, 1H, $BnOCH_2CHOHCH_2$), 3.51 (dd, J = 3.6, 9.4 Hz, 1H, $BnOCH_2CHOHCH_2$), 3.40 (dd, J = 6.5, 9.4 Hz, 1H, $BnOCH_2CHOHCH_2$), 2.40 (dd, J = 1.5, 5.4 Hz, 1H, $BnOCH_2CHOHCH_2$), 2.39 (dd, J = 3.1, 5.4 Hz, 1H, $BnOCH_2CHOHCH_2$), 1.66 (s, 3H, CH_3), 1.65 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 161.1, 137.6, 128.6, 128.5, 128.1, 127.9, 106.7, 95.3, 67.5, 60.4, 37.9, 25.4, 24.7; HRMS (CI, NH_3) exact mass calcd for $(C_{16}H_{20}O_5 + NH_4)^+$ requires *m/z* 310.1664, found *m/z* 310.1654 . Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexanes:isopropanol), 1.0 mL/min; (*R*) enantiomer t_r = 17.7 min.; (*S*) enantiomer t_r = 22.6 min.; 92% ee.



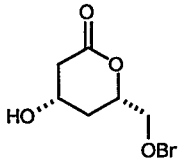
Determination of the Absolute Configuration of 4d by Correlation with the Decarboxylation Product of 4e (-)-S-4-hydroxy-5-benzyloxy-2-butanone.[8] To a solution of **4d** (100 mg, 0.340 mmol) in 1 mL toluene was added dioxane (1 mL) and H_2O (1 mL) and the resulting mixture was heated to 90°C for 2 h. After cooling to room temperature, the mixture was diluted ethyl acetate (10 mL) and poured into a separatory funnel. The aqueous layer was removed and the organic layer washed with brine, dried over Na_2SO_4, and concentrated. The resulting yellow oil was purified by flash chromatography to provide the pure ketone (68.0 mg, 0.33 mmol) 96% yield. The analytical data obtained from this material were identical in all respects to that obtained from decarboxylation of **4e**. R_f 0.24 (50% ethyl acetate/hexanes); $[\alpha]_D^{rt}$ -15.1, $[\alpha]_{546}^{rt}$ -14.9 (c 1.3, $CHCl_3$); IR (neat) 3440, 2917, 2859, 1711, 1355; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H, Ph**H**), 4.55 (AB, J = 12.1 Hz, 2H, $PhCH_2O$); 4.3 (m, 1H, $CH_2CHOHCH_2$), 3.48 (dd, J = 4.6, 9.5 Hz, 1H, C**H**OBn), 3.44 (dd, J = 6.0, 9.5 Hz, 1H, C**H**OBn); 2.68 (dd, J = 7.4, 17.2 Hz, 1H, $CHOHCHCOCH_3$), 2.62 (dd, J = 4.5, 17.2 Hz, 1H, $CHOHCHCOCH_3$), 2.18 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 137.8, 128.4, 127.8, 127.7, 73.4, 73.3, 73.1, 66.7, 46.6, 30.8; HRMS (CI, NH_3) exact mass calcd for $(C_{12}H_{16}O_3 + NH_4)^+$ requires *m/z* 226.1445 found *m/z* 226.1443.



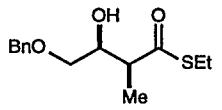
Preparation of (+)-3*S*,5*S*-Methyl-3,5-dihydroxy-6-(benzyloxy)hexanoate 4e. To a 5 mL round bottom flask containing a magnetic stirring bar was added $CuCl_2$ (7.0 mg, 0.05 mmol), (*S*,*S*)-bis(phenyloxazolinyl)pyridine (18.0 mg, 0.05 mmol) and $AgSbF_6$ (34.0 mg, 0.1 mmol). The flask was fitted with a serum cap and charged with dichloromethane (2 mL). The resulting suspension was stirred for 4 h and then filtered through a plug of cotton. The resulting clear blue solution was added over 15 min to a 20 mL round bottom flask at -78 °C containing benzyloxyacetaldehyde (1.0 g, 6.7 mmol) and the *bis* silyl ketene acetal of methyl acetoacetate (2.1 g, 8.0 mmol) in dichloromethane (2 mL). After 2 h at -78 °C, TLC indicated complete consumption of starting aldehyde (R_f 0.13, 20% ethyl acetate/hexanes) and a new higher R_f spot (R_f 0.39, 20% ethyl acetate/hexanes). The reaction mixture was then filtered through a 2.5 x 8 cm plug of silica gel with Et_2O (200 mL). Concentration of the ether solution gave a clear oil which was dissolved in THF (100 mL) and 1N HCl (10 mL). After standing at room temperature for 15 min, this solution was poured into a separatory funnel and diluted with Et_2O (100 mL). The aqueous layer was discarded and the organic layer washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL) and dried over anhydrous $MgSO_4$. Filtration and concentration of the resulting solution gave the hydroxy ketoester in 96% yield (1.7 g, 6.4 mmole). R_f 0.50 (50% ethyl acetate/hexanes); $[\alpha]_D^{rt}$ -13.7° (c 3.55, $CHCl_3$); IR (neat) 3438, 2864, 1740, 1716, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H, Ph**H**), 4.54 (s, 2H, $ArCH_2O$), 4.30 (m, 1H, $CH_2CHOHCH_2$), 3.65 (s, 3H, CO_2CH_3), 3.50 (dd, J = 4.5, 9.6 Hz, 1H, C**H**OBn), 3.41 (dd, J = 5.7, 9.6 Hz, 1H, C**H**OBn), 2.78 (d, J = 5.9 Hz, 2H, $COCH_2CO_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 168.6, 137.8, 128.5, 127.9, 127.8, 73.5, 73.1, 66.8, 52.4, 49.7, 46.3.; HRMS (CI, NH_3) exact mass calcd for $(C_{14}H_{18}O_5 + NH_4)^+$ requires *m/z* 284.1487, found *m/z* 284.1498; . This compound was subsequently reduced to the *anti* diol using tetramethylammonium acetoxyborohydride.[9] The ketoester was dissolved in CH_3CN (100 mL) and cooled to -35 °C. An acetic acid solution of tetramethylammonium acetoxyborohydride (11.8 g in 60 mL) was added to the ketoester over 30 min producing a milky white solution which was allowed to stir at -35 °C for 18 h and then quenched by the addition of a saturated solution of Rochelle salts (100 mL) and warming to room temperature. The resulting solution was diluted with ethyl acetate and made basic with a saturated solution of Na_2CO_3. The aqueous layer was discarded and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, and concentrated to give the *anti* diol in 91% yield (1.6 g, 6.1 mmol) as a white solid. m.p 61°C; R_f 0.40 (50% ethyl acetate/hexanes); $[\alpha]_D^{rt}$ +2.2; $[\alpha]_{546}^{rt}$ +6.3 (c 1.8, $CHCl_3$); IR (CH_2Cl_2) 3417 (br) 3030, 2949, 2863, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H, Ph**H**), 4.56 (s, 2H, $PhCH_2O$), 4.34 (m, 1H, $CHOHCH_2CO_2CH_3$), 4.14 (m, 1H, $CH_2CHOHCH_2$), 3.57 (s, 3H, CO_2CH_3), 3.46 (dd, J = 10.0, 4.0 Hz, 1H, C**H**OBn); 3.41 (dd, J = 9.7, 7.5 Hz, 1H, C**H**OBn); 3.01 (s, 1H, O**H**); 2.51 (d, J = 5.8 Hz, 1H, O**H**); 1.63 (m, 2H, $CH_2CO_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 173.0, 138.6, 134.7, 128.5, 127.9, 74.3, 73.4, 68.2, 66.3, 52.1, 41.3, 38.8; HRMS (CI, NH_3) exact mass calcd for $(C_{14}H_{20}O_5 + NH_4)^+$ requires *m/z* 286.1658, found *m/z* 286.1654. Product ratios were determined by HPLC with a Chiralcel OD-H column (90:10 hexanes:isopropanol), 1.0 mL/min; (3*R*,5*S*) t_r = 15.9 min.; (3*R*,5*R*) t_r = 17.9 min.; (3*S*,5*R*) t_r = 22.8 min.; (3*S*,5*S*) t_r = 29.5 min.; 15:1 *anti:syn*, 97% *anti* ee.



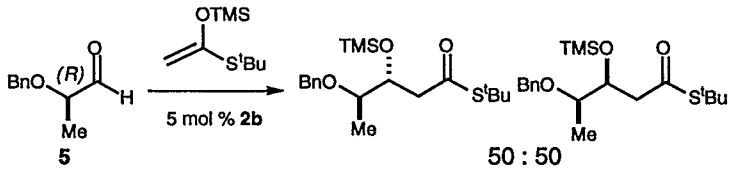
Determination of the Absolute Configuration of 4e by Conversion to (+)-3*S*, 5*S* Methyl 3,5-dihydroxy-6-(triisopropylsilyloxy)hexanoate. To a solution of diol **4e** (70 mg, 0.26 mmol) in MeOH (5 mL) was added Pd/C (20 mg) and the atmosphere was replaced with H_2 (balloon pressure). The resulting mixture was stirred for 2 h and filtered through Celite. Concentration gave a clear oil (66 mg), which was dissolved in CH_2Cl_2 (2 mL). Imidazole (20 mg, 0.30 mmol, 1.2 equiv.), DMAP (4 mg, 0.03 mmol, 0.1 equiv.), and TIPS-Cl (52 mg, 57 µL, 0.27 mmol, 1.1 equiv.) were added consecutively. The resulting solution was stirred for 4 h, diluted with CH_2Cl_2, and transferred to a separatory funnel containing 5 mL of a saturated NH_4Cl. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were dried over Na_2SO_4 and concentrated. The resulting oil was purified by flash chromatography to provide the pure silyl ether (79 mg, 0.24 mmol, 96% yield). The analytical data obtained from this material were identical to that previously reported.[7] R_f 0.40 (50% ethyl acetate/hexanes); $[\alpha]_D^{rt}$ +3.6, $[\alpha]_{546}^{rt}$ +4.5 (c 1.8, $CHCl_3$); IR (neat) 3440, 2939, 2866, 1733, 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (m, 1H, $CHOHCH_2CO_2CH_3$), 3.97 (m, 1H, $TIPSOCH_2CHOHCH_2$), 3.72 (dd, J = 4.1, 9.9 Hz, 1H, **CH**OTIPS), 3.71 (s, 3H, CO_2CH_3), 3.55 (dd, J = 7.5, 9.7 Hz, 1H, **CH**OTIPS), 3.02 (br s , 1H, **OH**), 2.53 (m, 2H, $CH_2CO_2CH_3$), 1.60 (m, 2H, $CHOHCH_2CHOH$), 1.06 (m, 21 H, OTIPS); ^{13}C NMR (100 MHz, $CDCl_3$) 173.1, 69.2, 67.5, 65.5, 51.8, 41.5, 38.6, 17.9, 11.9; HRMS (CI, NH_3) exact mass calcd for $(C_{16}H_{34}O_5Si + NH_4)^+$ requires *m/z* 352.2516, found m/z 352.2519.



Determination of the the Relative Configuration of 4e by Conversion to (+)-4*S*, 6*S* 4-hydroxy-6-[(benzyloxy)methyl)-2H-tetrahydropyran-2-one. To a stirring solution of diol **4e** (100 mg, 0.380 mmol) in MeOH (2 mL) was added 1N NaOH (1 mL). After stirring at room temperature for 1 h the reaction was quenched with 1N HCl (1.5 mL). The resulting solution was diluted with ethyl acetate and transferred to a separatory funnel. The organic layer was removed and the aqueous layer was extracted ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude acid as a clear oil (110 mg). This oil was dissolved in toluene and heated to 80°C for 12 h and then cooled to room temperature. This solution was concentrated and the resultant oil was purified by flash chromatography to provide the pure lactone (81 mg, 0.34 mmol 90% yield). The ^1H NMR data obtained from this material confirmed the presence of the *anti* diol in **4e**. R_f 0.20 (50% ethyl acetate/hexanes); $[\alpha]_D^{rt}$ +17.1, $[\alpha]_{546}^{rt}$ +19.4 (c 1.04, $CHCl_3$); IR (neat) 3439, 2926, 2862, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H, Ph**H**); 4.55 (s, 2H, $ArCH_2$); 4.40 (m, 1H, CH_2CHOCH_2OBn); 4.21 (m, 1H, **CH**OH); 3.64 (m, 2H, CH_2OBn); 2.82 (ddd, J = 1.3, 5.6, 17.2 Hz, 1H, $CH_{eq}CO$), 2.48 (dd, J = 7.3, 17.2 Hz, 1H, $CH_{ax}CO$); 2.24 (dtd, J = 1.3, 4.2, 13.8 Hz, 1H, $CHOHCH_{eq}CHOCH_2OBn$); 1.77 (dtd, J = 1.9, 8.5, 13.8 Hz, 1H, $CHOHCH_{ax}CHOCH_2OBn$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 137.4; 128.5; 128.0; 127.8; 76.23; 73.7; 71.6; 63.4; 39.4; 33.9; HRMS (CI, NH_3) exact mass calcd for $(C_{13}H_{16}O_4 + NH_4)^+$ requires m/z 254.1380, found m/z 254.1392.

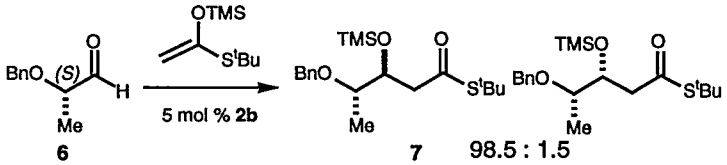


Preparation of (+)-2*S*,3*S*-Ethyl 4-Benzyloxy-3-hydroxy-2-methylbutanethioate 4f. Prepared according to the general procedure employing propionate silyl ketene acetal **3f** as 95:5 mixture of *E:Z* isomers (114 mg, 0.6 mmol, 130 µL), except that 2 mL (50 µmol, 10 mol%) of a 0.025 M solution of **2b** was used (this more concentrated catalyst solution was prepared analagously to above). Hydroxy thioethyl ester **4f** was obtained in 90% yield (121 mg, 0.45 mmole) as a clear oil. The analytical data obtained from this material (^1H NMR, ^{13}C NMR, and HRMS) were identical to that previously reported.[5] $[\alpha]_D^{rt}$ +41.1° (c 3.6, CH_2Cl_2); $[\alpha]_D^{26}$ (Lit.) -3.3° (c 1.0, $CHCl_3$) *syn:anti* 72:28, 90% syn ee (2*S*, 3*R*). Product ratios were determined by HPLC with a Chiralcel OD-H column (95.5:1.5:3 hexanes:isopropanol:ethyl acetate), 1.0 mL/min; (2*S*,3*S*) enantiomer t_r = 12.6 min.; (2*R*,3*R*) enantiomer t_r = 14.3 min.; (2*R*,3*S*) enantiomer t_r = 15.2 min.; (2*S*,3*R*) enantiomer t_r = 17.5 min.; 97:3 *syn:anti*, 97% syn ee.

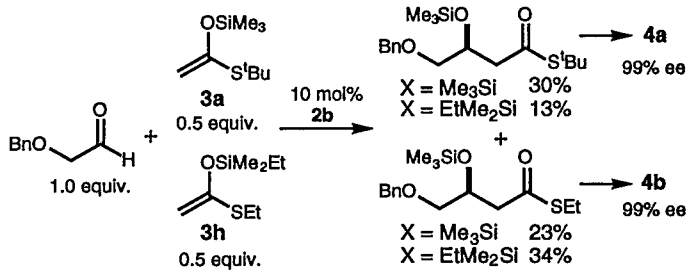


Addition of Silyl Ketene Acetal 3a to (*R*)-2-Benzyloxypropionaldehyde (5). To a 10 mL round bottom flask equipped with a magnetic stirring bar and fitted with a septum was added 2 mL (25 µmol, 5 mol%) of a 0.0125 M solution of **2b**. After cooling to -78 °C, (*R*)-2-benzyloxyproprionaldehyde[10] (82.2 mg, 0.50 mmol) was added followed by silyl ketene acetal **3a** (122 mg, 0.60 mmol, 153 µL). The resulting solution was stirred at -78 °C for 12 h at which point the aldehyde was completely consumed, as determined by TLC (30 % ethyl acetate/hexanes). The reaction mixture was then filtered through a 1.5 x 8 cm plug of silica gel with Et_2O (50 mL). Concentration of the ether solution gave the

products as the silyl ethers. For analytical purposes the silyl ether was removed by treating the resultant oil with THF (10 ml) and 1N HCl (2 mL). After standing at room temperature for 15 min, this solution was poured into a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). After mixing, the aqueous layer was discarded and the ether layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $MgSO_4$, filtered and concentrated to provide the hydoxy esters. The analytical data obtained from this material (^1H NMR) were identical to that previously reported.[11] The diastereomer ratio was determined by HPLC with a Chiralcel OD-H column (95:5 hexanes:ethyl acetate), 1.0 mL/min; (3*S*,4*R*) isomer (Felkin) t_r = 12.6 min.; (3*R*,4*R*) isomer (Chelation) t_r = 15.1 min.; 50:50 Chelation:Felkin.



Addition of Silyl Ketene Acetal 3a to (*S*)-2-Benzyloxypropionaldehyde (6). Performed as for the (*R*)-aldehyde (see above) except in this case (*S*)-2-benzyloxyproprionaldehyde[10] (82.2 mg, 0.50 mmol) was used and the reaction was complete within 2 h at -78° C. The analytical data obtained from this material (^1H NMR) were identical to that previously reported.[11] The diastereomer ratio was determined by HPLC with a Chiralcel OD-H column (95:5 hexanes:ethyl acetate), 1.0 mL/min; (3*R*,4*S*) isomer (Felkin) t_r = 14.4 min.; (3*S*,4*S*) isomer (Chelation) t_r = 16.5 min.; 98.5:1.5 Chelation:Felkin.

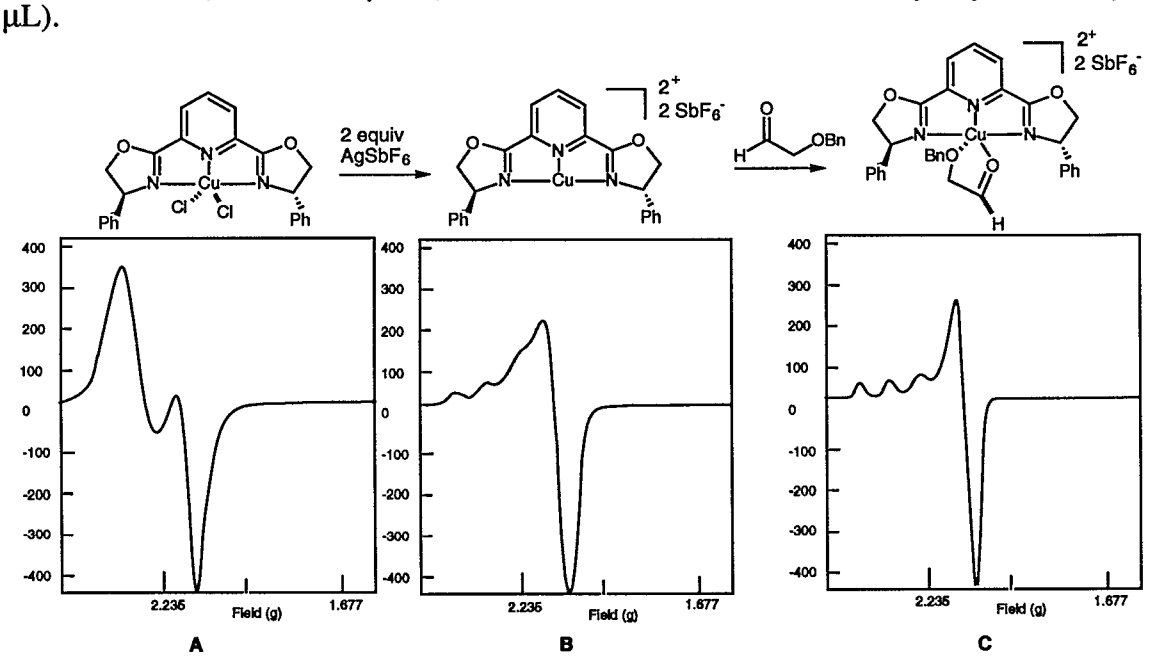


Crossover Experiments with Doubly-Labelled Silyl Ketene Acetals. Silyl ketene acetals **3a** (51.1 mg, 0.50 mmol) and **3h** (47.6 mg, 0.50 mmol) were weighed into a 10 ml round bottom flask equipped with a magnetic stirring bar. The flask was fitted with a septum and CH_2Cl_2 (1 mL) was added followed by benzyloxyacetaldehyde (74.8 mg, 0.50 mmol, 70.0 µL). This solution was cooled to -78 °C and 2 mL (50 µmol, 10 mol%) of a 0.025 M solution of **2b** (this more concentrated catalyst solution was prepared analagously to above) at -78 °C was added rapidly via cannula. The resulting solution was stirred at -78 °C for 30 min at which point the silyl ketene acetals were completely consumed, as determined by TLC (30% ethyl acetate/hexanes). The reaction mixture was then filtered through a 1.5 x 8 cm plug of silica gel with Et_2O (50 mL). Concentration of the ether solution gave the products as the silyl ethers. The product ratios were determined by GC with a DB 1701 column (220 °C, 10 psi) using a flame ionization detector and the identity of the peaks was confirmed by GCMS with detection of the MH^+ ion for each compound: SEt/OSiMe$_3$ t_r = 6.1 min, 23%, MH^+ = 327; S*t*Bu/OSiMe$_3$ t_r = 6.7 min, 30%, MH^+ = 355; SEt/OH t_r = 7.0 min, <1%, MH^+ = 255; S*t*Bu/OH t_r = 7.7 min, <1%, MH^+ = 283; SEt/OSiMe$_2$Et t_r = 8.0 min, 34%, MH^+ = 341; S*t*Bu/OSiMe$_2$Et t_r = 8.7 min, 13%, MH^+ = 369. To determine enantiomeric excess the silyl ethers were cleaved by treatment with THF (10 ml) and 1N HCl (2 mL). After standing at room temperature for 15 min, this solution was poured into a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). After mixing, the aqueous layer was discarded and the ether layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to provide the hydoxy esters. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column: **4a** (94.2:0.8:5.0 hexanes:isopropanol:ethyl acetate), 1.0 mL/min; (*R*) enantiomer t_r = 16.3 min.; (*S*) enantiomer t_r = 17.9 min.; 99% ee; **4b** (98:2 hexanes:isopropanol), 1.0 mL/min; (*S*) enantiomer t_r = 31.6 min.; (*R*) enantiomer t_r = 35.7 min.; 99% ee.

To further elucidate the mechanism of silyl scrambling two control experiments were performed. In the first experiment, genuine samples of the trimethylsilyl ether of **4a** and the dimethylethylsilyl ether of **4b** were prepared and subjected to the same conditions as above (10 mol% catalyst **2b** in CH_2Cl_2, -78 °C, 30 min). After filtration through silica gel, the material was analyzed by GC with a DB 1701 column (220 °C, 10 psi) and only the starting silyl ethers were observed (i.e. the trimethylsilyl ether of **4b** and the dimethylethylsilyl ether of **4a** were not observed). This result indicates the catalyst is not effecting exchange of the silyl groups after formation of the product. In the second experiment, silyl ketene acetals **3a** and **3h** were subjected to the same conditions as above (10 mol% catalyst **2b** in CD_2Cl_2, -78 °C, 30 min) in the *absence of any aldehyde.* The volatile components were then vacuum-transferred away from the catalyst at the low temperature. ^1H NMR analysis of the resultant material showed only **3a** and **3h** (**3b** and the dimethylethylsilyl ketene acetal of *tert-*

butylthioacetate were not observed) indicating that the silyl ketene acetals are not subject to silyl exchange by the catalyst. These two experiments eliminate the starting silyl ketene acetals and the product silyl ethers from a role in the silyl exchange and indicate that silyl crossover occurs during the course of the reaction.

ESR Spectra of the (*S*,*S*)-Bis(phenyloxazolinyl)pyridine-Cu(II)-complexes. Continuous wave electron spin resonance (ESR) spectroscopy was performed at 132 K on a Bruker ESP 300 E spectrometer operating at 9.4 GHz. The magnetic field was measured with a Bruker NMR gaussmeter (ER 083C) and the spectrometer frequency measured with a Hewlett-Packard 5350B frequency counter. **A**: (*S*,*S*)-Bis(phenyloxazolinyl)pyridine-Cu(II)-chloride, A suspension of $CuCl_2$ (7.0 mg, 0.05 mmol) and (*S*,*S*)-bis(phenyloxazolinyl)pyridine (18.0 mg, 0.05 mmol) in dichloromethane (2 mL) was vigorously stirred for 4h yielding a bright yellow solid. **B**: (*S*,*S*)-Bis(phenyloxazolinyl)pyridine-Cu(II)-hexafluoroantimonate (**2b**), A 0.0125 M solution of **2b** was used (see above). **C**: (*S*,*S*)-Bis(phenyloxazolinyl)pyridine-Cu(II)-hexafluoroantimonate benzyloxyacetaldehyde complex, A 0.0125 M solution of **2b** (1 mL, 12.5 μmol) was treated with an excess of benzyloxyacetaldehyde (9.4 mg, 62,5 μmol, 9 μL).



$g_{\perp} = 2.09$

$g_{\parallel} = 2.28$

$A_{\parallel} = 180.2$ G

$g_{\parallel} / A_{\parallel} = 126 \times 10^4$

References and Notes

1) Perrin, D. D. and Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed., Pregamon Press, Oxford, 1988.

2) (a) For the preparation of ligand **1** see: Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726-8. (b) For the peparation of ligand **2** see: Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics*, **1991**, *10*, 500-8. (c) For the preparation of the the Cu(II) complexes of both ligand systems see: Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798-800.

3) Garner, P.; Park, J. M. *Syn. Commun.* **1987**, *17*, 189-93.

4) (a) **3a** and **3b**: Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 297-300. (b) **3c**: Kita, Y.; Segawa, J.; Yasuda, J. H.; Tamura, Y. *J. Chem. Soc., Perkin I* **1982**, 1099-1104. (c) **3d**: Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, 42, 839-45. (d) **3e**: Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688-93. (e) **3f**: Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Solastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893-909.

5) Mikami, K.; Matsukawa, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 4077-8.

6) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *Tetrahedron Lett.* **1983**, *46*, 5143-5146.

7) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem Pharm Bull.* **1994**, *42*, 839-45.

8) Sato, M.; Sunami.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435-44.

9) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741-50.

10) Takai, K; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247-51.

11) Gennari, C. and Cozzi, P. G. *Tetrahedron* **1988**, *44*, 5965-74.