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# Synthesis and Evaluation of New 1,7-Dioxaspiro[5.5]undecane Ligands: Implications for the Use of Diols in the Desymmetrization of *meso* Epoxides

Debasis Patra, Lihua Yang and Nancy I. Totah*

*Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA*

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**Abstract**—The synthesis and preliminary evaluation of two new chiral 1,7-dioxaspiro[5.5]undecane ligands is described. The compounds of interest are readily available in enantiomerically pure form. Chiral organotitanium complexes prepared from these ligands catalyze the ring opening reaction of *meso* epoxides by $TMSN_3$. A key observation suggests that silylation of the ligand competes with catalyst turnover in this application. Implications for the use of diol ligands are discussed. © 2000 Elsevier Science Ltd. All rights reserved.

## Introduction

Despite recent advances in asymmetric catalysis, the efficient intermolecular transfer of asymmetry remains elusive in a variety of applications. Though in certain cases, designed catalyst systems provide promising results and a basis for further development, more frequently the nature of the specific catalyst is not easily defined, and thus the factors that govern enantioselectivity are difficult to identify. As a result, progress in the development of asymmetric processes will continue to benefit from the identification of new ligands and catalyst systems.

Along these lines, we recently reported a novel chiral organotitanium species for the ring opening reactions of *meso* epoxides.[1] The backbone of this reagent was the 4S,6S,8S,9R-spiroketal ligand **1** (Fig. 1) which is prepared in >99% ee from propargyl alcohol in 13 steps and 12% overall yield. Though use of the corresponding ligand **1**–$Ti(OiPr)_4$ complex showed initial promise as a catalyst in the desymmetrization of *meso* epoxides,[2] we considered further development of this system to be limited by the length of the ligand **1** synthesis. Since that time, we have been working on modified ligand systems with an eye toward minimizing the length of the synthetic sequence while at the same time maintaining the basic ligand framework. Though the specific nature of the ligand **1**–$Ti(iOPr)_4$ catalyst system was unknown, we anticipated that the methyl group at C9 would have little effect on the efficient intermolecular transfer of asymmetry in light of its distance from the chelating functionality of the ligand **1** complex. We envisaged that this modification would allow an expedient entry to the spiroketal ligand **2** that maintains the basic structural features of the parent system. Herein, we describe an expedient approach to the synthesis of 1,7-dioxaspiro[5.5]undecane ligands of this type, and report our findings on the mechanistic implications of using diols as chiral modifying agents for the enantioselective ring opening reaction of *meso* epoxides.[3]

## Results and Discussion

Our initial objective was to develop a more efficient method for the synthesis of 1,7-dioxaspiro[5.5]undecane based ligands. Toward this end, we envisaged the enantioselective synthesis of ligand **2** via sequential homologation of acetone dimethylhydrazone,[4] with subsequent oxidation and spirocyclization of the resulting linear intermediate. As such, the synthesis of ligand **2** was achieved as depicted below (Scheme 1). Thus, lithiation of acetone dimethylhydrazone **3** with *n*BuLi followed by treatment with 4-bromo-1-butene provided the dimethylhydrazone **4** which was isolated, but used without further purification. Subsequent lithiation of this intermediate (**4**) and aldol reaction with 3-(*t*-butyldimethylsilyloxy)propanal (**5**)[5] gave, upon hydrolysis, the β-hydroxyketone **6**. From here, asymmetric dihydroxylation[6] gave the crude trihydroxyketone **7** which was treated


**Figure 1.**

*Keywords*: asymmetric induction; catalysis; spiro compounds; asymmetric synthesis.

* Corresponding author. E-mail: nancy.totah@uiowa.edu


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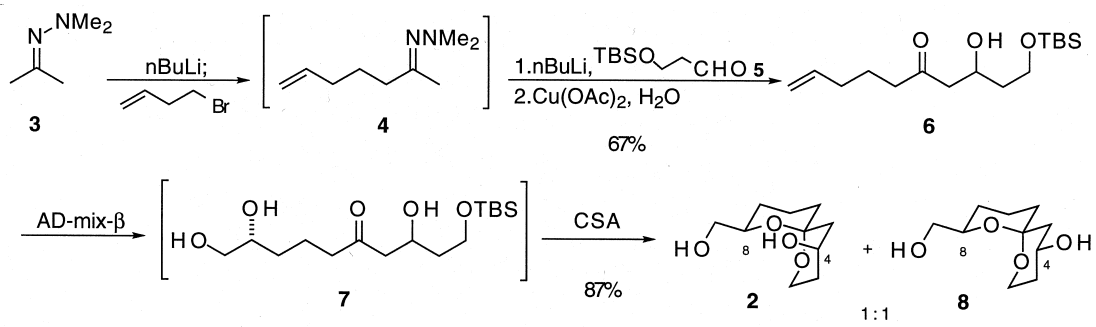



**Scheme 1.**

directly with camphorsulfonic acid to provide an approximately 1:1 mixture of non-racemic axial (**2**) and equatorial (**8**) alcohols that could be separated by careful flash column chromatography. By this process, ligand **2** can be prepared in five steps and 29% overall yield.

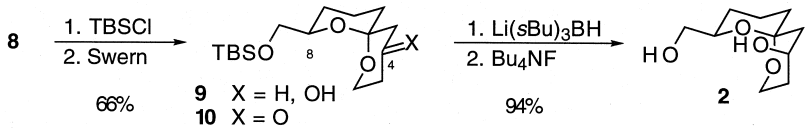
Though, in this sequence, formation of the equatorial alcohol **8** reduces the overall yield of the desired ligand **2**, this side-product can be cleanly converted to the desired axial isomer via selective silylation of the primary alcohol (**9**), Swern oxidation of the hydroxyl group at C4 (**10**), followed by reduction with Li(*s*-Bu)$_3$BH, and deprotection (Scheme 2).[7] In this way, the overall yield of the desired ligand **2** is increased to 47% starting from acetone dimethylhydrazone.

By the process described above, ligand **2** is obtained in 60% ee as determined by gas chromatography of monosilylated ligand **9** (OH axial)[8] using a chiral Cyclodex B column (J & W Scientific). However, compound **2** can be obtained in >99% ee after a single recrystallization from hexanes to remove the highly crystalline racemate.

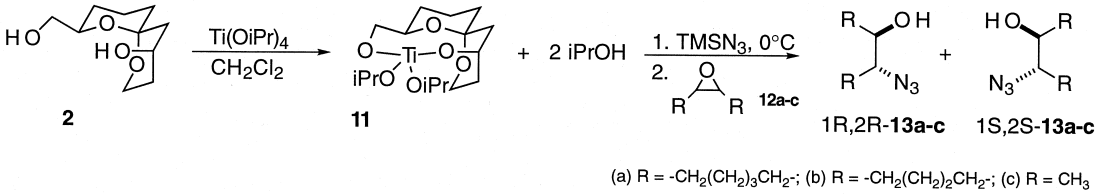
With the desired spiroketal ligand **2** in hand, our next objective was to evaluate the efficacy of this system as a chiral modifying agent for the ring opening reaction of *meso* epoxides with trimethylsilyl azide. Thus, the ligand **2**–Ti(OiPr)$_4$ complex **11** was generated in situ by combining equimolar amounts of the ligand **2** and Ti(OiPr)$_4$ in $CH_2Cl_2$ at room temperature (Scheme 3).[9] After 12 h, trimethylsilyl azide was added, and the resulting mixture aged at 0°C for a specific time period. Subsequent addition of the epoxide **12** then provides, cleanly, the corresponding *trans*-2-azido alcohol **13**.

We first investigated the ability of complex **11** to catalyze the reaction of cyclohexene oxide (**12a**) with trimethylsilyl azide using equimolar amounts of catalyst and substrate (Table 1, entries 1–5). In these experiments we found that enantioselectivity varied with reaction temperature and the aging period of the chiral titanium complex with $TMSN_3$. Thus, when the epoxide opening reaction is run at −10°C, the product azido alcohol **13a** is obtained in 42% ee after a 1 h aging time (entry 1), and in 59% ee when the aging time is doubled (entry 2). Presumably, this dependence on aging reflects the formation of an intermediate titanium azide which is thought to be the active catalytic species.[10] Further extension of the aging period (entries 3 and 4) appears to have little impact on selectivity. However, the enantioselectivity of the stoichiometric process can be moderately enhanced by decreasing the reaction temperature to −20°C (entry 5). Under these conditions the 1R,2R[11] azidohydrin **13a** is produced in 66% ee. This level of enantioselectvity is comparable to that obtained using the ligand **1**–Ti(OiPr)$_4$ complex (64% ee at −10°C after a 1 h aging period).[1] Additional studies demonstrated that the ligand **2** complex promotes the enantioselective ring opening reaction of cyclopentene oxide **12b** (entry 6) and *cis*-butene oxide **12c** (entry 7) to give the corresponding trans azido alcohols **13b** and **13c** in 41 and 30% ee, respectively.

As complexes of type **11** will ideally be utilized in substoichiometric amounts, we next explored the effect of decreasing the amount of ligand **2**–Ti(OiPr)$_4$ complex




**Scheme 2.**




(a) R = -$CH_2(CH_2)_3CH_2$-; (b) R = -$CH_2(CH_2)_2CH_2$-; (c) R = $CH_3$

**Scheme 3.**

**Table 1.** Enantioselective ring opening of cyclohexene oxide using ligand **2**–$Ti(OiPr)_4$ complex

| Entry | Epoxide | Catalyst: substrate ratio | Aging time ($TMSN_3$) (h) | Reaction temperature (°C) | Conversion[a] (%) | ee (%)[b] | Configuration[c] |
|---|---|---|---|---|---|---|---|
| 1 | **12a** | 1:1 | 1 | −10 | 46 | 42 | 1*R*,2*R* |
| 2 | **12a** | 1:1 | 2 | −10 | 75 | 59 | 1*R*,2*R* |
| 3 | **12a** | 1:1 | 6 | −10 | 92 | 58 | 1*R*,2*R* |
| 4 | **12a** | 1:1 | 9 | −10 | 91 | 60 | 1*R*,2*R* |
| 5 | **12a** | 1:1 | 9 | −20 | 51 | 66 | 1*R*,2*R* |
| 6 | **12b** | 1:1 | 9 | −20 | 51 | 41 | 1*R*,2*R* |
| 7 | **12c** | 1:1 | 9 | −20 | 57 | 30 | 1*R*,2*R* |
| 8 | **12a** | 1:4 | 3 | −20 | 61 | 52 | 1*R*,2*R* |
| 9 | **12a** | 1:4 | 6 | −20 | 60 | 50 | 1*R*,2*R* |
| 10 | **12a** | 1:4 | 9 | −20 | 61 | 55 | 1*R*,2*R* |
| 11 | **12a** | 1:8 | 6 | −20 | 55 | 35 | 1*R*,2*R* |

[a] Conversions were determined by gas chromatography using tetradecane as an internal quantitative standard. Routinely, the reaction was allowed to proceed for 48 h after addition of the epoxide.
[b] Enatioselectivities were determined by capillary GC of the corresponding 1-azido-2-trimethylsilyloxy derivatives using a chiral cyclodex B column.
[c] Absolute configurations are assigned by comparison to those reported by Jacobsen.[2b]

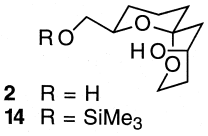
(entries 8–11). In these cases, as the ratio of catalyst to substrate is decreased, the enantioselectivity of the ring opening process erodes such that at a 1:4 ratio of catalyst to substrate (entries 8–10), the product azido alcohol is obtained in only 55% ee at −20°C, whereas at a 1:8 catalyst to substrate ratio (entry 11) only 35% ee is obtained. Here too, the impact of catalyst aging with $TMSN_3$ appears to be minimal beyond the initial incubation period of approximately 2 h.

The results of these studies clearly show that the amount of catalyst utilized has a significant impact on the enantioselectivity of the desymmetrization reaction. These results are consistent with the modification of the catalyst system as the epoxide opening reaction proceeds. In this regard, one possibility is silylation of the primary alkoxy function of the ligand at a rate that is competitive with catalyst turnover (e.g. silylation of the product).[12] This process may result in the formation of a new catalytic species that is able to promote epoxide opening, albeit at a slower rate and with a lower level of selectivity. Support for such a hypothesis is provided by the observation that significant amounts (ca. 15%) of monosilylated ligand **2** (e.g. **14**) are formed over the course of the reaction[13] (Fig. 2).

These results are reminiscent of the difficulties with catalyst turnover that are observed with the tartrate based diol ligands used by Sinou[12] and Oguni.[2c] Though in these cases, the observation of a silylated ligand by-product is not reported, in general, the silylation of diol ligands is perhaps not unexpected in light of the relative nucleophilicity of the ligating function (alkoxide) as compared to that of more successful catalyst systems in the desymmetrization of *meso* epoxides.[14] Indeed, for this application, high levels of enantioselectivity are generally observed with the use of multidentate ligands or those in which electronic effects decrease the nucleophilicty of the ligating functions. This information, combined with the results of the present studies suggests that an efficient ligand is one that is not readily silylated. As such, we anticipated that further improvement in the enantioselectivity of the epoxide opening reaction using 1,7-dioxaspiro-[5.5]undecane based ligands would necessitate further modification of our ligand system.

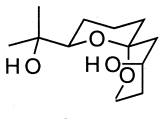
On the basis of these principles, we sought to reduce the proclivity of diol ligands of type **2** to undergo silylation. As such, we redesigned our system such that the hydroxymethyl side chain (1° alkoxy function) of ligand **2** was replaced by a more highly substituted (3°) ligating unit, and turned our attention to the synthesis and evaluation of the 1,7-dioxaspiro[5.5]undecane ligand **15** (Fig. 3).

In practice, the synthesis of ligand **15** proceeded by a sequence of reactions analogous to that described for ligand **2** (Scheme 4). Thus, lithiated acetone dimethylhydrazone **3** was treated with 5-bromo-2-methyl-2-pentene, and the resulting intermediate subjected to aldol condensation with the aldehyde **5** to give the corresponding β-hydroxyketone **17** in 60% yield upon hydrolysis. From here, asymmetric dihydroxylation and direct cyclization of the corresponding trihydroxyketone provided the spiroketal as a mixture of axial (**15**) and equatorial (**18**) alcohols that could not be separated. This mixture could be converted cleanly to the desired axial isomer **15** by a two step oxidation/reduction protocol as indicated below. In this way, the desired ligand **15** is prepared in seven steps and 28% overall yield from acetone dimethylhydrazone **3**. The enantiomeric purity of this ligand was >99% ee as



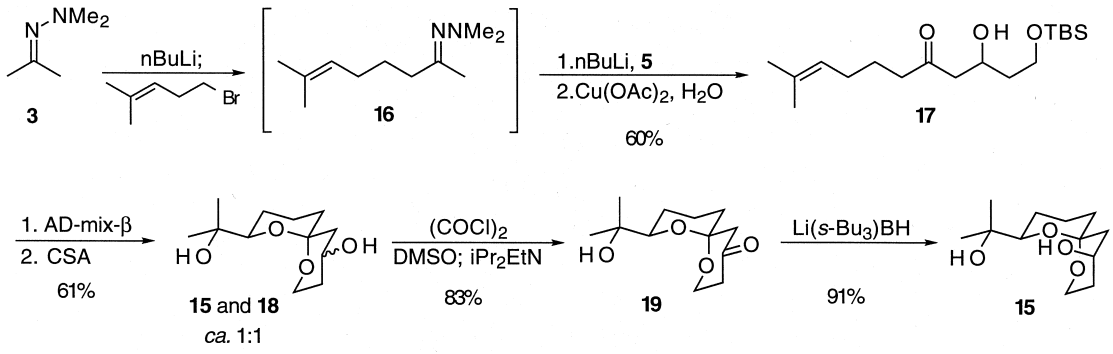

**2** R = H
**14** R = $SiMe_3$

**Figure 2.**




**15**

**Figure 3.**




**Scheme 4.**

determined by capillary GC of the ketone **19** using a chiral cyclodex B column.

The 5-bromo-2-methyl-2-pentene used in the initial alkylation step, though commercially available, is expensive; therefore, we routinely prepare this bromide in two steps from γ-butyrolactone[15] as a ca. 3:1 mixture of double bond isomers (e.g. 5-bromo-2-methyl-2-pentene, and its isomer **20**, Fig. 4). Though throughout the homologation sequence the two isomers are inseparable by silica gel chromatography, the presence of the undesired terminal olefin (e.g. **21**) is of little consequence because of the differential rates of dihydroxylation of the double bond isomers.[16] Indeed, upon asymmetric dihydroxylation and spirocyclization, the diols **15** and **18** are isolated cleanly from the reaction mixture along with unreacted hydroxyketone **21**. None of the spiroketal (e.g. **22**) resulting from the oxidation and cyclization of the terminal olefin **21** is identified.

With the successful preparation of ligand **15**, we were ready to evaluate the effect of increasing ligand substitution on the stereoselectivity of the desymmetrization reaction. More specifically, we were interested in seeing whether the incorporation of a tertiary alkoxy function would effectively address the issue of ligand silylation, and hence, catalyst turnover. Toward this end, the corresponding ligand **15**–$Ti(OiPr)_4$ complex was prepared as described previously and utilized in the epoxide opening reaction of cyclohexene oxide **12a** with $TMSN_3$ (Scheme 5). Unfortunately, while incorporation of the more highly substituted alkoxide function shut down the ligand silylation pathway, ligand **15** provides significantly lower enantioselectivity in the desymmetrization process, producing the 1*S*,2*S* azido alcohol **13a** with selectivities of up to only 31% ee under a variety of reaction conditions. A corresponding decrease in reaction rate was also observed.[17] Presumably, this loss of selectivity originates with the increased steric requirements of both catalyst formation and subsequent reaction.

In conclusion, we have developed an efficient, enantioselective approach to 1,7-dioxaspiro[5.5]undecane ligands **2** and **15** from readily available starting materials. By this route, ligands **2** and **15** are available in 29 and 28% overall yields, respectively, a substantial improvement over our previous route to the related ligand **1**. As the enantioselectivity of the ligand synthesis is derived from the Sharpless asymmetric dihydroxylation protocol, either enantiomeric form of these and related ligands should be readily accessible. In addition, we have demonstrated the ability of the ligand **2**–$Ti(OiPr)_4$ complex to promote the ring opening reaction of *meso* epoxides with trimethylsilyl azide. Though the enantioselectivities observed in these examples vary from modest to good (up to 66% ee in stoichiometric applications; 55% ee at 25% catalyst loading using ligand **2**), a key observation in this study is the presence of the monosilylated ligand **14** that is formed over the course of the epoxide opening reaction. This result suggests that ligand silylation competes with catalyst turnover, the possibility of which will have broader implications

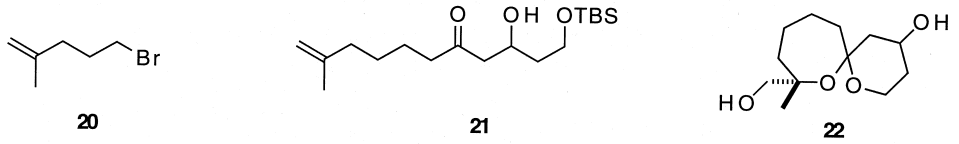
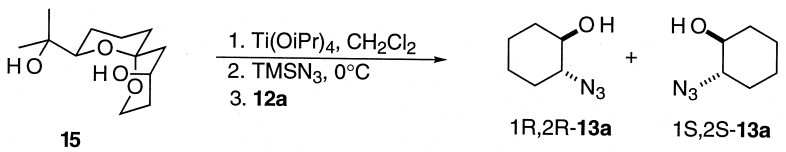



**Figure 4.**




**Scheme 5.**

for the use of diol ligands in the present application. Though silylation is not observed when the corresponding ligand **15**–$Ti(OiPr)_4$ complex is used, the increased steric demands of this catalyst system detract from the efficiency and selectivity in the epoxide opening reaction. While these results suggest that diol ligands such as these will be less useful for the present application, we have demonstrated the feasibility of using a simplified 1,7-dioxaspiro[5.5]-undecane skeleton as a chiral modifying agent for the intermolecular transfer of asymmetry. As such, these new ligands may well find application in a variety of other processes, particularly those in which silylating agents are not utilized.

## Experimental

### General methods

All air sensitive reactions were performed in oven-dried glassware under an atmosphere of argon. Reaction solvents were dried over $CaH_2$ (dichloromethane) or sodium/benzophenone ketyl (tetrahydrofuran) and were distilled just prior to use. $Ti(OiPr)_4$ was distilled under high vacuum prior to use. All other reagents were reagent grade and purified where necessary. $^1H$ NMR and $^{13}C$ spectra were recorded on Bruker AC-300 or Bruker WM 360 spectrometers. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual $CHCl_3$ ($\delta$ 7.27) as the internal standard. High resolution mass spectra were obtained by the University of Iowa Mass Spectrometry Laboratory. Elemental Analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Gas chromatographic (GC) analyses were carried out on a Varian 3400 CX instrument equipped with FID detectors and 30 M AT-WAX (Altech) and chiral Cyclodex B (30 mm id×0.25 m film; J & W Scientific) columns.

### Experimental procedures

**6-Hepten-2-one *N*,*N*-dimethylhydrazone (4).** To a stirred solution of acetone dimethylhydrazone **3** (4.30 g, 42.5 mmol) in THF (128 mL) was added *n*-butyllithium (17.0 mL of a 2.5 M solution in hexane) at −78°C. Stirring was continued for 2.5 h over which time a white precipitate formed. A solution of 4-bromo-1-butene (4.4 mL, 43 mmol) in 20 mL THF was then added dropwise via cannula. After an additional 2 h at −78°C, the reaction mixture was allowed to warm slowly to room temperature overnight. The resulting clear yellow solution was quenched by the addition of saturated $NH_4Cl$ (aq). The mixture was then extracted with ether, and the combined extracts washed with brine, then dried over $Na_2SO_4$. Removal of solvent in vacuo afforded 5.70 g (87%) of crude 6-hepten-2-one dimethylhydrazone **4** as a 4:1 mixture of isomers that was used without further purification (yellow oil). $^1H$ NMR (300 MHz, $CDCl_3$): (major isomer) $\delta$ 5.80 (1H, m), 5.07–4.93 (2H, m), 2.42 (6H, s), 2.20 (2H, m), 2.08 (2H, m), 1.94 (3H, s), 1.60 (2H, m).

**1-(*t*-Butyldimethylsilyloxy)-3-hydroxy-9-decen-5-one (6).** To a stirred solution of crude 6-hepten-2-one dimethylhydrazone **5** (0.77 g, 5.0 mmol) in 17.5 mL THF was added *n*-butyllithium (2.1 mL of a 2.5 M solution in hexane) at −78°C. After 4 h, a solution of 3-(*t*-butyldimethylsilyloxy)-propanal **5** (0.99 g, 5.25 mmol) in 17 mL THF was added. After an additional 5 h, the reaction mixture was warmed slowly to room temperature overnight. The reaction was quenched by the addition of saturated $NH_4Cl$ (aq), then transferred to a separatory funnel and extracted with ether. The combined organics were washed with brine and dried over $Na_2SO_4$. Subsequent removal of the solvent in vacuo afforded 1.53 g of crude 1-(*t*-butyldimethylsilyloxy)-3-hydroxy-9-decen-5-one dimethylhydrazone as yellow oil. This material was dissolved in 20 mL THF and added dropwise to a stirred solution of $Cu(OAc)_2\cdot H_2O$ (2.51 g, 12.6 mmol) in 59 mL water and 39 mL THF at room temperature. Upon complete addition, the reaction mixture was stirred for 20 h, over which period a rust colored precipitate deposited. The reaction mixture was concentrated in vacuo, then partitioned between ethyl acetate and saturated $NH_4Cl$ (aq) (adjusted to pH 8–9 using $NH_3\cdot H_2O$). The layers were separated, the aqueous layer back extracted with ethyl acetate, and the combined organics washed sequentially with saturated $NH_4Cl$ (aq) (pH 8–9), water and brine, then dried over $Na_2SO_4$ and concentrated in vacuo. Purification of the residue by flash column chromatography ($SiO_2$; hexane/ethyl acetate, 9:1) afforded 1.00 g (67%, three steps) of 1-(*t*-butyldimethylsilyloxy)-3-hydroxy-9-decen-5-one **6** as a light-yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.77 (1H, m), 5.06–4.96 (2H, m), 4.27 (1H, m), 3.83 (2H, m), 3.59 (1H, d, $J$=2.7 Hz, OH), 2.63 (1H, dd, $J$=16.8, 7.7 Hz), 2.55 (1H, dd, $J$=16.8, 4.6 Hz), 2.46 (2H, t, $J$=7.3 Hz), 2.07 (2H, m), 1.74–1.63 (4H, m), 0.90 (9H, s), 0.08 (6H, s). $^{13}C$ NMR (90 MHz, $CDCl_3$): $\delta$ 211.0, 137.9, 115.3, 67.2, 61.5, 49.6, 42.8, 38.3, 33.0, 25.9 (3C), 22.5, 18.2, −5.5 (2C). IR (film): 3499, 2930, 2858, 1710 $cm^{-1}$. HRMS (FAB): Calcd for $C_{16}H_{33}O_3Si$: 301.2199 ($[M+H]^+$), found: 301.2194.

**(−)-(4*S*,6*S*,8*R*)-8-(Hydroxymethyl)-1,7-dioxaspiro-[5.5]-undecan-4-ol (2).** AD-mix-β (2.1 g) was dissolved in 15 mL *t*-BuOH/$H_2O$ (1:1) at room temperature, then cooled to 0°C and an orange solid precipitated. 1-(*t*-Butyldimethylsilyloxy)-3-hydroxy-9-decen-5-one **6** (0.430 g, 1.43 mmol) was then added in one portion (1 mL *t*-BuOH was used to complete the transfer). After 6 h, the reaction was quenched by addition of solid $Na_2SO_3$ (2.3 g), then transferred to a separatory funnel and extracted with ethyl acetate. The combined extracts were dried over $Na_2SO_4$, filtered and concentrated in vacuo. The resulting residue was dissolved in 15 mL $CH_2Cl_2/CH_3OH$ (95:5). Camphorsulfonic acid (0.17 g, 0.72 mmol) was added, and the resulting solution stirred for 3 h at room temperature. The reaction mixture was then diluted with ethyl acetate, and washed with saturated $Na_2CO_3$ (aq) and water, respectively. The aqueous portion was back extracted with ethyl acetate, and the combined organics dried over $Na_2SO_4$, filtered, and concentrated in vacuo to afford a ca. 1:1 mixture of axial (**2**) and equatorial (**8**) alcohols. Purification by flash column chromatography ($SiO_2$; hexane/ethyl acetate, 1:1 to 1:2 to 0:1) gave 0.102 g (35%) of the axial isomer **2** (colorless oil; $[\alpha]_D^{21}=-88.8°$, $CHCl_3$, $c$=2.6; after a single recrystallization from hexanes), 0.032 g (11%) of the equatorial isomer **8** (colorless oil), and 0.118 g (41%) an isomeric mixture of alcohols (**2** and **8**) (total 0.252 g, 87% combined yield).

(−)-(4S,6S,8R)-8-(hydroxymethyl)-1,7-dioxaspiro[5.5]-undecan-4-ol (−)-(**2**): $^1$H NMR (360 MHz, $CDCl_3$): δ 4.21 (1H, d, *J*=9.8 Hz), 4.10–4.00 (2H, m), 3.81 (1H, m), 3.64–3.34 (3H, m), 2.72 (1H, t, *J*=6.1 Hz), 1.94–1.25 (10H, m). $^{13}$C NMR (90 MHz, $CDCl_3$): δ 97.8, 71.1, 65.7, 64.5, 55.1, 40.3, 34.8, 31.9, 26.0, 17.8. IR (film): 3429, 3336, 2945, 1061 cm$^{-1}$. HRMS (FAB): Calcd for $C_{10}H_{18}O_4Na$: 225.1103 ([M+Na]$^+$), found 225.1099. Anal Calcd for $C_{10}H_{18}O_4$ C 59.39, H 8.97; found C 59.34, H 8.94. (4R,6S,8R)-8-(hydroxy-methyl)-1,7-dioxaspiro[5.5]-undecan-4-ol (**8**): $^1$H NMR (360 MHz, $CDCl_3$): δ 4.13 (1H, m), 3.76–3.45 (5H, m), 2.05 (1H, ddd, *J*=12.4, 4.8, 2.0 Hz), 1.89 (3H, m), 1.73–1.25 (6H, m).

**7-Methyl-6-octen-2-one *N*,*N*-dimethylhydrazone (16).** To a stirred solution of acetone dimethyl-hydrazone **3** (0.300 g, 3.00 mmol) in 15 mL THF was added *n*-butyllithium (1.2 mL of a 2.5 M solution in hexane) at −78°C. Stirring was continued for 2 h at −78°C, and resulted in the gradual formation of a white precipitate. A solution of 5-bromo-2-methyl-2-pentene (0.490 g, 3.00 mmol) in 5 mL THF was then added dropwise. The reaction mixture was stirred for an additional 2 h, after which time it was allowed to warm slowly to room temperature. The resulting clear yellow solution was quenched by addition of saturated, aqueous $NH_4Cl$, the aqueous portion extracted with ether, and the combined organics washed with brine and dried over $MgSO_4$. Removal of solvent in vacuo provided 0.470 g (86%) of crude 7-methyl-6-octen-2-one *N*,*N*-dimethyl-hydrazone **16** as a yellow oil that was used without further purification (ca. 5:1 mixture of hydrazone isomers). $^1$H NMR (300 MHz, $CDCl_3$): (major isomer) δ 5.11 (1H, m), 2.43 (6H, s), 2.19 (2H, m), 1.99 (2H, m), 1.94 (3H, s), 1.68 (3H, d, *J*=1.0 Hz), 1.58 (3H, d, *J*=0.3 Hz), 1.55 (2H, m).

**1-(*t*-Butyldimethylsilyloxy)-3-hydroxy-10-methyl-9-undecen-5-one (17).** To a stirred solution of 7-methyl-6-octen-2-one *N*,*N*-dimethylhydrazone **16** (0.440 g, 2.4 mmol) in 10 mL THF was added *n*-butyllithium (0.96 mL of a 2.5 M solution in hexanes) at −78°C and the resulting mixture stirred for 4 h. A solution of 3-(*t*-butyldimethyl-silyloxy)propanal **5** (0.545 g, 2.90 mmol) in 5 mL THF was then added. After additional 5 h at −78°C, the reaction mixture was allowed to warm to room temperature. The reaction was quenched with saturated, aqueous $NH_4Cl$ and the aqueous portion extracted with ether. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford 0.876 g of the crude dimethylhydrazone as a yellow oil. The crude product was then dissolved in 10 mL THF and added dropwise to a stirred solution of $Cu(OAc)_2 \cdot H_2O$ (1.21 g, 6 mmol) in 50 mL of 3:2 water:THF at room temperature. The color of the reaction mixture changed from blue to green and finally a rust colored precipitate deposited. After 15 h, the reaction mixture was concentrated in vacuo, then partitioned between ethyl acetate and saturated aqueous $NH_4Cl$ (adjusted to pH 8–9 with aqueous ammonia). The aqueous layer was extracted with ethyl acetate, and the combined extracts washed sequentially with saturated aqueous $NH_4Cl$ (pH 8–9), water and brine, then dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography ($SiO_2$; hexane/ethyl acetate, 7:1) afforded 0.470 g (60% over two steps) of 1-(*t*-butyl-dimethylsilyloxy)-3-hydroxy-10-methyl-9-undecen-5-one **17** as a pale yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 5.04 (1H, m), 4.22 (1H, m), 3.79 (2H, m), 3.59 (1H, d, *J*=2.7 Hz), 2.56 (2H, m), 2.39 (2H, t, *J*=7.4 Hz), 1.95 (2H, q, *J*=7.2 Hz), 1.65 (3H, d, *J*=0.9 Hz), 1.60 (4H, m), 1.55 (3H, s), 0.86 (9H, s), 0.04 (6H, s). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 211.2, 132.2, 123.6, 66.9, 61.2, 49.4, 43.0, 38.3, 27.2, 25.8 (3C), 25.6, 23.7, 18.1, 17.6, −5.6 (2C). IR (film): 3576, 2932, 2859, 1710 cm$^{-1}$. HRMS (FAB): Calcd for $C_{18}H_{36}O_3SiNa$ 351.2331 ([M+Na]$^+$), found 351.2337.

**(6*S*, 8*R*)-8-(2-Hydroxy-2-propyl)-1,7-dioxaspiro[5.5]undecan-4-ol (15 and 18).** AD-mix-β (2.1 g) and methanesulfonamide (0.145 g, 1.52 mmol) was dissolved in 15 mL *t*-BuOH/$H_2O$ (1:1) at room temperature, then cooled to 0°C and an orange solid precipitated. Neat 1-(*t*-butyl-dimethylsilyloxy)-3-hydroxy-10-methyl-9-undecen-5-one **17** (0.500 g, 1.52 mmol) was then added, and 1 mL *t*-BuOH was used to complete the transfer. After 24 h at 0°C, the reaction was quenched by addition of 2.3 g $Na_2SO_3$ and stirred at room temperature for 30 min. The resulting heterogeneous mixture was then extracted with ethyl acetate, and the combined extracts dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in 15 mL $CH_2Cl_2$/MeOH (95:5); camphorsulfonic acid (0.18 g, 0.76 mmol) was added and the resulting solution stirred for 4 h. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $Na_2CO_3$ and water, and the aqueous washings back extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, concentrated in vacuo, and the residue purified by flash chromatography ($SiO_2$; hexanes/ethyl acetate, 1:2) to afford 0.280 g (81%) of (6S,8R)-8-(2-hydroxy-2-propyl)-1,7-dioxaspiro[5.5]undecan-4-ol as a mixture of axial **15** and equatorial **18** alcohols that could not be separated (clear viscous oil). $^1$H NMR (300 MHz, $CDCl_3$): δ 4.13–3.52 (4.5H, m), 3.39 (0.5H, dd, *J*=11.7, 2.2 Hz), 2.26 (1H, br s), 2.03 (1H, m), 1.92–1.75 (3H, m), 1.70–1.58 (4H, m), 1.56–1.30 (2H, m), 1.24 (1.5H, s), 1.20 (1.5H, s), 1.19 (1.5H, s), 1.13 (1.5H, s).

**(−)-(6*S*, 8*R*)-8-(2-Hydroxy-2-propyl)-1,7-dioxaspiro[5.5]-undecan-4-one (19).** To a solution of oxalyl chloride (0.080 mL, 0.92 mmol) in 5 mL $CH_2Cl_2$ at −78°C was slowly added a solution of DMSO (0.13 mL, 1.8 mmol) in 2 mL $CH_2Cl_2$. After 5 min, a solution of (6*S*,8*R*)-8-(2-hydroxy-2-propyl)-1,7-dioxaspiro[5.5]-undecan-4-ol **17** (0.085 g, 0.37 mmol) in $CH_2Cl_2$ was added dropwise and stirred for 1 h at −78°C. Diisopropylethylamine (0.5 mL, 3.0 mmol) was added, the reaction mixture stirred for 15 min, then allowed to warm to room temperature. The reaction mixture was diluted with water, extracted with $CH_2Cl_2$, and the organic extracts washed sequentially with 1% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography ($SiO_2$; hexanes/ethyl acetate, 1:1) afforded 0.070 g (83%) of (6*S*,8*R*)-8-(2-hydroxy-2-propyl)-1,7-dioxaspiro[5.5]-undecan-4-one **19** as a clear viscous oil. ($[\alpha]_D^{22}$=−98.5°, $CHCl_3$, *c*=1.7); $^1$H NMR (300 MHz, $CDCl_3$): *δ* 4.00 (1H, m), 3.93 (1H, dt, *J*=11.7, 3.1 Hz), 3.43 (1H, dd, *J*=11.7, 1.9 Hz), 2.59 (1H,

m), 2.46 (2H, s), 2.32 (1H, dd, $J$=14.4, 1.5 Hz), 2.13 (1H, broad s), 1.93–1.81 (2H, m), 1.73–1.60 (2H, m), 1.48–1.26 (2H, m), 1.16 (3H, s), 1.12 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 205.4, 100.2, 76.3, 71.5, 59.0, 52.3, 40.9, 34.4, 25.9, 24.1, 23.8, 18.3. IR (neat): 3468, 2951, 1721 cm$^{-1}$. HRMS (FAB): Calcd for $C_{12}H_{20}O_4Na$ 251.1259 ($[M+Na]^+$), found 251.1262.

**(−)-(4*S*, 6*S*, 8*R*)-8-(2-Hydroxy-2-propyl)-1,7-dioxaspiro-[5.5]undecan-4-ol (15).** To a solution of (6*S*, 8*R*)-8-(2-hydroxy-2-propyl)-1,7-dioxaspiro[5.5]undecan-4-one **19** (0.065 g, 0.28 mmol) in 2 mL THF was added Li(*s*-Bu)$_3$BH (0.63 mL of a 1 M solution in THF) dropwise at −78°C. After stirring for 1 h, the reaction mixture was allowed to warm to 0°C and quenched by the addition of 10% aqueous NaOH (1.9 mL) and 30% $H_2O_2$ (1.3 mL). The resulting mixture was allowed to warm slowly to room temperature overnight and then diluted with ethyl acetate. The aqueous layer was saturated with NaCl and extracted with ethyl acetate. The combined extracts were washed with saturated, aqueous $Na_2S_2O_3$ and brine, then dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography ($SiO_2$; ethyl acetate, 1:2) afforded 0.060 g (91%) of (4*S*,6*S*,8*R*)-8-(2-hydroxy-2-propyl)-1,7-dioxaspiro[5.5]undecan-4-ol **15** as a white crystalline solid. ($[\alpha]_D^{25}$=−86.3°, $CHCl_3$, $c$=1.8); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.03–3.92 (3H, m), 3.58 (1H, dd, $J$=11.7, 4.6 Hz), 3.51 (1H, dd, $J$=11.7, 2.1 Hz), 2.31 (1H, broad s), 1.89–1.71 (3H, m), 1.67–1.54 (5H, m), 1.40 (1H, dd, $J$=13.8, 4.7 Hz), 1.33 (1H, m), 1.20 (3H, s), 1.15 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 97.9, 76.6, 71.4, 64.2, 55.2, 40.6, 35.0, 31.9, 26.7, 25.0, 24.4, 18.2. IR (neat): 3403, 2950 cm$^{-1}$. Anal Calcd for $C_{12}H_{22}O_4$ C 62.58, H 9.63; found C 62.46, H 9.68.

## General procedure for epoxide opening reactions

The procedure used for entry 5 in Table 1 is representative: To a solution of ligand **2** (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 12 h, the reaction mixture was cooled to 0°C, treated with azidotrimethylsilane (0.012 mL, 0.09 mmol), and stirred for an additional 9 h. Tetradecane (0.012 mL, 0.045 mmol) was added as an internal standard, followed by cyclohexene oxide **12a** (0.0046 mL, 0.045 mmol). The reaction mixture cooled immediately to −20°C (cryocool). After 48 h, an aliquot was removed from the reaction mixture, quenched with saturated, aqueous $NaHCO_3$, extracted with ether, and analyzed directly by capillary GC using an AT-WAX column (Altech; $T$=50°C (1 min) to 200°C (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 h, 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 Cyclodex-B chiral column (J & W Scientific; $T$=120°C). Enantiomers of 1-azido-2-(trimethyl-silyloxy)cyclohexane **13a** were baseline resolved.

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