

Kinetic resolution in the asymmetric dihydroxylation of 1,7-dioxaspiro[5.5]undec-4-enes

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Abstract: The asymmetric dihydroxylation of unsaturated spiroacetals **1**, **2**, **3** was effected using the cinchona alkaloid ligands (DHQ)₂-PHAL, (DHQD)₂-PHAL and DHQ-IND, DHQD-IND with OsO₄, K₃Fe(CN)₆ and methanesulfonamide. Kinetic resolution of the spiroacetals was achieved and the reactions were monitored by chiral gas chromatography.
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Introduction

The synthesis of spiroacetals has attracted considerable attention from synthetic chemists due to their presence in a range of biologically active natural products.¹ Many of these spiroacetals, notably the fruit fly pheromones² and the avian toxins, the talaromycins³ contain hydroxylated 1,7-dioxaspiro[5.5]undecane ring systems. In view of the wide range of naturally occurring hydroxylated 1,7-dioxaspiro[5.5]undecanes which exhibit biological activity we have investigated the asymmetric dihydroxylation of the 1,7-dioxaspiro[5.5]undec-4-enes **1**, **2**, **3** as an attractive method for the resolution of these unsaturated spiroacetals.

The osmium catalyzed asymmetric dihydroxylation (AD) of alkenes developed by Sharpless, has provided a powerful method to selectively place oxygen functionality onto an unsaturated hydrocarbon skeleton.⁴ In general the phthalazine based cinchona alkaloid ligands (DHQ)₂-PHAL and (DHQD)₂-PHAL effect *syn*-hydroxylation of four classes of olefin (mono, *gem*-di, *trans*-di and trisubstituted alkenes) affording vicinal diols in high enantiopurity.⁵ The pyrimidine based ligands (DHQ)₂-PYR and (DHQD)₂-PHAL provide a method for asymmetric dihydroxylation of tetrasubstituted alkenes⁶ whilst the indoline⁷ [DHQ-IND and DHQD-IND], diphenyl pyrazinopyridazine⁸ [(DHQ)₂-DPP and (DHQD)₂-DPP], and diphenyl phthalazine⁸ [(DHQ)₂-DP-PHAL and (DHQD)₂-DP-PHAL] based ligands provide improvements in the enantiomeric excesses obtained in the asymmetric dihydroxylation of *cis*-alkenes which were the most difficult class of alkene to succumb to successful asymmetric dihydroxylation.

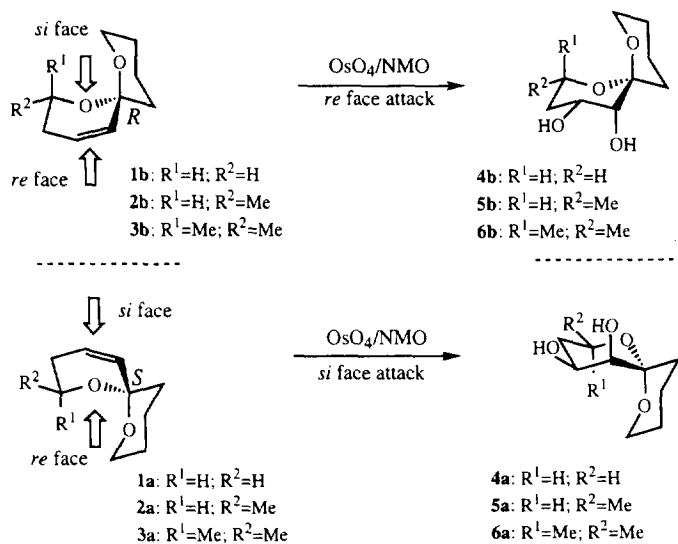
In the present work we were concerned that our substrates are *cis*-disubstituted cyclic olefins which are the most difficult substrates in the dihydroxylation process. Whilst a study of the asymmetric dihydroxylation of spiroacetals has not yet been reported, we were encouraged by the kinetic resolution of mono- and bicyclic alkenes recently achieved by Zwanenburg *et al.*⁹ and an unusually efficient kinetic resolution using AD.¹⁰ During the course of this work Mavridis *et al.*¹¹ also reported the chiral recognition of (*R*)-(-)-1,7-dioxaspiro[5.5]undecane by chiral cyclodextrin hosts.

Results and discussion

The stereoselective *syn*-hydroxylation of the unsaturated spiroacetals **1**, **2**, **3** using a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide as reoxidant in aqueous acetone has been reported.¹² Spiroacetals **1**, **2**, **3** exhibited an intrinsic diastereofacial bias such that hydroxylation took place from the least hindered face of the olefin affording only the diastereomer of the diol (as a racemic mixture) in which the hydroxyl group α - to the spiro centre was *anti* to the C–O bond of

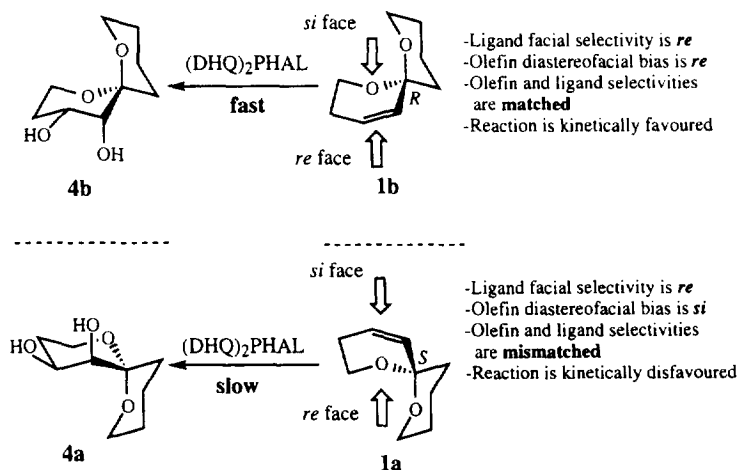
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the neighbouring tetrahydropyran ring (Scheme 1). None of the other diastereomer was detected in the crude reaction mixture. It was therefore envisaged that by “matching” or “mismatching” the facial preference of the AD ligands with the diastereofacial bias of the olefin that kinetic resolution of the olefin enantiomers could be achieved affording preferentially one diol diastereomer in enantiomeric excess.



Scheme 1. The olefin facial selectivity.

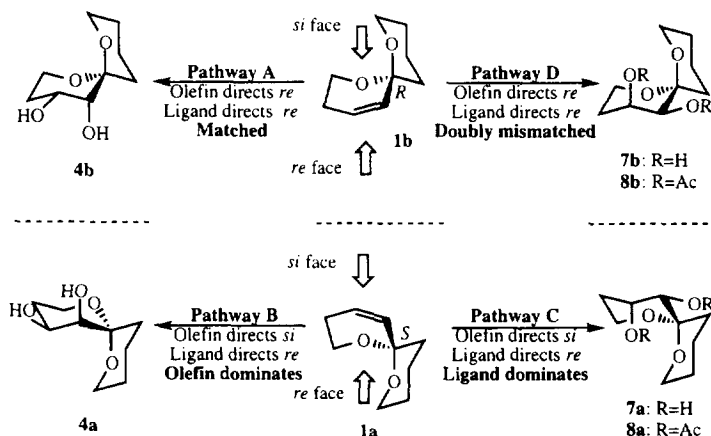
If the ligand facial preferences as predicted by the Sharpless mnemonic, are combined with the intrinsic diastereofacial bias of olefin **1** we can expect to achieve some degree of kinetic resolution of the enantiomers of olefin **1**. Firstly considering the AD of the *R*-enantiomer **1b**, using $(\text{DHQ})_2\text{PHAL}$ as the chiral ligand (Scheme 2), the ligand prefers to direct dihydroxylation to the *re*-face of the olefin and the olefin diastereofacial bias also directs dihydroxylation to the *re*-face of the alkene. The ligand and olefin facial preferences are “matched” and the reaction is kinetically favoured.



Scheme 2. Combined ligand and olefin facial selectivities.

Conversely considering the *S*-enantiomer, **1a**, using (DHQ)₂-PHAL as the chiral ligand, the ligand prefers to direct dihydroxylation to the *re*-face, however, the olefin diastereofacial bias is such that dihydroxylation is directed to the *si*-face of the alkene. The ligand and olefin facial preferences are “mismatched” and the reaction is kinetically disfavoured relative to the *R*-enantiomer. If it is assumed that the olefin diastereofacial bias were stronger than the ligand facial selectivity, kinetic resolution of the olefin enantiomers **1a** and **1b** would be observed, affording diol **4b** in enantiomeric excess.

There are four possible reaction pathways available for the AD of racemic olefin **1** using (DHQ)₂-PHAL as the chiral ligand (Scheme 3). Pathway A should be the fastest as the ligand and olefin facial selectivities are matched and therefore the corresponding transition state should have the lowest energy. Pathway D should be the slowest as both the ligand and the olefin prefer to direct dihydroxylation to the *re*-face of **1b**, whereas formation of **7b** requires dihydroxylation at the *si*-face of olefin **1b**. The transition state leading to formation of **7b** would therefore have the highest energy. In reaction pathways B and C the olefin prefers to direct dihydroxylation to the *si*-face of **1a** whereas the ligand prefers to direct dihydroxylation to the *re*-face of **1a**. If the facial selectivity of the olefin dominates, then **4a** is formed preferentially (pathway B) whereas if the ligand facial selectivity dominates, **7a** is formed preferentially (pathway C). Given the high intrinsic diastereoselectivity observed in the hydroxylation of olefin **1** with OsO₄/NMO, the olefin facial selectivity may well override the facial selectivity of the ligand. If it is assumed that pathway B is kinetically favoured over pathway C then the relative rates of reaction would follow the order A>B>C>D.



Scheme 3. Asymmetric dihydroxylation of olefin **1** with (DHQ)₂-PHAL as ligand.

We therefore have a predictive model for the stereochemical outcome of the AD of olefin **1** with (DHQ)₂-PHAL. An analogous but opposite argument can be outlined for the AD of olefin **1** with (DHQD)₂-PHAL. In order to evaluate the validity of the predictions outlined above, the Sharpless AD reaction was performed on olefins **1**, **2** and **3** using the ligands (DHQ)₂-PHAL, (DHQD)₂-PHAL, DHQ-IND and DHQD-IND.

The asymmetric dihydroxylation of unsaturated spiroacetal olefin **1**, carried out using OsO₄ (2.0 mol%), (DHQ)₂-PHAL (10 mol%), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3 equiv) and MeSO₂NH₂ (1.0 equiv) for 257 h at 0°C, afforded diol **4**¹² in 90% yield (based on recovered starting material) after purification by flash chromatography. A second diastereomer was also isolated from the reaction mixture albeit in much lower yield (5%, based on recovered starting material) and was assigned as diol **7**.

In the ¹H NMR spectrum for diol **7**, 5-H resonated as a double doublet at δ_H 3.20, *J*_{5,OH} 11.4 and *J*_{5,4} 3.4 Hz, establishing that 5-H was axial, and 4-H was equatorial. 4-H resonated as a one proton multiplet at δ_H 3.95–4.02 precluding direct assignment of the stereochemistry for 4-H therefore diol

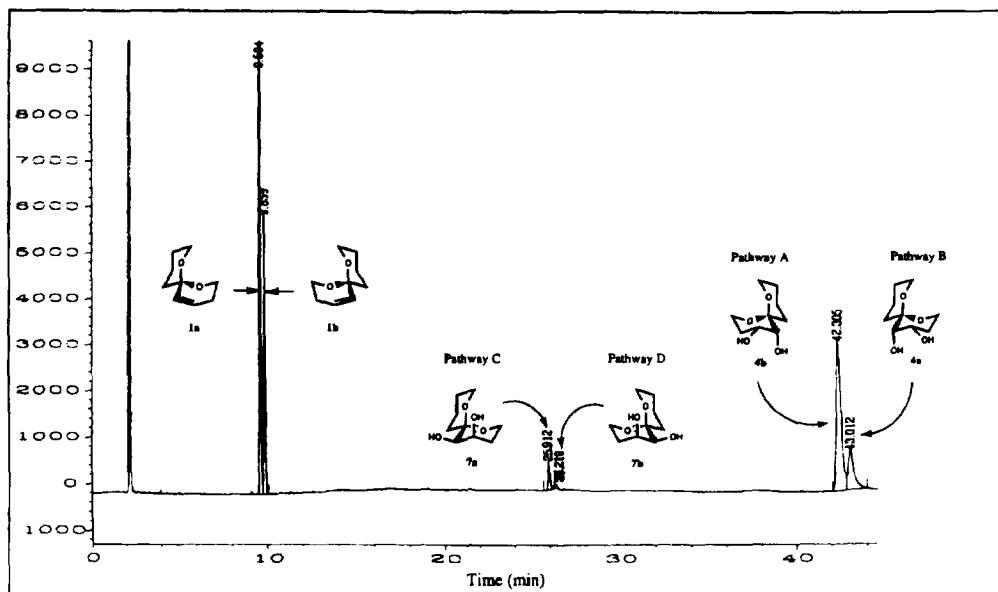


Figure 1. Gas chromatography — (DHQ)₂-PHAL and alkene **1** after 257 h at 0°C.

7 was converted to its diacetate derivative **8**. In the ¹H NMR spectrum for diacetate **8**, 5-H resonated as a doublet at δ_{H} 4.76, $J_{5,4}$ 3.8 Hz and 4-H resonated as a double double doublet at δ_{H} 5.27, $J_{4,5}$ 3.8, $J_{4,3\text{ax}}$ 3.0 and $J_{4,3\text{eq}}$ 3.0 Hz establishing that 5-H was axial orientation and 4-H was equatorial.

The asymmetric dihydroxylation of unsaturated spiroacetal olefin **1** using OsO₄ (2.0 mol%), (DHQD)₂-PHAL (10 mol%), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3 equiv) and MeSO₂NH₂ (1.0 equiv) for 257 h at 0°C afforded diol **4** and the diastereomeric diol **7** in 58% yield and 23% yield respectively, after purification by flash chromatography. Diol **4** was optically active with $[\alpha]_{\text{D}}$ -50.3 (c 0.64, CHCl₃) using (DHQ)₂-PHAL and $[\alpha]_{\text{D}}$ +21.9 (c 0.42, CHCl₃) using (DHQD)₂-PHAL. The absence of literature values for the specific rotation of each enantiomer precluded direct determination of the enantiomeric excesses. An alternative determination of the ee was therefore required. The assignment of absolute configuration is based upon the Sharpless mnemonic.

The Mosher ester derivatives¹³ of diol **4** proved difficult to synthesize thus prompting the use of chiral gas chromatography in order to determine the enantiomeric excess. Gas chromatographic analysis of the AD reaction mixture [(DHQ)₂-PHAL, 257 h at 0°C] was performed on a J&W permethylated β -cyclodextrin in DB[®]-1701 chiral column (Figure 1). Baseline resolved peaks with retention times of 9.59 and 9.86 minutes in a relative ratio of 2.35:1 were assigned to the *S*- and *R*-enantiomers respectively of the starting olefin **1**. The *S*-enantiomer **1a** was therefore determined to be in 40% enantiomeric excess. Baseline resolved peaks with retention times of 25.91 and 26.22 minutes in a relative ratio of 10:1 respectively were assigned to diol **7a** and diol **7b** respectively establishing that the enantiomeric excess of **7a** was 82%. Finally baseline resolved peaks with retention times of 42.30 and 43.01 minutes in a relative ratio of 3.2:1 were assigned to diol **4b** and diol **4a** respectively thus the enantiomeric excess of **4b** was 52%.

Gas chromatographic analysis of the AD reaction mixture [(DHQD)₂-PHAL, 18 h at 0°C] was also performed on a J&W permethylated β -cyclodextrin in DB[®]-1701 chiral column (Figure 2). Baseline resolved peaks with retention times of 9.52 and 9.76 minutes in a relative ratio of 1:5.1 were assigned to the *S*- and *R*-enantiomers respectively of the starting olefin **1** establishing the enantiomeric excess of **1b** to be 67%. Baseline resolved peaks with retention times of 25.74 and 26.13 minutes in a relative ratio of 1:13 respectively were assigned to diol **7a** and diol **7b** respectively therefore the enantiomeric

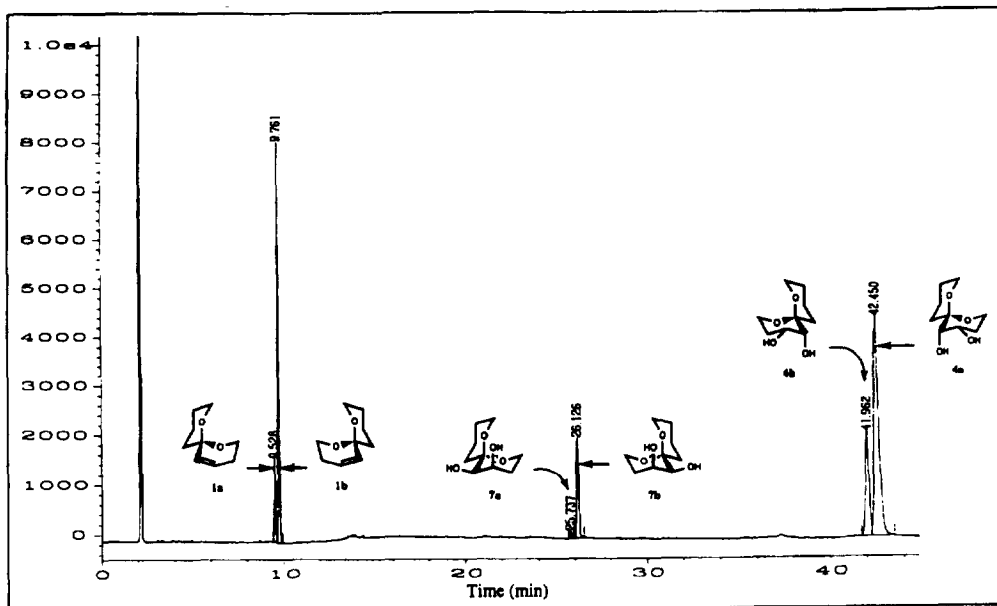


Figure 2. Gas chromatography —(DHQD)₂-PHAL and alkene **1** after 18 h at 0°C.

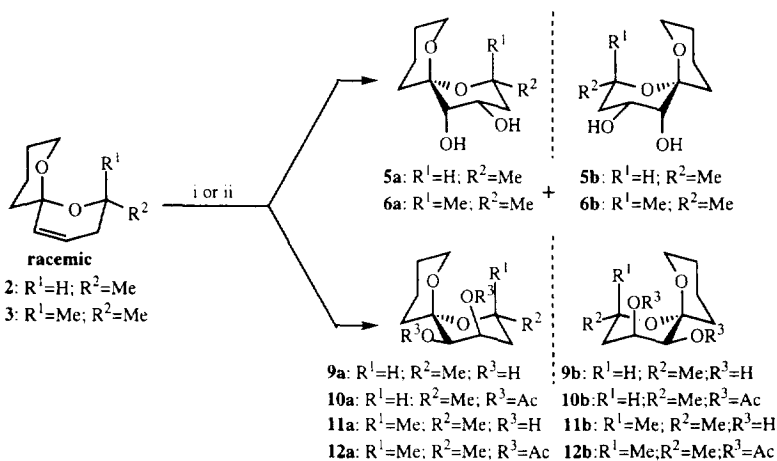
excess of **7b** was 86%. Finally baseline resolved peaks with retention times of 41.96 and 42.45 minutes in a relative ratio of 1:2.7 were assigned to diol **4b** and diol **4a** respectively establishing the enantiomeric excess of diol **4a** to be 46%.

In order to confirm that the signals observed in the chiral gas chromatography experiments were due to the diols **4a**, **4b**, **7a** and **7b**, the chiral GC experiment was run with CI mass spectrometry as the detection system. This experiment yielded baseline resolved peaks with retention times of 9.14 and 9.38 minutes exhibiting protonated parent ions at m/z 155 in the mass spectrum confirming that these signals corresponded to the olefin enantiomers. Baseline resolved peaks with retention times of 25.04 and 25.48 minutes were also observed exhibiting protonated parent ions at m/z 189 in the mass spectrum confirming that these signals corresponded to the enantiomers **7a** and **7b**. Finally baseline resolved peaks with retention times of 39.05 and 40.31 minutes were observed exhibiting protonated parent ions at m/z 189 in the mass spectrum confirming that these signals corresponded to the enantiomers **4b** and **4a**.

To complete the gas chromatographic investigation of the enantiomer distribution, authentic samples of racemic diol **4** and racemic alkene **1** were analysed by chiral gas chromatography. This experiment yielded baseline resolved peaks with retention times of 9.47 and 9.71 minutes in a relative ratio of 1:1 for the racemic olefin **1**. Baseline resolved peaks with retention times of 41.57 and 42.25 minutes in a relative ratio of 1:1 were observed for the racemic diol **4**. These results confirm that the AD of spiroacetal olefin **1** has induced chirality into diols **4** and **7**.

Having successfully synthesised diols **4** and **7** in enantiomeric excess, the AD of olefins **2** and **3** was investigated in order to determine the effect that methyl substituents at C-2 would have on the AD of the spiroacetal ring system. The asymmetric dihydroxylation of olefin **2** using OsO₄ (2.0 mol%), (DHQ)₂-PHAL (10 mol%), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3 equiv) and MeSO₂NH₂ (1.0 equiv) for 257 h at 0°C afforded diol **5** and diol **9** in 74% and 3% yield respectively (based on recovered starting material) after purification by flash chromatography (Scheme 4). The asymmetric dihydroxylation of unsaturated spiroacetal olefin **2** using OsO₄ (2.0 mol%), (DHQD)₂-PHAL (10 mol%), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3 equiv) and MeSO₂NH₂ (1.0 equiv), for 257 h at 0°C, afforded diol **5** and diol **9** in 82% yield and 4% yield respectively (based on recovered starting material). The stereochemistry

assigned to diol **9** was confirmed upon conversion to the diacetate **10** in a similar fashion to that described above for diol **7**.



Scheme 4. Reagents and conditions: (i) OsO₄ (2 mol%), (DHQ)₂-PHAL (10 mol%), MeSO₂NH₂ (1.0 equiv), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3.0 equiv), *t*-BuOH/H₂O (1:1) 12 ml, 257 h, 0°C, **5** (74%), **9** (3%) or **6** (75%), **11** (1%), (ii) OsO₄ (2 mol%), (DHQD)₂-PHAL (10 mol%), MeSO₂NH₂ (1.0 equiv), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3.0 equiv), *t*-BuOH/H₂O (1:1) 12 ml, 257 h, 0°C, **5** (82%), **9** (4%) or **6** (80%), **11** (1%).

Diol **5** was optically active with $[\alpha]_D -30.1$ (c 0.48, CHCl₃) using (DHQ)₂-PHAL as chiral ligand and $[\alpha]_D +28.7$ (c 0.98, CHCl₃) using (DHQD)₂-PHAL as chiral ligand. Gas chromatographic analysis of the AD reaction mixture using (DHQ)₂-PHAL for 300 h at 0°C, was performed on a J&W permethylated β-cyclodextrin in DB[®]-1701 chiral column. Baseline resolved peaks with retention times of 8.75 and 9.08 minutes in a relative ratio of 2.1:1 were assigned to the *S*- and *R*-enantiomers respectively of the starting spiroacetal olefin **2**. The enantiomeric excess of the *S*-enantiomer **2a** was therefore 36%. Baseline resolved peaks with retention times of 25.11 and 26.01 minutes in a relative ratio of 9.1:1 respectively were assigned to diol **9a** and diol **9b** respectively. Diol **9a** was therefore determined to be in 80% enantiomeric excess. Finally baseline resolved peaks with retention times of 36.69 and 37.50 minutes in a relative ratio of 4.5:1 were assigned to diol **5b** and diol **5a** respectively, establishing that **5b** was present in 64% enantiomeric excess.

Gas chromatographic analysis of the AD reaction mixture in which (DHQD)₂-PHAL was employed as the chiral ligand, for 257 h at 0°C, was also performed on a J&W permethylated β-cyclodextrin in DB[®]-1701 chiral column. Baseline resolved peaks with retention times of 8.77 and 9.06 minutes in a relative ratio of 1:2.15 were assigned to the *S*- and *R*- enantiomers respectively of the starting spiroacetal olefin **2**. The *R*-enantiomer, **2b** was therefore determined to be in 37% enantiomeric excess. Baseline resolved peaks with retention times of 23.17 and 23.66 minutes in a relative ratio of 1:10 respectively were assigned to diol **9a** and diol **9b** respectively, thus the enantiomeric excess of **9b** was 82%. Finally baseline resolved peaks with retention times of 43.75 and 44.76 minutes in a relative ratio of 1:3.5 were assigned to diol **5b** and diol **5a** respectively, establishing the enantiomeric excess of **5a** to be 56%.

The asymmetric dihydroxylation of olefin **3** using OsO₄ (2.0 mol%), (DHQ)₂-PHAL (10 mol%), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3 equiv) and MeSO₂NH₂ (1.0 equiv), for 257 h at 0°C, afforded diol **6** and diol **11** in 75% and 1% yield respectively (based on recovered starting material) after purification by flash chromatography (Scheme 4). Treatment of olefin **3** with OsO₄ (2.0 mol%), (DHQD)₂-PHAL (10 mol%), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3 equiv) and MeSO₂NH₂ (1.0 equiv), for 257 h at 0°C, afforded diol **6** and diol **11** in 80% and 1% yield respectively after purification by flash chromatography.

Table 1. Evolution of %e.e. for olefin **1** and diols **4** and **7** using (DHQ)₂-PHAL/(DHQD)₂-PHAL

| Ligand | Time (h) | %ee (1) | %ee (7) | %ee (4) | % Conversion (7) | % Conversion (4) |
|---------------------------|----------|---------|---------|---------|------------------|------------------|
| (DHQ) ₂ -PHAL | 18 | 4.6 | 59.8 | 66.3 | 0.6 | 10.2 |
| | 42 | 6.8 | 63.7 | 65.7 | 0.6 | 11.3 |
| | 113 | 18.7 | 70.6 | 62.3 | 1.5 | 27.3 |
| | 257 | 40.3 | 82.0 | 51.9 | 2.8 | 44.9 |
| (DHQD) ₂ -PHAL | 18 | 67.3 | 85.7 | 46.1 | 9.5 | 65.6 |
| | 42 | 49.2 | 90.5 | 25.7 | 14.4 | 81.3 |
| | 113 | 4.0 | 91.1 | 23.6 | 15.4 | 84.6 |
| | 257 | 0.0 | 91.1 | 23.6 | 15.4 | 84.6 |

Diol **6** was optically active with $[\alpha]_D -15.6$ (c 0.56, CHCl₃) using (DHQ)₂-PHAL and $[\alpha]_D +16.7$ (c 0.76, CHCl₃) using (DHQD)₂-PHAL. Gas chromatographic analysis of the AD reaction mixture in which (DHQ)₂-PHAL was employed as the chiral ligand, for 257 h at 0°C, was also performed on a J&W permethylated β-cyclodextrin in DB[®]-1701 chiral column. Baseline resolved peaks with retention times of 9.30 and 9.63 minutes in a relative ratio of 1.5:1 were assigned to the *S*- and *R*-enantiomers respectively of olefin **3**. The *S*-enantiomer, **3a** was therefore determined to be in 19% enantiomeric excess. Baseline resolved peaks with retention times of 27.23 and 27.32 minutes in a relative ratio of 3.1:1 respectively were assigned to diol **11a** and diol **11b** respectively, establishing the enantiomeric excess of **11a** to be 51%. Finally baseline resolved peaks with retention times of 43.65 and 44.83 minutes in a relative ratio of 2.34:1 were assigned to diol **6b** and diol **6a** respectively. Diol **6b** was therefore determined to be in 40% enantiomeric excess.

Gas chromatographic analysis of the AD reaction mixture in which (DHQD)₂-PHAL was employed as the chiral ligand, after 257 h at 0°C, in a similar fashion established the enantiomeric excess of **3b** to be 7%, **11b** to be 56% and **6a** to be 39%.

The evolution of the enantiomeric excess for olefins **1**, **2**, **3** and for diols **4**, **5**, **6**, **7**, **9**, **11** as well as the percentage conversions for the diol diastereomers, with respect to time, are summarised in Tables 1–3 and Figs 3 and 4. Considering the reaction of olefin **1** with (DHQ)₂-PHAL as the chiral ligand (Table 1, Figure 3). The enantiomeric excess of the *S*-olefin **1a** increases steadily throughout the initial stages of the reaction. Reaction pathways B and C which consume the *S*-enantiomer **1a** have the olefin and ligand selectivities mismatched, whereas reaction pathway A, which consumes the *R*-enantiomer **1b** have the olefin and ligand selectivities matched (Scheme 3). Thus the *R*-enantiomer **1b** is consumed at a greater rate than the *S*-enantiomer **1a** and the enantiomeric excess of the *S*-enantiomer **1a** increases. There will be a point in the course of the reaction where, as the concentration of the *R*-enantiomer **1b** decreases, the rate of reaction of the *S*-enantiomer **1a** begins to exceed that of the *R*-enantiomer **1b**. At this point the enantiomeric excess of the *S*-olefin **1a** would begin to decrease, however this point of the reaction was not attained within the time frame that this reaction was monitored. In the analogous AD reaction using (DHQD)₂-PHAL this point was reached after 18 h and the enantiomeric excess of the corresponding *R*-enantiomer begins to decrease until the olefin **1** is completely consumed (Figure 4).

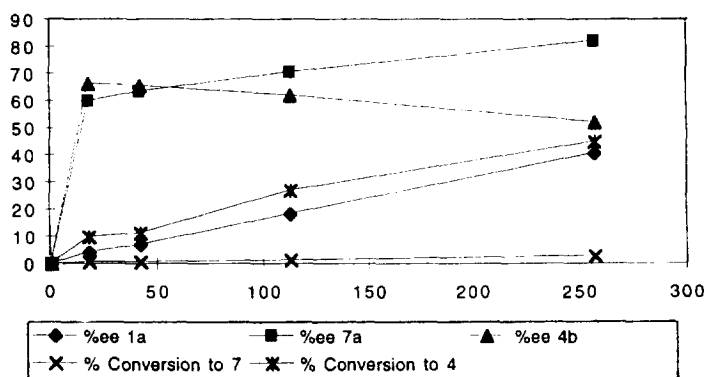
Considering next the evolution of the enantiomeric excess for diol **4b**. Reaction pathway A affording diol **4b** has the olefin and ligand facial selectivities matched, whereas reaction pathway B has the olefin and ligand selectivities mismatched. Thus in the initial stages of the reaction, the enantiomeric excess of diol **4b** increases rapidly. As the reaction progresses the concentration of the *R*-enantiomer of the olefin **1b** decreases relative to the *S*-enantiomer **1a**, hence the rate of reaction of **1a** also decreases. A point is reached, after 18 h, where the rate of reaction of the *S*-enantiomer **1a** via pathway B exceeds

Table 2. Evolution of %e.e. for olefin 2 and diols 5 and 9 using (DHQ)₂-PHAL/(DHQD)₂-PHAL

| Ligand | Time (h) | %ee (2) | %ee (9) | %ee (5) | % Conversion (9) | % Conversion (5) |
|---------------------------|----------|---------|---------|---------|------------------|------------------|
| (DHQ) ₂ -PHAL | 18 | 2.3 | 55.2 | 74.7 | 0.4 | 5.2 |
| | 42 | 4.8 | 60.0 | 68.9 | 1.9 | 20.4 |
| | 113 | 17.2 | 80.1 | 65.8 | 2.3 | 35.9 |
| | 257 | 35.6 | 80.2 | 63.8 | 2.4 | 36.1 |
| (DHQD) ₂ -PHAL | 18 | 2.6 | 64.5 | 70.9 | 0.7 | 5.4 |
| | 42 | 5.8 | 71.4 | 67.6 | 2.2 | 26.0 |
| | 113 | 16.0 | 75.4 | 61.9 | 3.6 | 32.8 |
| | 257 | 36.9 | 82.3 | 55.8 | 4.6 | 41.7 |

Table 3. Evolution of %e.e. for olefin 3 and diols 6 and 11 using (DHQ)₂-PHAL/(DHQD)₂-PHAL

| Ligand | Time (h) | %ee (3) | %ee (11) | %ee (6) | % Conversion (11) | % Conversion (6) |
|---------------------------|----------|---------|----------|---------|-------------------|------------------|
| (DHQ) ₂ -PHAL | 18 | 1.6 | 48.1 | 61.9 | 0.7 | 8.9 |
| | 42 | 3.8 | 49.2 | 57.7 | 1.7 | 18.6 |
| | 113 | 10.1 | 50.1 | 42.7 | 1.8 | 27.4 |
| | 257 | 18.6 | 51.2 | 40.3 | 2.5 | 47.8 |
| (DHQD) ₂ -PHAL | 18 | 0.6 | 51.9 | 34.8 | 0.2 | 6.1 |
| | 42 | 0.6 | 52.3 | 37.8 | 0.7 | 14.3 |
| | 113 | 5.9 | 54.2 | 39.4 | 1.4 | 27.6 |
| | 257 | 6.8 | 63.6 | 38.6 | 1.6 | 31.9 |

Figure 3. Evolution of enantiomeric excess for olefin 1 and diols 7 and 4 using (DHQ)₂-PHAL.

the rate of reaction of the *R*-enantiomer **1b** via pathway A. Thus the rate of formation of diol **4a** exceeds that of diol **4b** and the enantiomeric excess of diol **4b** begins to decrease.

At the completion of the AD reaction we would still expect to observe an enantiomeric excess of diol **4b** over diol **4a** since throughout the course of the reaction, the *S*-enantiomer of the olefin **1a** is also consumed by pathway C affording the diastereomeric diol **7a**. Although reaction pathway D also competes with reaction pathway A, the formation of diol **7b** requires attack at the *si*-face of olefin **1b** which is neither favoured by the olefin or the ligand. Thus the rate of reaction via pathway D is

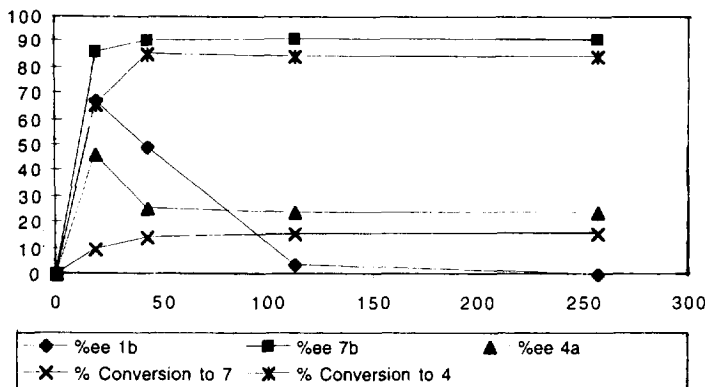


Figure 4. Evolution of enantiomeric excess for olefin **1** and diols **7** and **4** using (DHQD)₂-PHAL.

extremely slow compared with the rate of reaction via pathway A. Pathway C consumes much more of the *S*-enantiomer **1a** than pathway D consumes of the *R*-enantiomer **1b**. Therefore an enantiomeric excess of **4b** could be observed at 100% conversion due to the loss of some of the *S*-enantiomer of the olefin **1a** to the formation of the minor diol **7a**.

Finally considering the evolution of the enantiomeric excess for diol **7a**. Pathway C affording diol **7a** is *via* attack at the *re*-face of the *S*-enantiomer of olefin **1**. In this reaction pathway, the olefin prefers to direct dihydroxylation to the *si*-face of **1a**, whereas the ligand prefers to direct attack to the *re*-face of **1a**. Reaction pathway D that leads to diol **7b** requires dihydroxylation from the *si*-face of olefin **1b**, which is neither favoured by the olefin nor the ligand, hence the reaction rate is very slow. The enantiomeric excess of **7a** increases rapidly in the initial stages of the reaction. Although the rate of reaction of olefin **1a** *via* pathway C decreases as **1a** is consumed over time, it always exceeds the rate of reaction of the *R*-enantiomer **1b** *via* pathway D. Thus the enantiomeric excess of diol **7a** continues to increase slowly as the reaction progresses.

An analogous argument to that outlined above can be made for the reaction of olefin **1** with (DHQD)₂-PHAL as the chiral ligand, however in this case it is the *S*-olefin **1a** that has both the ligand and olefin facial selectivities matched. The rate of reaction using (DHQD)₂-PHAL proceeds faster than the corresponding reaction using (DHQ)₂-PHAL. As the concentration of **1a** decreases, the reaction rate of the *R*-olefin **1b** begins to exceed that of the *S*-enantiomer and the enantiomeric excess of the *S*-olefin **1a** decreases until the olefin has been completely consumed (Table 1, Figure 4).

The AD of olefins **1**, **2**, **3** was studied using the chiral ligands DHQ-IND and DHQD-IND which Sharpless recommends for *cis*-olefins.⁴ Thus treatment of olefin **1** using OsO₄ (2.0 mol%), DHQ-IND (10 mol%), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3 equiv) and MeSO₂NH₂ (1.0 equiv), for 257 h at 0°C, afforded diol **4** and diol **7** in 74% and 13% yield respectively, after purification by flash chromatography. Use of OsO₄ (2.0 mol%), DHQD-IND (10 mol%), K₃Fe(CN)₆ (3.0 equiv), K₂CO₃ (3 equiv) and MeSO₂NH₂ (1.0 equiv) afforded diol **4** and diol **7** in 78% and 3% yield respectively, after purification by flash chromatography.

Gas chromatographic analysis of the AD reaction mixture (as described above), using DHQ-IND as the chiral ligand, established the enantiomeric excess of **1a** to be 18%, **7a** to be 56% and **4b** to be 37%. Using DHQD-IND as the chiral ligand, the enantiomeric excess of **1b** was 67%, **7b** was 78% and **4a** was 25%. The AD of olefins **2** and **3** was also performed using DHQ-IND and DHQD-IND and the results are summarised in Table 4. These latter results established that better enantiomeric excesses for diols **4**, **5**, **6** were achieved employing the phthalazine based ligands (DHQ)₂-PHAL and (DHQD)₂-PHAL than using the indoline based ligands DHQ-IND and DHQD-IND.

In summary the Sharpless mnemonic for predicting facial preferences for asymmetric dihydroxylation

Table 4. %e.e. for olefins **1**, **2**, **3** and diols **4**, **5**, **6**, **7**, **9**, **11** using DHQ-IND and DHQD-IND

| Ligand | Olefin | %ee olefin | %ee minor diol | %ee major diol | %Conversion minor diol | %Conversion major diol |
|----------|----------|------------|----------------|----------------|------------------------|------------------------|
| DHQ-IND | 1 | 18 | 56 | 37 | 3.2 | 40.7 |
| DHQD-IND | 1 | 67 | 78 | 25 | 9.7 | 75.3 |
| DHQ-IND | 2 | 51 | 71 | 34 | 6.7 | 66.2 |
| DHQD-IND | 2 | 16 | 49 | 33 | 6.2 | 61.5 |
| DHQ-IND | 3 | 15 | 46 | 37 | 5.6 | 65.2 |
| DHQD-IND | 3 | 64 | 92 | 28 | 9.6 | 78.5 |

Key: *minor*= minor diastereomers isolated from the AD reaction, namely **7,9,11**
major= major diastereomers isolated from the AD reaction, namely **4,5,6**

tion, combined with the established intrinsic diastereofacial bias of the olefin, has been used to explain the observed kinetic resolution of spiroacetals **1,2,3**. Thus, spiroacetals **1,2,3** can be partially resolved by selecting appropriate conditions as described herein.

Experimental

General details

Melting points were determined using a Reichert Kofler block and are uncorrected. Infrared absorption spectra were recorded using Perkin Elmer 1600 Series FTIR spectrometer as Nujol Mulls or thin films between sodium chloride plates. ¹H NMR spectra were obtained using either a Bruker AM 400 or Bruker AC 200 spectrometer. ¹³C NMR data were recorded using a Bruker AM 400 or Bruker AC 200 spectrometer. ¹³C NMR spectra were interpreted with the aid of DEPT 135 and DEPT 90 experiments. Low resolution mass spectra were recorded using a VG 70-SE spectrometer operating at an accelerating voltage of 70eV. High resolution mass spectra were recorded at a nominal resolution of 5000 or 10000 as appropriate. Flash chromatography was performed using Merck Kieselgel 60 (230–400 Mesh) using 1:1 hexane–ethyl acetate as eluent. Spiroacetals **1**, **2**, **3** were prepared as described previously.¹⁴ Gas chromatographic analysis was performed using a Hewlett Packard 5890 Series II gas chromatograph equipped with a split/splitless injector and a flame ionisation detector. A J&W permethylated β-cyclodextrin in DB[®]-1701 chiral column was used with a column head pressure of 100 kPa and a temperature profile of 120°C for 10 minutes then 10°C min⁻¹ to 160°C, then isocratic at 160°C for 120 minutes. Analytical grade helium was used as the carrier gas.

1. Using (DHQ)₂-PHAL as the chiral ligand

[4S*,5S*,6S*]-1,7-Dioxaspiro[5.5]undecane-4,5-diol **4** and [4R*,5R*,6R*]-1,7-dioxaspiro[5.5]-undecane-4,5-diol **7**

A biphasic slurry of (±)-**1** (185 mg, 1.2 mmol), (DHQ)₂-PHAL (94 mg, 0.12 mmol), potassium ferricyanide (1.19 g, 3.6 mmol), potassium carbonate (500 mg, 3.6 mmol) and methanesulfonamide (114 mg, 1.2 mmol) in water/*t*-butanol (1:1) (12 cm³) was cooled to 0°C. Osmium tetroxide (0.3 cm³ of a 2.5 wt% solution in *t*-butanol, 0.02 mmol) was added and the reaction mixture stirred at 0°C for a further 257 h. Sodium metabisulphite (1.5 g, 7.9 mmol) was added and the reaction mixture allowed to warm to room temperature. After extraction with ethyl acetate (3×50 cm³), the combined organic extracts were washed with water (10 cm³) and dried over sodium sulphate. Removal of the solvent under reduced pressure gave a pale tan oil which was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford: diol **7** [5 mg, 5%, based on recovered **1** (94 mg)] as a colourless oil [Found: M⁺H (CI, NH₃) 189.1129. C₉H₁₇O₄ requires: M⁺H 189.1127]; ν_{\max} (Nujol) cm⁻¹ 3640–3210 (br, s, OH), 1094, 1010 (s, C–O); δ_{H} (200 MHz, CDCl₃) 1.38–2.16 (8H, m, 3-CH₂, 9-CH₂, 10-CH₂ and 11-CH₂), 2.62 (1H, d, $J_{\text{OH,5}}$ 11.4 Hz, 5-OH), 3.20 (1H, dd, $J_{5,\text{OH}}$ 11.4 and $J_{5,4}$

3.4 Hz, 5-H), 3.52–3.62 (2H, m, 8-CH₂), 3.70–3.87 (3H, m, 2-CH₂ and 4-OH), 3.95–4.02 (1H, m, 4-H); δ_C (50 MHz, CDCl₃) 17.6, 24.6, 30.0, 32.5 (CH₂, C-3, C-9, C-10 and C-11), 54.1, 61.3 (CH₂, C-8 and C-2), 68.6, 71.4 (CH, C-4 and C-5), 96.9 (quat, C-6); m/z (CI, NH₃) 189 (M⁺H, 35%), 171 (M⁺H–H₂O, 52), 153, (29), 115 (61), 101 (100), 85 (32). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 25.91 and 26.22 minutes in a relative ratio of 10:1. The enantiomeric excess was therefore determined to be 82%.¹⁵ Diol **4** [100 mg, 90% based on recovered **1** (94 mg)] as colourless needles m.p. 123–125°C (lit.¹², m.p. 124–125°C); $[\alpha]_D^{22}$ –50.3 (c 0.64 CHCl₃). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 42.30 and 43.01 minutes in a relative ratio of 3.2:1. The enantiomeric excess was therefore determined to be 52%.

[4R,5R*,6S*]-1,7-Dioxaspiro[5.5]undec-4,5-diyl diacetate 8*

The title compound **8** was prepared from diol **7** (3.0 mg, 0.02 mmol), triethylamine (6 mg, 0.06 mmol), acetic anhydride (4 mg, 0.04 mmol) and 4-dimethylaminopyridine (1 mg) in dichloromethane (5 cm³). Removal of the solvent under reduced pressure gave a pale yellow oil that was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford **8** (3.8 mg, 88%) as a colourless oil [Found: M⁺H (CI, NH₃), 273.1330. C₁₃H₂₀O₆ requires: M⁺H, 273.1338]; ν_{\max} (Nujol) cm⁻¹ 1720 (s, C=O), 1269 [s, C–O (ester)], 1020 (s, C–O); δ_H (200 MHz, CDCl₃) 1.24–1.87 (5H, m, 9-CH₂, 10-CH₂ and 11ax-H), 1.93–2.03 (1H, m, 3-CH₂), 2.10 (3H, s, Ac), 2.12 (3H, s, Ac), 2.15–2.34 (1H, m, 11eq-H), 3.53, (1H, ddd, $J_{8ax,8eq}$ 11.0, $J_{8ax,9ax}$ 4.6 and $J_{8ax,9eq}$ 1.8 Hz, 8ax-H), 3.75–3.78 (2H, m, 8eq-H and 2eq-H), 3.96 (1H, ddd, $J_{2ax,2eq}$ 11.8, $J_{2ax,3ax}$ 11.8 and $J_{2ax,3eq}$ 2.7 Hz, 2ax-H), 4.76 (1H, d, $J_{5,4}$ 3.8 Hz, 5-H), 5.27 (1H, ddd, $J_{4,5}$ 3.8, $J_{4,3ax}$ 3.0 and $J_{4,3eq}$ 3.0 Hz, 4-H) m/z (CI, NH₃) 273 (M⁺H, 60%), 213 (M⁺H–C₂H₄O₂, 20%), 195 (15), 172 (42), 153 (100), 135 (25), 114 (35), 101 (80).

[2R,4S*,5S*,6S*]-2-Methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 5 and [2R*,4R*,5R*,6S*]-2-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 9*

A biphasic slurry of (\pm)-**2** (204 mg, 1.2 mmol), (DHQ)₂–PHAL (94 mg, 0.12 mmol), potassium ferricyanide (1.19 g, 3.6 mmol), potassium carbonate (500 mg, 3.6 mmol) and methanesulfonamide (114 mg, 1.2 mmol) in water/*t*-butanol (1:1) (12 cm³) was cooled to 0°C. Osmium tetroxide (0.3 cm³ of a 2.5 wt% solution in *t*-butanol, 0.02 mmol) was added and the reaction mixture stirred at 0°C for a further 257 h. Work-up as described above gave a pale tan oil which was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford: diol **9** [3 mg, 3% based on recovered **2** (124 mg)] as a colourless oil [Found: M⁺H (CI, NH₃) 203.2611. C₁₀H₁₈O₄ requires: M⁺H 203.2605]; ν_{\max} (Nujol) cm⁻¹ 3643–3217 (br, s, OH), 1086, 1018 (s, C–O); δ_H (200 MHz, CDCl₃) 1.22 (3H, d, $J_{Me,2}$ 6.3 Hz, Me), 1.37–2.16 (8H, m, 3-CH₂, 9-CH₂, 10-CH₂ and 11-CH₂), 2.57 (1H, d, $J_{OH,5}$ 10.4 Hz, 5-OH), 3.19 (1H, d, $J_{5,OH}$ 10.4 Hz, 5-H), 3.51–3.73 (2H, m, 2-H and 4-OH), 3.91–4.00 (3H, m, 4-H and 8-CH₂); m/z (CI, NH₃) 203 (M⁺H, 31%), 212 (M⁺H–H₂O, 43), 115 (61), 101 (100), 85 (32). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 25.11 and 26.01 minutes in a relative ratio of 9.1:1. The enantiomeric excess was therefore determined to be 80%.¹⁵ Diol **5** [71 mg, 74% based on recovered **2** (124 mg)] as a colourless oil; $[\alpha]_D^{22}$ –30.1 (c 0.54, CHCl₃). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 36.69 and 37.50 minutes in a relative ratio of 4.5:1. The enantiomeric excess was therefore determined to be 64%.

[2R,4R*,5R*,6S*]-2-Methyl-1,7-dioxaspiro[5.5]undec-4,5-diyl diacetate 10*

The title compound **10** was prepared from diol **9** (3.0 mg, 0.02 mmol), triethylamine (6 mg, 0.06 mmol), acetic anhydride (4 mg, 0.04 mmol) and 4-dimethylaminopyridine (1 mg) in dichloromethane (5 cm³). Removal of the solvent under reduced pressure gave a pale yellow oil that was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford diacetate **10** (3.9 mg, 91%)

as a colourless oil ν_{\max} (Nujol) cm^{-1} 1720 (s, C=O), 1269 [s, C–O (ester)], 1020 (s, C–O); δ_{H} (200 MHz, CDCl_3) 1.24–1.87 (5H, m, 9- CH_2 , 10- CH_2 and 11 $_{\text{ax}}$ -H), 1.93–2.03 (1H, m, 3- CH_2), 1.21 (3H, D, $J_{\text{Me},2}$ 6.3 Hz, Me), 1.35–1.97 (8H, m, 3- CH_2 9- CH_2 10- CH_2 and 11- CH_2), 2.11 (3H, s, Ac), 2.12 (3H, s, Ac), 3.71–3.76 (1H, m, 2-H), 4.06–4.17 (2H, m, 8- CH_2), 4.73 (1H, d, $J_{5,4}$ 4.0 Hz, 5-H), 5.27 (1H, ddd, $J_{4,5}$ 4.0, $J_{4,3_{\text{ax}}}$ 3.5 and $J_{4,3_{\text{eq}}}$ 3.5 Hz, 4-H).

[4S,5S*,6S*]-2,2-Dimethyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 6 and [4R*,5R*,6S*]-2,2-dimethyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 11*

A biphasic slurry of (\pm)-**3** (224 mg, 1.2 mmol), (DHQ)₂-PHAL (96 mg, 0.12 mmol), potassium ferricyanide (1.20 g, 3.6 mmol), potassium carbonate (498 mg, 3.6 mmol) and methanesulfonamide (116 mg, 1.2 mmol) in water/*t*-butanol (1:1) (12 cm^3) was cooled to 0°C. Osmium tetroxide (0.3 cm^3 of a 2.5 wt% solution in *t*-butanol, 0.02 mmol) was added and the reaction mixture stirred at 0°C for a further 257 h. Work-up as described above gave a pale tan oil which was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford: diol **11** [0.5 mg, 1% based on recovered **3** (110 mg)] as a colourless oil [Found: M^+H (Cl, NH_3) 217.2911. $\text{C}_{10}\text{H}_{20}\text{O}_4$ requires: M^+H 217.2956]; ν_{\max} (Nujol) cm^{-1} 3638–3204 (br, s, OH), 1078, 1009 (s, C–O); δ_{H} (200 MHz, CDCl_3) 1.20 (3H, s, Me), 1.35 (3H, s, Me), 1.38–2.16 (8H, m, 3- CH_2 , 9- CH_2 , 10- CH_2 and 11- CH_2), 2.65 (1H, d, $J_{\text{OH},5}$ 9.8 Hz, 5-OH), 3.25 (1H, dd, $J_{5,\text{OH}}$ 9.8 and $J_{5,4}$ 4.0 Hz, 5-H), 3.43 (1H, d, $J_{\text{OH},4}$ 9.8 Hz, 4-OH), 3.61–3.69 (2H, m, 8- CH_2), 3.94 (1H, ddd, $J_{4,5}$ 4.0, $J_{4,3_{\text{ax}}}$ 3.7 and $J_{4,3_{\text{eq}}}$ 3.5 Hz, 4-H); m/z (Cl, NH_3) 217 (M^+H , 31%), 212 ($\text{M}^+\text{H}-\text{H}_2\text{O}$, 43), 115 (61), 101 (100), 85 (32). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 27.23 and 27.52 minutes in a relative ratio of 3.1:1. The enantiomeric excess was therefore determined to be 51%.¹⁵ Diol **6** [93 mg, 75% based on recovered **3** (110 mg)] as colourless needles, m.p. 93–95°C (lit.¹², m.p. 94–96°C); $[\alpha]_{\text{D}}^{22}$ –15.6 (c 0.48, CHCl_3). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 43.65 and 44.83 minutes in a relative ratio of 2.34:1. The enantiomeric excess was therefore determined to be 40%.

II. Using (DHQD)₂-PHAL as the chiral ligand

[4S,5S*,6S*]-1,7-Dioxaspiro[5.5]undecane-4,5-diol 4 and [4R*,5R*,6S*]-1,7-dioxaspiro[5.5]undecane-4,5-diol 7*

A biphasic slurry of (\pm)-**1** (187 mg, 1.2 mmol), (DHQD)₂-PHAL (96 mg, 0.12 mmol), potassium ferricyanide (1.23 g, 3.6 mmol), potassium carbonate (500 mg, 3.6 mmol) and methanesulfonamide (116 mg, 1.2 mmol) in water/*t*-butanol (1:1) (12 cm^3) was cooled to 0°C. Osmium tetroxide (0.3 cm^3 of a 2.5 wt% solution in *t*-butanol, 0.02 mmol) was added and the reaction mixture stirred at 0°C for a further 257 h. Work-up as described above gave a pale tan oil which was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford: diol **7** (51 mg, 23%) as a colourless oil. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 25.86 and 26.24 minutes in a relative ratio of 1:21. The enantiomeric excess was therefore determined to be 91%.¹⁵ Diol **4** (131 mg, 58%) as colourless needles m.p. 123–125°C (lit.¹², m.p. 124–125°C). $[\alpha]_{\text{D}}^{22}$ +21.88 (c, 4.2×10^{-3} , CHCl_3). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 42.15 and 42.73 minutes in a relative ratio of 1:1.65. The enantiomeric excess was therefore determined to be 24%.

[2R,4S*,5S*,6S*]-2-Methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 5 and [2R*,4R*,5R*,6S*]-2-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 9*

A biphasic slurry of (\pm)-**2** (211 mg, 1.2 mmol), (DHQD)₂-PHAL (98 mg, 0.12 mmol), potassium ferricyanide (1.21 g, 3.6 mmol), potassium carbonate (490 mg, 3.6 mmol) and methanesulfonamide (112 mg, 1.2 mmol) in water/*t*-butanol (1:1) (12 cm^3) was cooled to 0°C. Osmium tetroxide (0.3 cm^3 of a 2.5 wt% solution in *t*-butanol, 0.02 mmol) was added and the reaction mixture stirred at 0°C for a further 257 h. Work-up as described above gave a pale tan oil which was purified by flash

chromatography using hexane–ethyl acetate (6:4) as eluent to afford: diol **9** [4 mg, 4% based on recovered **2** (114 mg)] as a colourless oil. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 23.17 and 23.66 minutes in a relative ratio of 1:10. The enantiomeric excess was therefore determined to be 82%.¹⁴ Diol **5** [87 mg, 82% based on recovered **2** (114 mg)] as a colourless oil; $[\alpha]_D^{22} +28.7$ (c 0.98, CHCl₃). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 36.56 and 37.21 minutes in a relative ratio of 1:3.5. The enantiomeric excess was therefore determined to be 56%.

[4S,5S*,6S*]-2,2-Dimethyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 6 and [4R*,5R*,6S*]-2,2-dimethyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 11*

A biphasic slurry of (±)-**3** (229 mg, 1.2 mmol), (DHQD)₂-PHAL (94 mg, 0.12 mmol), potassium ferricyanide (1.21 g, 3.6 mmol), potassium carbonate (480 mg, 3.6 mmol) and methanesulfonamide (120 mg, 1.2 mmol) in water/*t*-butanol (1:1) (12 cm³) was cooled to 0°C. Osmium tetroxide (0.3 cm³ of a 2.5 wt% solution in *t*-butanol, 0.02 mmol) was added and the reaction mixture stirred at 0°C for a further 257 h. Work-up as described above gave a pale tan oil which was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford: diol **11** [0.7 mg, 1% based on recovered **3** (114 mg)] as a colourless oil. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 26.33 and 27.53 minutes in a relative ratio of 1:3.5. The enantiomeric excess was therefore determined to be 56%.¹⁵ Diol **6** [66 mg, 80% based on recovered **3** (150 mg)] as colourless needles m.p. 93–95°C (lit.¹² m.p. 94–96°C); $[\alpha]_D^{22} +16.7$ (c, 0.76, CHCl₃). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 43.75 and 44.76 minutes in a relative ratio of 1:2.3. The enantiomeric excess was therefore determined to be 39%.

III. Using DHQ-IND as the chiral ligand

[4S,5S*,6S*]-1,7-Dioxaspiro[5.5]undecane-4,5-diol 4 and [4R*,5R*,6S*]-1,7-dioxaspiro[5.5]undecane-4,5-diol 7*

A biphasic slurry of (±)-**1** (94 mg, 0.61 mmol), DHQ-IND⁷ (85 mg, 0.14 mmol), potassium ferricyanide (0.6 g, 1.8 mmol), potassium carbonate (250 mg, 1.8 mmol) and methanesulfonamide (60 mg, 0.6 mmol) in water/*t*-butanol (1:1) (6 cm³) was cooled to 0°C. Osmium tetroxide (0.15 cm³ of a 2.5 wt% solution in *t*-butanol, 0.01 mmol) was added and the reaction mixture stirred at 0°C for a further 257 h. Work-up as described above gave a pale tan oil, that was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford: diol **7** [10 mg, 13% based on recovered **1** (53 mg)] as a colourless oil. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 25.59 and 25.99 minutes in a relative ratio of 3.5:1. The enantiomeric excess was therefore determined to be 56%. Diol **4** [35 mg, 74% based on recovered **1** (53 mg)] as colourless needles, m.p. 121–127°C (lit.¹², m.p. 124–125°C). Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 41.55 and 42.25 minutes in a relative ratio of 2.2:1. The enantiomeric excess was therefore determined to be 37%.

[2R,4S*,5S*,6S*]-2-Methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 5 and [2R*,4R*,5R*,6S*]-2-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 9*

A biphasic slurry of (±)-**2** (118 mg, 0.69 mmol), DHQ-IND (83 mg, 0.14 mmol), potassium ferricyanide (0.6 g, 1.8 mmol), potassium carbonate (250 mg, 1.8 mmol) and methanesulfonamide (60 mg, 0.6 mmol) in water/*t*-butanol (1:1) (6 cm³) was cooled to 0°C. Osmium tetroxide (0.15 cm³ of a 2.5 wt% solution in *t*-butanol, 0.01 mmol) was added and the reaction mixture stirred at 0°C for a further 300 h. Work-up as described above gave a pale tan oil that was purified by flash chromatography using hexane–ethyl acetate (6:4) as eluent to afford: diol **9** [3 mg, 4% based on recovered **2** (61 mg)] as a colourless oil. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 24.79 and 25.14 minutes in a relative ratio of 5.8:1. The enantiomeric excess was

therefore determined to be 71%. Diol **5** [35 mg, 51% based on recovered **2** (61 mg)] as a colourless oil. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 36.09 and 36.85 minutes in a relative ratio of 2.0:1. The enantiomeric excess was therefore determined to be 34%.

[4S,5S*,6S*]-2,2-Dimethyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 7 and [4R*,5R*,6S*]-2,2-dimethyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 11*

A biphasic slurry of (\pm)-**3** (110 mg, 0.60 mmol), DHQ-IND (80 mg, 0.14 mmol), potassium ferricyanide (0.6 g, 1.8 mmol), potassium carbonate (250 mg, 1.8 mmol), and methanesulfonamide (60 mg, 0.6 mmol) in water/*t*-butanol (1:1) (6 cm³) was cooled to 0°C. Osmium tetroxide (0.15 cm³ of a 2.5 wt% solution in *t*-butanol, 0.01 mmol) was added and the reaction mixture stirred at 0°C for a further 300 h. Work-up as described above gave a pale tan oil that was purified by flash chromatography using hexane-ethyl acetate (6:4) as eluent to afford: diol **11** (0.6 mg, 1% based on recovered starting material, 34 mg) as a colourless oil. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 26.84 and 27.12 minutes in a relative ratio of 2.7:1. The enantiomeric excess was therefore determined to be 46%. Diol **7** [77 mg, 78% based on recovered **3** (34 mg)]. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 43.15 and 44.31 minutes in a relative ratio of 2.2:1. The enantiomeric excess was therefore determined to be 37%.

IV. Using DHQD-IND as the chiral ligand

[4S,5S*,6S*]-1,7-Dioxaspiro[5.5]undecane-4,5-diol 4 and [4R*,5R*,6S*]-1,7-dioxaspiro[5.5]undecane-4,5-diol 7*

A biphasic slurry of (\pm)-**1** (100 mg, 0.65 mmol), DHQD-IND (91 mg, 0.16 mmol), potassium ferricyanide (0.6 g, 1.8 mmol), potassium carbonate (250 mg, 1.8 mmol), and methanesulfonamide (64 mg, 0.7 mmol) in water/*t*-butanol (1:1) (6 cm³) was cooled to 0°C. Osmium tetroxide (0.15 cm³ of a 2.5 wt% solution in *t*-butanol, 0.01 mmol) was added and the reaction mixture stirred at 0°C for a further 257 h. Work-up as described above gave a pale tan oil that was purified by flash chromatography using hexane-ethyl acetate (6:4) as eluent to afford: diol **7** [3 mg, 3% based on recovered **1** (22 mg)] as a colourless oil. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 25.47 and 25.85 minutes in a relative ratio of 1:8. The enantiomeric excess was therefore determined to be 78%. Diol **4** [74 mg, 78% based on recovered **1** (22 mg)] for which gas chromatographic analysis showed two baseline resolved peaks with retention times of 41.08 and 41.61 minutes in a relative ratio of 1:1.65. The enantiomeric excess was therefore determined to be 25%.

[2R,4S*,5S*,6S*]-2-Methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 5 and [2R*,4R*,5R*,6S*]-2-methyl-1,7-dioxaspiro[5.5]undecane-4,5-diol 9*

A biphasic slurry of (\pm)-**2** (102 mg, 0.60 mmol), DHQD-IND (83 mg, 0.14 mmol), potassium ferricyanide (0.6 g, 1.8 mmol), potassium carbonate (250 mg, 1.8 mmol), and methanesulfonamide (60 mg, 0.6 mmol) in water/*t*-butanol (1:1) (6 cm³) was cooled to 0°C. Osmium tetroxide (0.15 cm³ of a 2.5 wt% solution in *t*-butanol, 0.01 mmol) was added and the reaction mixture stirred at 0°C for a further 300 h. Work-up as described above gave a pale tan oil that was purified by flash chromatography using hexane-ethyl acetate (6:4) as eluent to afford: diol **9** [5 mg, 5% based on recovered **2** (13 mg)]. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 34.64 and 35.07 minutes in a relative ratio of 1:2.9. The enantiomeric excess was therefore determined to be 49%. Diol **5** [88 mg, 83% based on recovered **2** (13 mg)] as a colourless oil for which chromatographic analysis showed two baseline resolved peaks with retention times of 36.12 and 36.93 minutes in a relative ratio of 1:2. The enantiomeric excess was therefore determined to be 33%.

[4S*,5S*,6S*]-2,2-Dimethyl-1,7-dioxaspiro[5.5]undecane-4,5-diol **6** and [4R*,5R*,6S*]-2,2-dimethyl-1,7-dioxaspiro[5.5]undecane-4,5-diol **11**

A biphasic slurry of (\pm)-**3** (138 mg, 0.75 mmol), DHQ-IND (86 mg, 0.14 mmol), potassium ferricyanide (0.6 g, 1.8 mmol), potassium carbonate (250 mg, 1.8 mmol), and methanesulfonamide (60 mg, 0.6 mmol) in water/*t*-butanol (1:1) (6 cm³) was cooled to 0°C. Osmium tetroxide (0.15 cm³ of a 2.5 wt% solution in *t*-butanol, 0.01 mmol) was added and the reaction mixture stirred at 0°C for a further 168 h. Work-up as described before gave a pale tan oil that was purified by flash chromatography using hexane-ethyl acetate (6:4) as eluent to afford: diol **11** [0.6 mg, 1% based on recovered **3** (53 mg)] as a colourless oil. Gas chromatographic analysis of this material showed two baseline resolved peaks with retention times of 26.84 and 27.12 minutes in a relative ratio of 1:27. The enantiomeric excess was therefore determined to be 93%. Diol **6** [73 mg, 74% based on recovered **3** (53 mg)] for which gas chromatographic analysis showed two baseline resolved peaks with retention times of 43.06 and 44.56 minutes in a relative ratio of 1:1.8. The enantiomeric excess was therefore determined to be 28%.

General procedure for monitoring the asymmetric dihydroxylation reaction with respect to time

Aliquots of the AD reaction mixture (0.5 cm³) for olefins **1**, **2**, **3** were taken after the reaction had progressed for 18 h, 42 h, 113 h, and 257 h, respectively. The aliquots were immediately quenched with sodium metabisulphite and allowed to warm to room temperature. After extraction with ethyl acetate, the aliquots were washed with two molar potassium hydroxide, then water, and dried over sodium sulphate. The solvent was removed at reduced pressure and the samples dissolved in 0.5 ml HPLC grade dichloromethane. Chiral gas chromatographic analysis was performed using an identical procedure to that outlined previously. The enantiomeric excesses and percentage conversions for olefins **1**, **2**, **3** to diols **4**, **5**, **6**, **7**, **9**, **11** respectively, are summarised in Tables 1–3 and Figs 3 and 4.

Acknowledgements

We thank the University of Sydney and the Australian Research Council for financial support. We thank Professor K.B. Sharpless and Dr M. Vannieuwenhze (Scripps Research Institute) for helpful advice and Dr Chris Easton (Australian National University) for bringing reference 10 to our attention.

References

1. For reviews on spiroacetals see: (a) Boivin, T.L.B. *Tetrahedron*, **1987**, *43*, 3309. (b) Perron, F., Albizzati, K.F. *Chem. Rev.*, **1989**, *89*, 1617.
2. Fletcher, M.T.; Kitching, W.B. *Chem. Rev.*, **1995**, 799.
3. (a) Lynn, D.G.; Phillips, N.J.; Hutton, W.C.; Shabanowitz, J.; Fennell, I.; Cole, R.J. *J. Am. Chem. Soc.*, **1982**, *104*, 7319. (b) Philips, N.J.; Cole, R.J.; Lynn, D.G. *Tetrahedron Lett.*, **1987**, *28*, 1619.
4. For reviews on the asymmetric dihydroxylation reaction see: (a) Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.*, **1994**, *94*, 2483. (b) Balavoine, G.A.; Manoury, E. *Appl. Organomet. Chem.*, **1995**, *9*, 199.
5. Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.*, **1992**, *57*, 2768 and references cited therein.
6. Morikawa, K.; Park, J.; Andersson, P.G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1993**, *115*, 8463.
7. Wang, L.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1992**, *114*, 7568.
8. Becker, H.; King, S.B.; Tanniguchi, M.; Vanhessche, K.P.M., Sharpless, K.B. *J. Org. Chem.*, **1995**, *60*, 3940.
9. Bakkeren, F.J.A.D.; Klunder, A.J.H.; Zwanenburg, B. *Tetrahedron*, **1996**, *52*, 7901.
10. Gardiner, J.M.; Norret, M.; Sadler, I.H. *J. Chem. Soc. Chem. Commun.*, **1996**, 2709.
11. Yannakopoulou, K.; Mentzafos, D.; Mavridis, I.M.; Dandika, K. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 2480.

12. Brimble, M.A.; Nairn, M.R. *Aust. J. Chem.*, **1993**, *46*, 195.
13. Dale, J.A.; Dull, D.L.; Mosher, H.S.; *J. Org. Chem.*, **1968**, *33*, 2543.
14. Brimble, M.A.; Edmonds, M.K.; Williams, G.M. *Tetrahedron*, **1992**, *48*, 6455.
15. Optical rotations for this diastereomer were not obtained due to their instability when using a small amount of compound in a relatively large amount of solvent, resulting in variable readings.

(Received in UK 24 March 1997)