Electronic Supplementary Information:

Ligand-Accelerated Vanadium-Catalysed Epoxidation in Water

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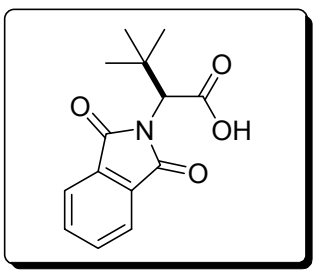
Experimental

General Methods. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 25 ^oC unless otherwise indicated with an error of <±0.1. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded in deuterated solvents as specified, ^1H at 400 MHz and ^{13}C at 100.6 MHz. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film between KBr plates or for $CHCl_3$ solutions. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen in oven-dried glassware twice evacuated and filled with nitrogen. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use as follows: diethyl ether from lithium aluminium hydride; tetrahydrofuran from sodium/benzophenone; dichloromethane from calcium hydride, toluene from sodium. Petroleum ether refers to the fraction boiling in the range of 40-60 ^oC. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR and MS data and by TLC behaviour.

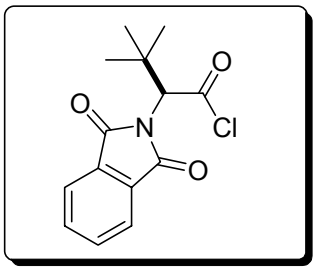
Allylic alcohols **4**, **5**, **8**, **10, 11** were purchased from Sigma-Aldrich and used as received. Synthesis of benzhydryl hydroxylamine, ligands **1** and **2** was reported previously.[1]

Synthesis of ligand 3.

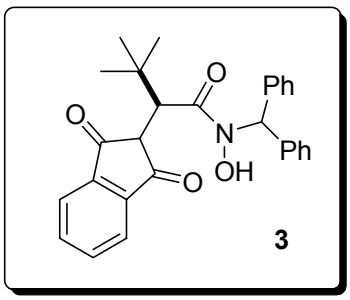


(*S*)-(-)-2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3,3-dimethyl-butyric acid.[2] In a 250 mL flask fitted with a water separator (Dean Stark) and a reflux condenser were placed L-*tert*-leucine (1.31 g, 10 mmol), finely ground phthalic anhydride (1.48

g, 10 mmol), toluene (20 mL) and triethylamine (0.13 mL, 10 mmol). The flask was heated with an electric mantle so as to maintain a vigorous reflux. Separation of the water is rapid at the beginning but becomes slower with time and is virtually over in 1.5 hours. After 2h the water separator and the condenser were disconnected, and the volatile material was removed from the mixture under reduced pressure. The solid residue was stirred with 20 mL of cold water and 0.2 mL of concentrated hydrochloric acid until all the lumps were broken. The mixture was filtered under suction, and the product was washed with cold water (3 × 5 mL). The obtained white crystals (2.46 g, 94%) were used in the next step without further purification: $[\alpha]_D$ -54.2 (*c* 1.00, EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (s, 9H, CH_3), 4.53 (s, 1H, CH), 7.93-7.99 (m, 4H, arom), consistent with the literature data.[3]



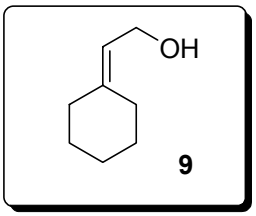
(*S*)-2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3,3-dimethyl-butyryl chloride. Phosphorus pentachloride (191 mg, 0.92 mmol) was added in one portion to a stirred solution of *N*-phthalic protected acid (200 mg, 0.76 mmol) in anhydrous ether (3 mL) in a 50 mL round bottom flask under nitrogen atmosphere. After stirring at room temperature for 2 h, *n*-hexane (15 mL) was added and the mixture was left in a freezer overnight. The precipitated crystals were quickly separated by filtration, washed with *n*-hexane, and used immediately in the next step.



(*S*)-(-)-*N*-Benzhydryl-2-(1,3-dioxo-indan-2-yl)-N-hydroxy-3,3-dimethyl-butyramide (3).[1] A solution of benzhydryl hydroxylamine (152 mg, 0.76 mmol) in dry dichloromethane (3 mL) was added to a solution of acid chloride (200 mg, 0.76 mmol) in dry dichloromethane (3 mL) under nitrogen atmosphere at –10 ^oC (cryocooler). The resulting mixture was stirred at –10 ^oC for 30 min and then it was allowed to warm to room temperature. After 2 h, the reaction was quenched with a 10% aqueous solution of Na_2CO_3 (0.8 mL). A saturated solution of ammonium chloride was added and the mixture was extracted with dichloromethane. The organic extracts were dried over $MgSO_4$ and concentrated in *vacuo* to afford a brown oil. Purification, using column chromatography on silica gel (15 × 3 cm) with an *n*-hexane-ethyl acetate mixture (4:1) furnished **3** (115 mg, 34%) as white crystals, which

gave positive red-wine coloured stain with $FeCl_3$ on TLC: $[\alpha]_D$ –0.4 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H, CH_3), 4.85 (s, 1H, CH), 7.06-7.56 (m, 14H, arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6 (CH_3), 123.3 (CH), 128.3 (CH), 133.9 (CH), 137.5 (C), 167.5 (CO), IR (KBr) ν_{max} 3415, 3207, 2965, 1772, 1693, 1670, 1496, 1454, 1391, 1334, 1188, 1103, 891, 738 cm^{-1}; HRMS (EI) *m*/*z* 442.1889 ($C_{27}H_{26}O_4N_2$ requires 442.1893).

Synthesis of allylic alcohol 9



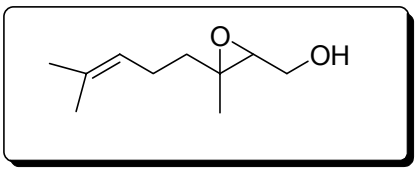
Step 1. A solution of cyclohexanone (1.25 g, 12.6 mmol) was added to a solution of ethyl(triphenylphosphoranyl)acetate (4.4 g, 12.6 mmol) in dry *p*-xylene (10 mL) and the mixture was heated under reflux for 24 h. The solvent was then removed under reduced pressure, the residue was purified by column chromatography on silica gel (25 × 4 cm) using a 10:1 mixture petroleum-ether/ethyl-acetate as eluent to furnish *cyclohexylidene-acetic acid ethyl ester* as a colourless oil (1.72 g, 82%): ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 3H, CH_3), 1.59-1.71 (m, 6H, CH_2), 2.18-2.24 (m, 2H, CH_2), 4.16 (q, *J* = 7.2 Hz, 2H, OCH_2), 5.63 (s, 1H, CH), consistent with the literature data.[4]

Step 2. Following a literature protocol,[5] a 1.5M solution of DIBAL-H in toluene (12.6 mL, 18.9 mmol) was added to a solution of cyclohexylidene-acetic acid ethyl ester (1.59 g, 9.45 mmol) in dry ether (12 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 20 h. Then, the mixture was diluted with ether (25 mL), cooled to 0 °C, and quenched by a careful addition of brine (25 mL), followed by a dropwise addition of 4M HCl (25 mL). The aqueous layer was extracted with ether (3 × 50 mL), the combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (25 × 4 cm) using a 10:1 mixture petroleum ether - ethyl acetate as eluent furnished allylic alcohol **45** as a colourless oil (706 mg, 59%): ^1H NMR (400 MHz, $CDCl_3$) δ 1.51-1.60 (m, 6H, CH_2), 2.13-2.22 (m, 2H, CH_2), 4.16 (d, *J* = 7.2 Hz, 2H, OCH_2), 5.39 (t, *J* = 7.2 Hz, 1H, CH), consistent with the literature data.

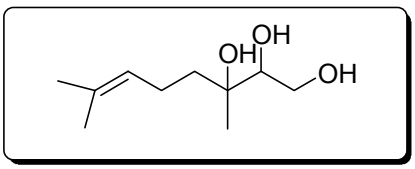
General Procedure for Asymmetric Epoxidation in toluene. Ligand (1.8 mol%) and $(i\text{-PrO})_3VO$ (2.5 μL, 10 μmol) were dissolved in dry toluene (3 mL) under nitrogen atmosphere and the resulting deep brown solution was stirred at room temperature for 30 min. Allylic alcohol (1 mmol) was then added in one portion and the mixture was stirred for at room temperature for 10 min and then cooled to –20 °C. A 5M solution of *t*-BuOOH in nonane (0.3 mL) was added and the mixture was stirred at –20 °C overnight (~20 h). The solution was then washed with water (10 mL), the aqueous phase was extracted with dichloromethane (2 × 20 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated in *vacuo* to give a brown oil. Purification of the products was accomplished by column

chromatography on silica gel (15 × 3 cm) with an *n*-hexane-ethyl acetate mixture (4:1). The absolute configuration of the epoxide products was assigned by comparison of their optical rotations with the literature data; the enantiomeric excess was determined using chiral GC or HPLC.

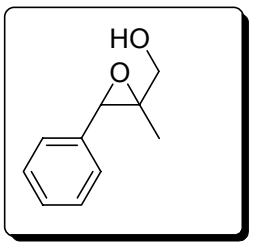
General Procedure for Asymmetric Epoxidation in Water. Vanadyl sulphate hydrate (3.3 mg, 20 μmol or 5.0 mg, 30 μmol), ligand **1** (10.7 mg, 22 μmol or 16.0 mg, 33 μmol) and allylic alcohol (1 mmol) were added to distilled water (3 mL) for the reactions at 0 ^{o}C or a 3:1 water/methanol solution (3 mL) for the reactions at –20 ^{o}C. The mixture was stirred at room temperature for 30 min and then cooled to 0 ^{o}C or –20 ^{o}C. A 70% aqueous solution of *t*-BuOOH (0.2 mL, 1.5 mmol) was added and the mixture was stirred at the same temperature overnight (~20 h). The reaction mixture was then quenched with a concentrated solution of Na_2SO_3 (10 mL) and after stirring for 1 h at 0 ^{o}C it was extracted with dichloromethane (2 × 20 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated in *vacuo* to give a brown oil. Purification of the products was accomplished in the same way as described for the reaction in toluene.



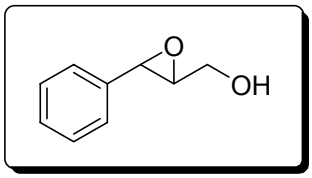
(2*S*, 3*S*)-(–)-3,7-Dimethyl-2,3-epoxy-oct-6-en-1-ol was isolated as a clear oil: $[\alpha]_D$ - 1.9 (c 1.00, $CHCl_3$). **Chiral GC** (Supelco α-Dex 120 column; oven temp. 110 ^{o}C for 2 min, then 1^{o}C/min to 200 ^{o}C, $t_{S,S}$ = 21.22, $t_{R,R}$ = 21.63) showed 69% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.41-1.5 (m, 2H), 1.62 (s, 3H), 1.65 (s, 3H), 2.06-2.12 (m, 2H), 2.23 (bs, 1H), 2.98 (dd, *J* = 6.6, 4.3 Hz, 1H), 3.68 (dd, *J* = 12.2, 6.6 Hz, 1H), 3.83 (dd, *J* = 12.2, 4.1Hz), 5.08 (t, *J* = 6.7 Hz, 1H), consistent with the literature data.[6]



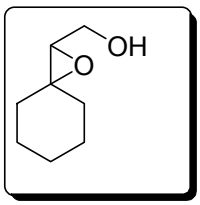
3,7-Dimethyloct-6-ene-1,2,3-triol was isolated quantitatively as a white wax solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.37-1.45 and 1.56-1.64 (m, 2H), 1.62 (s, 3H), 1.69 (s, 3H), 2.08-2.15(m, 2H), 2.80 (bs, 1H), 3.45-3.50 (m, 1H), 3.73-3.77 (m, 2H), 5.10-5.13 (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7 (CH_3OH), 22.2 (CH_2), 23.3 (CH_3), 25.7 (CH_3), 37.8 (CH_2), 63.2 (CH_2OH), 76.5 (CHOH), 124.1 (CH), 132.0 (C), HRMS (CI/ISO) *m*/*z* 189.1489 ($C_{10}H_{21}O_3$ requires 189.1491), consistent with the literature data.[7]



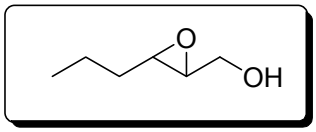
(2*S*, 3*S*)-(–)-2-Methyl-3-phenyl-2,3-epoxy-propan-1-ol was isolated as a clear oil: $[\alpha]_D$ - 6.1 (c 1.00, $CHCl_3$). **Chiral GC** (Supelco α-Dex 120 column; oven temp. 110 °C for 2 min, then 1 °C/min to 200 °C, $t_{R,R}$ = 25.54, $t_{S,S}$ = 27.00) showed 59% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3H), 2.16 (bs, 1H), 3.77 (d, *J* = 12.5 Hz, 1H), 3.88 (d, *J* = 12.5 Hz, 1H), 4.24 (s, 1H), 7.28-7.39 (m, 5H), consistent with the literature data.[6]



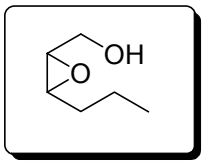
(2*R*,3*R*)-(+)-3-Phenyloxiranemethanol was isolated as a beige solid: m.p. 33-36 °C $[\alpha]_D$ +59 (c 1.00, $CHCl_3$). **Chiral HPLC** (OD-H 0.7 mL/ min; solvent: hexane-2-propanol 95/5, $t_{R,R}$ = 21.89, $t_{S,S}$ = 28.33) showed 57% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77-1.80 (m, 1H), 3.25 (m, 1H), 3.80-3.87 (m, 1H), 3.94 (d, *J* = 2.1 Hz, 1H), 4.05-4.17 (m, 1H), 7.28-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9 (CH), 61.6 (CH_2), 62.8 (CH), 126.1 (CH), 128.7 (CH), 128.9 (CH), 137.0 (C), consistent with the literature data.[8]



(+)-(1-Oxa-spiro[2.5]oct-2-yl)-methanol was isolated as a clear, colourless oil: $[\alpha]_D$ +13.9 (*c* 1.00, $CHCl_3$). **Chiral GC** (Supelco β-Dex 120 column, oven temp. 110 °C for 2 min, then 1 °C/min to 200 °C, $t_{(-)}$ = 23.08, $t_{(+)}$ = 23.77) showed 72% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 1.43-1.53 (m, 8H), 1.57-1.66 (m, 2H), 2.91 (dt, *J* = 7.2, 4.0 Hz, 2H), 3.61 (dd, *J* = 12, 7.2 Hz), 3.78 (dd, *J* = 12.0, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (CH_2), 29.5 (CH_2), 35.4 (CH_2), 60.9 (CH_2), 64.4 (CH), consistent with the literature data.[9]



(*2R, 3R*)-(+)-2,3epoxy-1-hexanol was isolated as a clear oil: $[\alpha]_D$ +17.7 (*c* 1.00, $CHCl_3$); for GC analysis the product was converted into trifluoroacetate derivative by stirring with an excess (1.5 eq.) of trifluoroacetic anhydride in dichloromethane at 20°C for 1 h. **Chiral GC** (Supelco β-Dex 120 column, oven temp. 70 °C for 2 min, then 1 °C/min to 200 °C, $t_{(S, S)}$ = 12.20, $t_{(R, R)}$ = 12.46) showed 70% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 0.91 (t, *J* = 4.8 Hz, 3H), 1.34-1.52 (m, 4H), 2.88 (dt, *J* = 4.4, 2.8 Hz, 2H), 3.54 (dd, 12.8, 4.4 Hz, 1H), 3.85 (dd, 12.8, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 19.3 (CH_2), 33.6 (CH_2), 55.9 (CH), 58.6 (CH), 61.8 (CH_2), consistent with the literature data.[10]



(2*S*, 3*R*)-(−)-2,3-epoxy-1-hexanol was isolated as a clear oil: $[\alpha]_D$ –2.3 (c 1.00, $CHCl_3$); for GC analysis the product was converted into trifluoroacetate derivative for GC analysis the product was converted into trifluoroacetate derivative by stirring with an excess (1.5 eq.) of trifluoroacetic anhydride in dichloromethane at 20°C for 1 h. **Chiral GC** (Supelco β-Dex 120 column, oven temp. 70 °C for 2 min, then 1 °C/min to 200 °C, $t_{(R, S)}$ = 12.91, $t_{(S, R)}$ = 13.32) showed 63% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ, 0.91 (t, *J* = 4.8 Hz, 3H), 1.35-1.52 (m, 4H), 2.28 (bs, 1H), 2.98 (dt, *J* = 6.8, 4.0 Hz, 1H), 3.09 (dt, *J* = 6.8, 4.0 Hz, 1H), 3.59 (dd, *J* = 12.0, 6.8 Hz, 1H), 3.79 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 19.9 (CH_2), 29.9 (CH_2), 57.0 (CH), 57.20 (CH), 60.9 (CH_2), consistent with the literature.[11]

References

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