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A New Chiral Titanium Species for the Ring Opening Reactions of Meso Epoxides

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Abstract: The synthesis of a new chiral ligand **1** based on the conformationally defined 1,7-dioxaspiro[5.5]undecane ring system is reported. Generation of the corresponding ligand **1**-Ti(OiPr)$_4$ complex as a catalyst and its use in the enantioselective ring opening reaction of cyclohexene oxide with $TMSN_3$ is described. © 1997 Elsevier Science Ltd.

INTRODUCTION

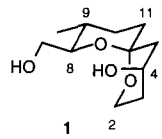
Epoxides are versatile intermediates in organic synthesis. They are easily prepared, are susceptible to reaction by a large number of reagents, and they frequently react with high levels of regio- and stereoselectivity. As such, the ring opening reactions of non-racemic epoxides, with subsequent synthetic manipulation, allows access to a wide variety of target molecules in enantiomerically pure form. Ready access to such substrates has been enhanced by the seminal discovery of Sharpless[1] involving the asymmetric epoxidation of allylic alcohols. In contrast, the enantioselective epoxidation of isolated olefins is only just developing as a viable synthetic process.[2]

An alternate approach to non-racemic epoxide derivatives is the enantioselective ring opening reaction of a meso epoxide with an achiral nucleophile in the presence of a chiral Lewis acid.[3,4] Desymmetrization reactions of this type are particularly useful in that they provide a mechanism by which to generate two stereogenic centers in a single operation. One of the most successful applications of this strategy has been the addition of trialkylsilyl azides to simple meso epoxides. Recently, Nugent[5] and Jacobsen[6] have reported highly enantioselective processes of this type using chiral zirconium and chromium based catalyst systems respectively.

Organotitanium species are known to promote the addition of nucleophiles to epoxides under mild conditions.[7] The advantage of using titanium in this application is its high abundance, the possibility of adjusting its reactivity and selectivity by modifying ligands, and its relative inertness toward redox processes. In addition, titanium species generally exhibit low toxicity relative to some of the other metals that have been used in this application. Unfortunately, though titanium is able to serve effectively as a Lewis acid catalyst for these transformations, modest enantioselectivities have generally been reported in the presence of chiral titanium species. One notable exception is the work of Oguni whereby titanium complexes of tartrate esters were shown to promote the ring opening reaction of cyclohexene oxide with $TMSN_3$ in up to 63% ee.[8]

As part of an ongoing program aimed at the development of new reagents and catalysts for use in enantioselective organic transformations, we are exploring the properties of 1,7-dioxaspiro[5.5]undecane based systems for use as chiral ligands in the intermolecular transfer of asymmetry. Toward this end, we are investigating the use of these systems as chiral modifiers for the asymmetric ring opening reactions of meso epoxides. Herein, we describe the synthesis and use of one such system, the 4S, 6S, 8S, 9R-ligand **1** (*Figure 1*), for the preparation of chiral titanium complexes, and report our progress in the use of these complexes as catalysts for the ring opening reaction of meso epoxides with trimethylsilyl azide.

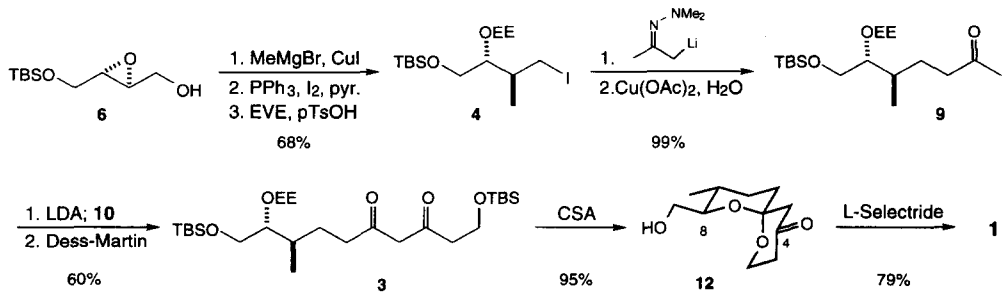
Figure 1



RESULTS AND DISCUSSION

The enantioselective synthesis of ligand **1** was achieved via sequential homologation of acetone dimethylhydrazone **2**,[9] with subsequent cyclization of the resulting linear intermediate **3** to provide the basic ligand framework. Toward this end, iodide **4** was prepared in 4 steps from monoprotected 2-butene-1,4-diol **5**. Thus, Sharpless asymmetric epoxidation of the olefin **5** (L-(+)-DET, $Ti(OiPr)_4$, tBuOOH,)[10] proceeded with high levels of enantioselectivity to give 2S, 3S-epoxide **6** in 80% yield. Subsequent addition of methylmagnesium bromide in the presence of copper(I) iodide proceeded regioselectively to give the desired 1,3-diol **7**. From here, selective iodination of the primary alcohol (**8**), followed by protection of the secondary alcohol as its ethoxyethyl ether afforded iodide **4** (*Scheme 1*).[11] Treatment of this intermediate **4** with lithiated acetone dimethylhydrazone gave a mixture of hydrazone diastereomers that were not separated, but rather treated directly with copper(II) acetate in aqueous THF to provide the corresponding ketone **9**. Lithiation of this intermediate with LDA and subsequent treatment with 3-silyloxypropanal **10**[12] provided the β-hydroxyketone **11** which was subsequently oxidized to the corresponding diketone **3** with Dess-Martin periodinane.[13] Deprotection of the hydroxyl functions in the presence of camphorsulfonic acid occurred with concomitant spirocyclization to provide the spiroketal **12** as a single isomer. Here, relative stereochemical control is provided by the hydroxymethyl group at C-8.[14] Stereoselective reduction of the C-4 ketone then provided 4S, 6S, 8S, 9R-ligand **1**.[15]

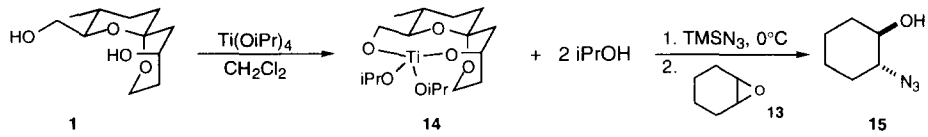
Scheme 1



In this sequence, the absolute configuration of the ligand is derived from the asymmetric epoxidation protocol (SAE) developed by Sharpless.[1] Epoxide **6** can thus be prepared in >95 %ee using the stoichiometric SAE reaction as determined by ^{19}F NMR on the corresponding Mosher ester.[16] More conveniently, this transformation (**5** → **6**) is conducted using the catalytic SAE protocol, though the optical purity of the product **6** is slightly lower (*ca.* 90% ee).[1b] In any event, ligand **1** can be obtained in optically pure form (>99 %ee[17]) by a single recrystallisation from hexane to remove the highly crystalline racemate.

We first investigated the reaction of cyclohexene oxide **13** with trimethylsilyl azide using a stoichiometric amount of the ligand **1**-Ti(OiPr)$_4$ complex **14** (*Scheme 2*).[18] Typically, complex **14** was generated *in situ* by combining equimolar amounts of the ligand **1** and Ti(OiPr)$_4$. Trimethylsilyl azide was then added, and the resulting mixture aged at 0°C for a specific time period (*Table 1*). Subsequent addition of cyclohexene oxide provided, cleanly, the *trans*-2-azido alcohol **15**. Enantiomeric excesses were determined by capillary GC analysis of the corresponding silyl ethers using a chiral Cyclodex-B column. Absolute configurations are assigned in analogy to those reported by Jacobsen for this system by comparison of the relative retention times of individual enantiomers with those reported.[6]

Scheme 2



1 **14** **13** **15**

For the ring opening reaction of cyclohexene oxide (*Table 1*), we found that the enantioselectivity of this process varied significantly with reaction temperature (runs **B**, **E**), as well as with the aging period of the chiral titanium complex **14** with $TMSN_3$ (runs **A** - **D**). This dependence on aging presumably reflects the formation of an intermediate titanium azide which is thought to be the active species in the epoxide opening.[19] Best results (run **A**) were obtained when complex **14** was aged with $TMSN_3$ for 24 hours at 0°C, followed by addition of cyclohexene oxide at -10°C. Under these conditions the 1R, 2R azidohydrin **15** was produced in 74% ee.

Table 1: Enantioselective Cleavage of Cyclohexene Oxide with $TMSN_3$ Catalyzed by **14**

run	aging time ($TMSN_3$)	reaction temperature	% conversion[a]	ee (%)[b]	configuration
A	24 hour	-10°C	58	74% ee	1R, 2R
B	1 hour	-10°C	64	62% ee	1R, 2R
C	30 min	-10°C	62	59% ee	1R, 2R
D	none	-10°C	49	56% ee	1R, 2R
E	1 hour	23°C	75	18% ee	1R, 2R

[a] Determined by gas chromatography using tetradecane as an internal quantitative standard.
[b] Enantioselectivities were determined by capillary GC of the corresponding 1-azido-2-(trimethylsilyl-oxy)cyclohexane using a chiral Cyclodex B column.

In these reactions, the quality of Ti(OiPr)$_4$ used in the preparation of complex **14** has a distinct effect on the selectivity of the ring opening reaction. In cases where this reagent is not distilled prior to use, the aging period of complex **14** with $TMSN_3$ has a pronounced influence on both the enantioselectivity and absolute

configuration of the azidohydrin product in reactions conducted at -10°C. Thus, while at aging periods of 1 hour the purity of $Ti(OiPr)_4$ appears to be of little consequence, the 1R,2R azidohydrin being produced in 57% ee, an aging time of <30 min results in the formation of 1S,2S azidohydrin **15** in 17% ee. This latter result is in contrast to that obtained using freshly distilled $Ti(OiPr)_4$ (*Table 1*, run **A**), whereby the R,R antipode of **15** is formed in 56% ee in the absence of aging.

We have demonstrated the ability of ligand **1**-$Ti(OiPr)_4$ complexes to promote the ring opening reaction of meso epoxides with trimethylsilyl azide. Though the enantioselectivities observed in these examples vary from modest to good, these early results demonstrate the feasibility of using a modified 1,7-dioxaspiro[5.5]undecane skeleton as a chiral modifier for the intermolecular transfer of asymmetry. We are currently exploring the use of ligand **1**-metal complexes, and related catalyst systems, in the interest of improving the enantioselectivity of this ring opening reaction and developing a catalytic process.

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EXPERIMENTAL

General Methods:

All air sensitive reactions were performed in oven dried glassware under an atmosphere of argon. Reaction solvents were dried over CaH_2 (benzene, dichloromethane) or sodium/benzophenone ketyl (diethyl ether, tetrahydrofuran) and were distilled just prior to use. $Ti(OiPr)_4$ was distilled under high vacuum prior to use. Analytical thin layer chromatography was performed on EM silica gel 60F glass plates (0.25mm). Flash column chromatography was performed using EM silica gel 60 (230-400 mesh). ^1H NMR spectra were recorded on a Bruker AC-300 spectrometer. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual $CHCl_3$ as the internal standard (δ 7.27 ppm). ^{13}C NMR spectra were recorded on a Bruker AC-300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual $CHCl_3$ as the internal standard (δ 77.0 ppm). IR spectra were obtained with a Mattson Cygnus 25 instrument. Mass spectra were obtained on a VG ZAB-HF high resolution instrument by the University of Iowa Mass Spectrometry Laboratory. Elemental analyses were conducted by Robertson Laboratories, Inc.; Madison, NJ or Quantitative Technologies, Inc.; Whitehouse, NJ. Gas chromatographic (GC) analyses were carried out on a Varian 3400 CX instrument equipped with FID detectors and 30M AT-WAX (Altech) and chiral Cyclodex B (30mm id x 0.25m film; J&W Scientific) columns.

Experimental Procedures:

(2S,3S)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,3-epoxy-1-butanol (6): To a stirred suspension of powdered 4Å molecular sieves (3 g) in 500 mL CH_2Cl_2 at -20° C was added freshly distilled titanium (IV) isopropoxide (2.20 mL, 1.39 mmol) and L-(+)-diethyl tartrate (1.52 mL, 8.88 mmol). *t*-Butylhydroperoxide (20 mL, 5-6 M in decane), predried over 4Å molecular sieves, was then added dropwise. Upon complete addition of the hydroperoxide, the reaction mixture was stirred for 35 minutes and a solution of the corresponding monosilylated *trans*-2-butene-1,4-diol **5** (10.0 g, 49.4 mmol) in 50 mL CH_2Cl_2 added dropwise. The reaction mixture was then warmed to 0° C and stirred overnight. The resulting mixture was poured into a freshly prepared, stirred solution of ferrous sulfate (17.0 g, 61.1 mmol) and tartaric acid (5.2 g, 34.6 mmol) in 52 mL

of water, which had been cooled to 0° C. The ice bath was removed and stirring was continued for 10 minutes. After this time the layers were separated and the aqueous back extracted with ether (2x). The combined organic extracts were then treated with 7 mL of a precooled solution of 30% NaOH (w/v) in brine and stirred vigorously for 1 hour at 0° C. The layers were separated, the aqueous layer was extracted with ether (2x), and the combined extracts dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2; hexane: ethyl acetate, 4:1) provided 8.60 g (80%) of the epoxide as a colorless liquid. ^1H NMR ($CDCl_3$): δ 3.94-3.82 (2H, m), 3.69-3.55 (2H, m), 3.08 (2H, m), 2.30 (1H, t), 0.85 (9H, s), 0.03 (3H, s), 0.02 (3H, s). ^{13}C NMR ($CDCl_3$): δ 62.63, 61.31, 55.87, 55.80, 25.78, 18.26, -5.43, -5.41. IR (film): 3446 (s), 2955 (vs), 1474 (s). HRMS (FAB): Calcd for $C_{10}H_{22}O_3Si$ ($[M+Li]^+$): 225.1498, found: 225.1483.

(2R,3R)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methyl-1,3-butanediol (7): To a suspension of CuI (1.69 g. 8.87 mmol) in 300 mL ether/THF (5:1) at -8°C was added methylmagnesium bromide in ether (30 mL of a 3.0 M solution). The resulting greenish-grey precipitate was cooled to -40 °C and a solution of the epoxide (6.85 g, 29.6 mmol) in 23 mL ether was added dropwise. This mixture was stirred for 2 hr at -40°C then warmed to -20 °C and stirred overnight. The reaction was quenched while warming to room temperature by the careful addition of aqueous NH_4Cl (pH 8-9) until the precipitates turned grey and gas evolution was no longer in evidence. The solids were removed by filtration, rinsed with ethyl acetate, and the combined filtrates treated with additional NH_4Cl (pH 8-9) until the aqueous washes were no longer blue in color. These aqueous portions were then saturated with NaCl and back extracted with ethyl acetate (3x). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; hexane:ether, 1:2) afforded 6.06 g (87%) of the diol as a colorless, viscous oil. ^1H NMR ($CDCl_3$): δ 3.70 (3H, m), 3.54 (2H, m), 3.08, 1H, br t, J = 5.7 Hz; OH), 2.87 (1H, br d, J = 3.1 Hz; OH), 1.73 (1H, m), 0.91 (9H, s), 0.88 (3H, d, J = 7.0 Hz), 0.09 (6H, s). ^{13}C NMR ($CDCl_3$): δ 76.80, 67.35, 65.63, 37.40, 25.86, 18.28, 13.54, -5.36, -5.42. IR (film): 3359, 2927, 1466 cm^{-1} Anal. Calcd for $C_{11}H_{26}O_3Si$: C, 56.36%; H, 11.18%. Found: C, 56.12%; H, 11.25%.

(2R,3R)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-iodo-2-methyl-3-butanol (8): To a solution of the diol (4.89 g, 20.9 mmol) in 400mL dry benzene were added sequentially triphenylphosphine (8.2 g, 31.3 mmol), pyridine (5.2 mL, 64.7 mmol), and iodine (7.4 g, 29.2 mmol). The resulting orange, heterogeneous mixture was refluxed 1 hr, then cooled to room temperature and filtered through celite. The filtrate was concentrated *in vacuo*, then rediluted with hexane/ether (1:1), and stored at -10°C (freezer) overnight. After a second filtration, the solution was dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. Purification via flash chromatography (SiO_2; hexane:ethyl acetate, 20:1) resulted in the isolation of 6.00g (84%) of the iodide as a colorless liquid. ^1H NMR ($CDCl_3$): δ 3.75 (1H, dd, J = 9.9, 3.2 Hz), 3.54 (1H, m), 3.45 (2H, m), 3.42 (1H, m), 2.52 (1H, d, J = 4.4 Hz; OH), 1.48 (1H, m), 0.96 (3H, d, J = 6.6 Hz), 0.91 (9H, s), 0.09 (6H, s). ^{13}C NMR ($CDCl_3$): δ 74.55, 64.91, 37.31, 25.86, 18.25, 17.19, 14.18, -5.37, -5.45. IR (film): 3470, 2910, 1464 cm^{-1}. HRMS (CI): Calcd for $C_{11}H_{25}O_2SiI$ ($[M+H]^+$): 345.0748, found: 345.0740.

(2R,3R)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[(1-ethoxyethyl)-oxy]-1-iodo-2-methyl-3-butane (4): To a solution of the alcohol (6.00 g, 17.4 mmol) in 170 mL ether were added ethyl vinyl ether (3.3 mL, 34.8 mmol) and a catalytic amount of p-toluenesulfonic acid (*ca.* 0.2 g). After 4h at room temperature, the reaction mixture was transferred to a separatory funnel, washed sequentially with saturated $NaHCO_3$, water, and brine, and the organics dried over $MgSO_4$. Upon concentration, the residue was purified by flash chromatography (SiO_2; hexane:ethyl acetate, 20:1) to give 7.03g (93%) of the ethoxyethyl protected alcohol as

a clear, colorless liquid. ^{1}H NMR ($CDCl_3$): 1:1 mixture of diastereomers. δ 4.85 (0.5H, q, J = 5.3 Hz),4.79 (0.5H, q, J = 5.3 Hz), 3.80 - 3.25 (7H, m), 1.88 (1H, m), 1.33 (1.5H, d, J = 5.2 Hz), 1.32 (1.5H, d, J = 5.2 Hz), 1.22 (1.5H, t, J = 7.0 Hz), 1.21 (1.5H, t, J = 7.0 Hz), 1.06 (1.5H, d, J = 6.7 Hz), 1.03 (1.5H, d, J = 6.8 Hz), 0.90 (9H, s), 0.07 (6H, s). IR (film): 2920, 1458, 1374, 1248, 1099 cm^{-1} HRMS (CI): Calcd for $C_{15}H_{33}O_3SiI$ ($[M+H]^+$): 417.1245, found: 417.1312.

(5R,6R)-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-[(1-ethoxyethyl)-oxy]-5-methyl-2-heptanone (9): To a solution of acetone dimethylhydrazone (5.50 g, 54.9 mmol) in 200 mL THF at -78 °C was added nBuLi (22.0 mL of a 2.5 M solution in hexanes). The reaction mixture was warmed to -10° and allowed to stand overnight (freezer). The resulting yellow heterogeneous mixture was cooled back to -78 °C, and the iodide **4** (17.58 g, 42.22 mmol) in 20 mL THF introduced dropwise via cannula. Upon complete addition, the reaction mixture was allowed to warm to slowly to room temperature overnight. The reaction was quenched by addition of saturated, aqueous ammonium chloride, and partitioned between ether and water. The aqueous layer was extracted with ether (2x), and the combined organics washed with brine, then dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude dimethylhydrazone that was used without further purification.

To a solution of cupric acetate (21.1 g, 106 mmol) in 600 mL water/450 mL THF was added over 15 minutes the crude dimethylhydrazone (~42.2 mmol), prepared as above, in 150 mL THF. Over the course of the addition, the original blue color darkened to an olive green. The resulting solution was stirred overnight and, ultimately, a rust colored precipitate deposited on the sides of the flask. The reaction mixture was concentrated *in vacuo*, then partitioned between ethyl acetate and a saturated solution of ammonium chloride (pH 8-9). The organics were washed sequentially with saturated, aqueous ammonium chloride (pH 8-9), water and brine, then dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; hexane: ethyl acetate, 9:1) afforded 14.51 g (99%) of the ketone as a yellow liquid. ^{1}H NMR ($CDCl_3$): 1:1 mixture of diastereomers. δ 4.82 (0.5H, q, J=5.3 Hz), 4.68 (0.5H, 5.3 Hz), 3.69-3.34 (5H, m), 2.42 (2H, m), 2.10 (3H, s), 1.73 (2H, m), 1.40 (1H, m), 1.25 (3H, dd, J=1.8, 5.3 Hz), 1.14 (3H, t, J= 7.1 Hz), 0.85 (4H, m), 0.84 (9H, s), 0.01 (6H, s). IR (film): 2956 (vs), 1718 (vs) cm^{-1}. HRMS (FAB): Calcd for $C_{18}H_{38}O_4Si$ ($[M+Na]^+$): 369.2437, found: 369.2458.

(8R,9R)-1,10-bis-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-9-[(1-ethoxyethyl)-oxy]-3-hydroxy-8-methyl-5-decanone (11): A solution of lithium diisopropylamide (16.2 mmol) in 70 mL THF was prepared at -78 °C from diisopropylamine (2.3 mL, 18 mmol) and nBuLi (7.0 mL of a 2.3 M solution in hexanes). A solution of the ketone (4.67 g, 13.5 mmol) in 20 mL THF was added dropwise, and the resulting mixture stirred for 50 minutes. 3-Silyloxypropanal (6.07 g, 32.2 mmol) in 20 mL THF was added dropwise via cannula. After 30 minutes, the reaction mixture was quenched with saturated aqueous ammonium chloride, warmed to room temperature and diluted with ether. The organics were washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification via flash chromatography (SiO_2; hexane:ethyl acetate, 9:1) afforded 6.06 g (84%) of the β-hydroxy ketone as a complex mixture of diastereomers. ^{1}H NMR ($CDCl_3$): δ 4.83 (0.5H, q, J=5.2 Hz), 4.69 (0.5H, q, J=5.2 Hz), 4.23 (1H, m), 3.85-3.35 (8H, m), 2.60-2.30 (4H, m), 1.80-1.60 (4H, m), 1.26 (3H, dd, J=1.9, 5.2 Hz), 1.16 (3H, t, J=7.0 Hz), 0.88 (3H, m), 0.87 (18H, s), (0.02 12H, s). IR (film): 3556 (m), 2959 (vs), 1710 (s) cm^{-1} HRMS (FAB): Calcd for $C_{27}H_{58}O_6Si_2$ ($[M+Na]^+$): 555.3670, found: 557.3686.

(8R,9R)-1,10-bis-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-9-[(1-ethoxyethyl)-oxy]-8-methyl-3,5-decanedione (3): To a solution of the β-hydroxy ketone (1.3 g, 2.43 mmol) in 16 mL CH_2Cl_2 was added Dess-

Martin periodinane (1.45 g, 3.24 mmol), and the resulting heterogeneous mixture stirred at room temperature. After 4 hours, the reaction mixture was diluted with ether and stirred with saturated, aqueous $NaHCO_3$ and $Na_2S_2O_3$ (3.0 g, 19 mmol) until no solid remained. The organic layer was separated, washed with $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification was effected by flash chromatography (SiO_2; hexane: ethyl acetate, 19:1) providing 0.9226 g (71%) of the diketone as a colorless liquid. ^1H NMR ($CDCl_3$): δ 5.52 (1H, d, J=2.5 Hz), 4.84 (0.5H, q, J=5.3 Hz), 4.70 (0.5H, q, J=5.3 Hz), 3.85 (2H, t, J=6.4 Hz), 3.73-3.32 (6H, m), 2.45 (2H, t, J=6.4 Hz), 2.40-2.10 (2H, m), 1.75 (2H, m), 1.45 (1H, m), 1.28 (1.5H, d, J=5.3 Hz), 1.27 (1.5H, d, J=5.3 Hz), 1.17 (1.5H, t, J=7.0 Hz), 1.16 (1.5H, t, J=7.0 Hz), 0.93 (1.5H, d, J=6.8 Hz), 0.91 (1.5H, d, J=6.8 Hz), 0.86 (9H, s), 0.85 (9H, s), 0.03 (6H, d), 0.02 (6H, s). IR (film): 3423 (vs), 2964 (m), 1636 (s) cm^{-1}. HRMS (FAB): Calcd for $C_{27}H_{56}O_6Si_2$ ($[M+Na]^+$): 555.3513, found: 555.3506.

(6S,8S,9S)-8-hydroxymethyl-9-methyl-1,7-dioxaspiro[5.5]undecan-4-one (12): To a solution of the diketone (1.01 g, 1.90 mmol) in 16 mL CH_2Cl_2:MeOH (95:5) was added camphor sulfonic acid (0.22 g, 0.95 mmol), and the resulting solution stirred overnight. The reaction mixture was then diluted with ethyl acetate and washed with saturated aqueous sodium carbonate. The aqueous wash was back extracted with ethyl acetate (3x) and the combined extracts dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; hexanes: ethyl acetate, 1:1) provided 0.38g (95%) of the spiroketal as a colorless liquid. ^1H NMR ($CDCl_3$): δ 3.99 (1H, m), 3.89 (1H, td, J=3.0, 11.3 Hz), 3.67 (1H, m), 3.52 (1H, m), 3.32 (1H, m), 2.55 (1H, m), 2.43 (2H, m), 2.31 (1H, m), 1.92 (1H, m), 1.86 (1H, m), 1.56 (4H, m), 0.85 (d, 3H, J=6.1 Hz). ^{13}C NMR ($CDCl_3$): δ 205.49, 99.69, 76.23, 63.43, 59.09, 52.23, 41.05, 35.10, 30.02, 27.31, 17.18. IR (film): 3456 (m br), 2936 (s), 1722 (vs) cm^{-1}. HRMS (EI, 40 eV): Calcd for $C_{11}H_{18}O_4$ (M^+): 214.1206, found: 214.1222.

(4S,6S,8S,9R)-8-hydroxymethyl-9-methyl-1,7-dioxaspiro[5.5]undecan-4-ol (1): L-Selectride (1.8 mL of a 1 M solution in THF) was added slowly to a stirred solution of the ketone **12** (0.38 g, 1.8 mmol) in 10 mL THF at -78° C. After 2 hours the reaction mixture was warmed to 0° C and quenched by addition of 5.5 mL 30% H_2O_2 and 3.8 mL 10% aqueous NaOH (w/v). The resulting mixture was stirred, and allowed to warm slowly to room temperature overnight. The reaction mixture was then diluted with ethyl acetate, the aqueous layer was saturated with NaCl and extracted with ethyl acetate (3x). The combined organics were washed carefully with saturated, aqueous $Na_2S_2O_3$ (2x) and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; hexane: ethyl acetate, 1:3) resulted in the isolation of 0.3001 g (79%) of the spiroketal-diol as a colorless oil. ^1H NMR ($CDCl_3$): δ 4.05 (1H, m), 3.97 (1H, td, J=2.7, 12.5 Hz), 3.75 (1H, m), 3.58 (2H, m), 3.40 (1H, m), 1.86 (1H, m), 1.76 (1H, m), 1.70-1.40 (7H, m), 0.85 (3H, d, J=5.7 Hz). ^{13}C NMR ($CDCl_3$): δ 97.37, 76.41, 64.41, 63.14, 55.07, 40.16, 35.28, 31.81, 30.20, 26.98, 17.35. IR (CH_2Cl_2 solution): 3429 (s), 2930 (s), 1460 (m), 1438 (m), 1421 (m) cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09%; H, 9.32%. Found: C, 61.05%; H, 9.55%.

General Procedure for Epoxide Opening Reactions: The procedure used for Run **A** in *Table 1* is representative: To a solution of ligand **1** (1.0 mL of a 0.05 M solution in CH_2Cl_2) was added titanium (IV) isopropoxide (0.013 mL, 0.045 mmol) and the solution allowed to stir at room temperature. After 8 hours, the reaction mixture was cooled to 0° C, treated with azidotrimethylsilane (0.012 mL, 0.09 mmol), and stirred for an additional 24 hr. Tetradecane (0.012 mL, 0.045 mmol) was added as an internal standard, followed by cyclohexene oxide (0.0046 mL, 0.045 mmol). The reaction mixture cooled immediately to -10° C (freezer). After 48 hr, an aliquot was removed from the reaction mixture, quenched with saturated, aqueous $NaHCO_3$,

extracted with ether, and analyzed directly by capillary GC (AT-WAX column (Altech), T=50° (1 min) to 200° (20°/min)) to determine percent conversion. The remaining reaction mixture was treated directly with chlorotrimethylsilane (0.06 mL, 0.5 mmol) and triethylamine (0.12 mL, 0.9 mmol). After 2 hours, the reaction mixture was quenched with saturated, aqueous $NaHCO_3$, extracted with ether and the organic layer filtered through Celite. Enantioselectivities were determined by analysis of the ether layer by capillary GC using a chiral column (Cyclodex-B (J&W Scientific), T=120° C). Enantiomers of 1-azido-2-(trimethylsilyloxy)-cyclohexane were baseline resolved.

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10. Though the 2S,3S-epoxide was prepared for this application, either enantiomeric form of this epoxide, and hence either enantiomeric form of ligand **1**, is accessible via asymmetric epoxidation of the corresponding allylic alcohol.
11. The abbreviations used to depict protecting groups in this sequence are as follows: *tert*-butyldimethylsilyl (TBS), ethoxyethyl (EE).
12. 3-*t*-butyldimethylsilyloxypropanal **10** can be prepared in two steps from 1,3-propanediol (1. NaH, THF, TBSCl; 2. $(COCl)_2$, DMSO, CH_2Cl_2; iPr_2EtN).
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14. The A value for this substituent is expected to be on the order of 3.0 kcal/mol. As such, relative stereocontrol at the spirocenter is achieved by virtue of the anomeric effect.
15. Reduction of ketone **12** with $NaBH_4$ yields a 1:1 mixture of axial and equatorial alcohols. As such, the relative stereochemistry at this position can be determined by separation of the diol isomers, conversion to the corresponding bisacetates, and analysis of the ^1H NMR pattern of the C-4 hydrogen. Reduction of ketone **12** with L-Selectride provides exclusively the desired axial alcohol **1**.
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17. Optical purity was determined by capillary GC using a chiral Cyclodex B column (J&W Scientific).
18. The anticipated mode of complexation is as indicated in *Scheme 2*, though the specifics of this structure remain to be elucidated. Note that the ligand **1** is easily recovered in this stoichiometric application by filtration of the crude reaction mixture through a pad of silica, and subsequent elution with ethyl acetate.
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