Manganese Catalysts with Molecular Recognition Functionality for Selective Alkene Epoxidation

Supporting Information

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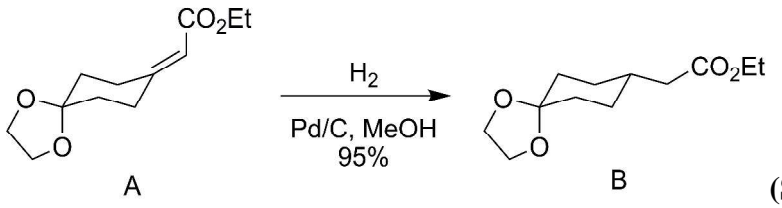
Substrate and Product Synthesis and Characterization.

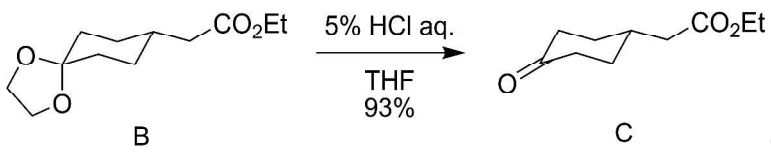
Substrate S1



(SI-1)

Ethyl 2-(1,4-dioxaspiro[4.5]decan-8-yl)acetate (**B**):

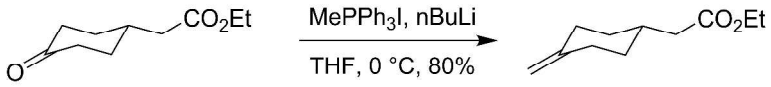
In a two-neck round bottom flask, a solution of **A** (2.005 g, 8.861 mmol) in 15 mL of MeOH was sparged with nitrogen for 15 minutes. Palladium on carbon (203 mg of a 10% by weight solid, 0.191 mmol) was added under a flow of nitrogen. The flask was then evacuated and back-filled with hydrogen gas three times before leaving to stir under an atmosphere of hydrogen (balloon). Monitoring the reaction by GC-MS showed complete consumption of starting material after 9 hours. The balloon of hydrogen was removed and the flask was evacuated and back-filled with nitrogen three times before opening the reaction to air and filtering over a pad of Celite, rinsing with ethyl acetate. The clear filtrate was concentrated and purified by silica gel flash chromatography (15% ethyl acetate/hexanes) to yield 1.87 g (92%) **B** as a colorless oil. Spectral data for this compound were in agreement with that previously reported.[1]



(SI-2)

Ethyl 2-(4-oxocyclohexyl)acetate (**C**):

A solution of **B** (1.57 g, 6.878 mmol) in 20 mL of THF and 10 mL of a 5% aqueous solution of HCl was stirred at ambient temperature. After no further conversion was observed by TLC (18 hours), the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed once with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel flash chromatography (10% ethyl acetate/hexanes) to yield 1.18 g (93%) of **C** as a colourless oil. Spectral data for this compound were in agreement with that previously reported.[2]



C D **(SI-3)**

Ethyl 2-(4-methylenecyclohexyl)acetate (**D**):

A suspension of methyltriphenylphosphonium iodide (6.25 g, 15.5 mmol) in 100 mL of tetrahydrofuran was cooled to 0 ºC under an atmosphere of nitrogen. n-butyllithium (8.20 mL of a 1.89 M solution in hexanes, 15.5 mmol) was added in drop-wise and the resulting deep yellow mixture was stirred for 60 minutes before cannulating in **C** (2.00 g, 10.9 mmol) as a solution in 10 mL of tetrahydrofuran. The solution was allowed to warm gradually to ambient temperature and stirred for 16 hours. An equal volume of pentane was then added and the resulting white precipitate was filtered off over a pad of celite. The filtrate was concentrated and adsorbed directly onto silica. Purification by silica gel flash chromatography (5% → 10% ethyl acetate/hexanes) yielded 1.58 g (80%) of **D**.

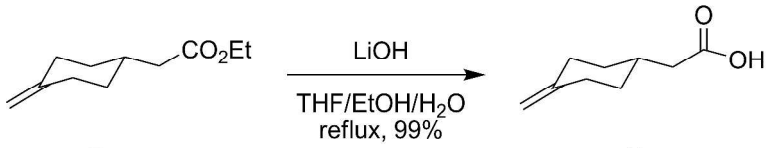
Spectral Data for **D**:

^{1}H NMR ($CDCl_3$, 500 MHz, δ): 4.57 (s, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.26-2.24 (m, 2H), 2.16 (d, *J* = 7.1 Hz, 2H), 2.02 (ddd, *J* = 13.0, 13.0, 3.8 Hz, 2H), 1.95-1.87 (m, 1H), 1.81-1.78 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.05 (dddd, *J* = 12.6, 12.6, 11.9, 3.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz, δ): 172.74, 148.65, 107.08, 60.02, 41.26, 34.28, 34.20 (2C), 33.98 (2C), 14.18.

IR (neat, cm^{-1}, υ): 2982 (s), 2933 (s), 2852 (m), 1737 (s), 1652 (m), 1444 (m), 1375 (m), 1342 (m), 1277 (m), 1245 (m), 1206 (m), 1048 (s), 1085 (m).

HRMS (EI, *m/z*): calculated 165.0318 for $[M+K]^+$, found 165.0320.



(SI-4)

2-(4-Methylenecyclohexyl)acetic acid (**S1**):

To a solution of **D** (502 mg, 2.75 mmol) in 15 mL of THF, 15 mL of EtOH, and 1 mL of H_2O was added $LiOH \cdot H_2O$ (138 mg, 3.29 mmol). The reaction mixture was heated to reflux. After 4 hours, no starting material could be seen by TLC so the reaction was cooled to ambient temperature and quenched with 0.1 N aqueous HCl. The reaction volume was reduced to ~ 2 mL by rotary evaporation under reduced pressure and the aqueous phase was extracted five times with DCM. The combined organic layers were then washed once with brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (60:139:1 ethyl acetate:hexanes:acetic acid), followed by azeotropic removal of the acetic acid by toluene, yielded 423 mg (99%) of **S1**.

Spectral Data for **S1**:

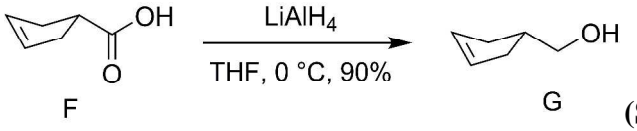
^{1}H NMR ($CDCl_3$, 500 MHz, δ): 11.56 (s, br, 1H), 4.61 (s, 2H), 2.30-2.28 (m, 2H), 2.25 (d, *J* = 7.1 Hz, 2H), 2.05 (ddd, *J* = 13.1, 13.1, 3.4 Hz, 2H), 1.98-1.90 (m, 1H), 1.88-1.85 (m, 2H), 1.10 (dddd, *J* = 12.3, 12.3, 12.3, 3.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz, δ): 179.71, 148.46, 107.30, 41.08, 34.08 (2C), 34.05, 33.93 (2C).

IR (neat, cm^{-1}, υ): 3068 (m), 2979 (s), 2937 (s), 2909 (s) 2851 (m), 1700 (s), 1649 (w), 1437 (w), 1426 (w), 1409 (m), 1293 (w), 1188 (w).

HRMS (EI, *m/z*): calculated 154.0994 for $[M]^+$, found 154.0989.

Synthesis of S3

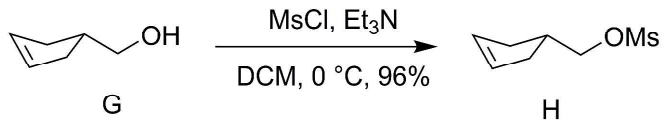


(SI-5)

Cyclopent-3-enecarboxylic acid (**G**):

A suspension of $LiAlH_4$ (2.75 g, 70.3 mmol) in 30 mL of THF was cooled to 0 °C under an atmosphere of nitrogen. A solution of **F** (2.00 g, 17.8 mmol) in 5 mL of THF was added drop-wise over 40 minutes. The reaction was warmed to ambient temperature and stirred for an additional 60 minutes before recooling to 0 °C. The excess $LiAlH_4$ was quenched with a few drops of acetone followed by a 1:1 mixture of 1 N aqueous NaOH and 1 N aqueous sodium tartrate solutions. The organic phase was diluted with ethyl acetate and the biphasic mixture was stirred vigorously until two distinct phases appeared

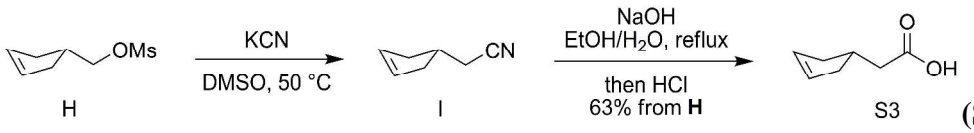
(~ 3 hours). The aqueous phase was then extracted three times with ethyl acetate and the combined organic phases were washed once with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel flash chromatography (30% ethyl acetate/hexanes) to yield 1.584 g (90%) of **G**. Spectral data for this compound were in agreement with previously that reported.[3]



(SI-6)

Cyclopent-3-enylmethyl methanesulfonate (**H**):

A solution of **G** (1.14 g, 11.6 mmol) in 50 mL of DCM was cooled to 0 °C under an atmosphere of nitrogen. Triethylamine (1.94 mL, 13.9 mmol) was added, followed by methanesulfonyl chloride (1.00 mL, 12.7 mmol). After 30 minutes, the reaction was warmed to ambient temperature and stirred for 18 hours. The reaction was then quenched with H_2O and the phases separated. The aqueous phase was extracted three times with ethyl acetate and then washed twice with water. The combined organic phases were then washed sequentially with saturated aqueous solutions of $NaHCO_3$ and brine, and then dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (20% ethyl acetate/hexanes) yielded 1.96 g (96%) of **H**. Spectral data for this compound were in agreement with that previously reported.[4]



(SI-7)

2-(cyclopent-3-enyl)acetic acid (**S3**):

A solution of **H** (812 mg, 4.61 mmol) in 40 mL of DMSO was sparged with nitrogen for 30 minutes. Potassium cyanide (1.37 g, 21.6 mmol) was added and the resulting yellow reaction mixture was immersed in an oil bath, pre-heated to 50 °C. After 75 hours the reaction was cooled to ambient temperature and poured into a separatory funnel containing 400 mL of water. The aqueous phase was extracted three times with pentane and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue (**I**) was then dissolved in a solution of ethanol (30 mL) and water (10 mL). Sodium hydroxide (1.53 g, 38.3 mmol) was added and the reaction was brought to reflux for 20 hours. After cooling to 0 °C, 20 mL of a 1 N aqueous solution of HCl was added and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel flash chromatography (40:59:1 ethyl acetate:hexanes:acetic acid) yielded 367 mg (63% over two steps) of **S3**.

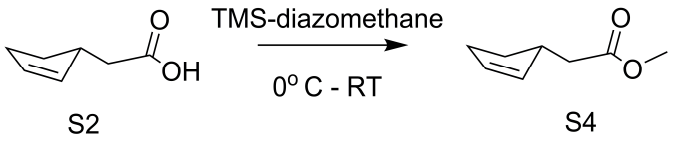
Spectral Data for **S3**:

^{1}H NMR ($CDCl_3$, 500 MHz, δ): 11.75 (s, br, 1H), 5.64 (s, 2H), 2.70-2.62 (m, 1H), 2.59-2.54 (m, 2H), 2.41 (d, *J* = 7.5 Hz, 2H), 2.03-2.00 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz, δ): 179.89, 129.34 (2C), 40.36, 38.55 (2C), 33.31.

IR (neat, cm^{-1}, υ): 2909 (s, br), 2676 (s, br), 1697 (s), 1615 (w), 1412 (s), 1351 (m), 1215 (s), 1070 (m).

Synthesis of S4

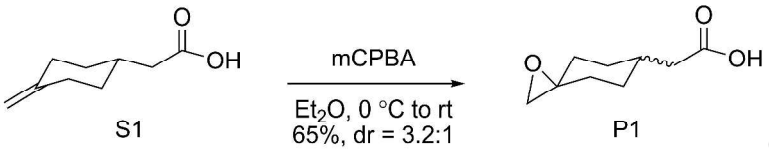


(**SI-8**)

(R)-methyl 2-(cyclopent-2-enyl)acetate (**S4**):

A solution of S2 (0.50 mL, 4.15 mmol) in 40 mL of a methanol/bezene mixture (2:7 ratio) was cooled to 0 °C. (Trimethylsilyl)diazomethane (2.50 mL of a 2.0 M solution in diethyl ether, 5.0 mmol) was added dropwise. The end of the addition was marked by a persistent yellow colour. The reaction was allowed to warm gradually to ambient temperature and was stirred for an additional 2 hours. Acetic acid (< 0.05 mL) was added dropwise until the yellow colour had disappeared. The solvent was removed under reduced pressure and the resulting colourless oil (570 mg, 98% yield) was used without further purification. Spectral data for this compound was in agreement with that reported for the commercially available substance.[5]

Synthesis of P1



(SI-9)

2-(1-oxaspiro[2.5]octan-6-yl)acetic acid (**P1**):

A solution of **S1** (32 mg, 0.21 mmol) in 4 mL of diethyl ether was cooled to 0 °C. mCPBA (70 mg of 77% maximum purity reagent, 0.406 mmol) was added in a single portion and the reaction was allowed to warm to ambient temperature. After 18 hours, the

reaction was concentrated and a crude NMR was taken to reveal and 3.2:1 ratio of diastereomers. Purification by silica gel flash chromatography (30% → 75% ethyl acetate/hexanes) yielded 23 mg (65%) of **P1** as an inseparable mixture of isomers.

Spectral Data for **P1** (major and minor isomers together):

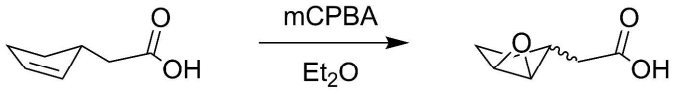
^{1}H NMR ($CDCl_3$, 500 MHz, δ): 2.66 and 2.60 (s, 2H), 2.33 (d, J = 7.0 Hz, 2H), 1.95-1.82 (m, 5H), 1.46-1.25 (m, 4H).

^{13}C NMR ($CDCl_3$, 125 MHz, δ): 178.91 (2C), 59.29, 58.14, 54.79, 53.99, 41.05, 40.51, 33.31 (2C), 32.81 (2C), 32.38 (2C), 31.51 (2C), 30.04 (2C).

IR (neat, cm^{-1}, υ): 2928, 1703, 1696, 1576, 1420, 1294, 1263.

HRMS (EI, *m/z*): calculated 193.0841 for $[M+Na]^+$, found 193.0834.

Synthesis of P2

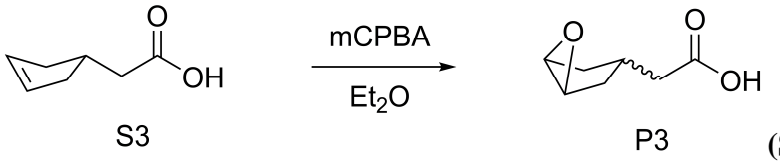


S2 P2 **(SI-10)**

2-(1-oxaspiro[2.5]octan-6-yl)acetic acid (**P2**):

A solution of **S2** (32 mg, 0.21 mmol) in 4 mL of diethyl ether was cooled to 0 °C. mCPBA (70 mg of 77% maximum purity reagent, 0.406 mmol) was added in a single portion and the reaction was allowed to warm to ambient temperature. After 18 hours, the reaction was concentrated and a crude NMR was taken to reveal and 4.5:1 ratio of diastereomers. Purification by silica gel flash chromatography (30% → 75% ethyl acetate/hexanes) yielded 23 mg (65%) of **P2** as an inseparable mixture of isomers. Spectral data for this compound were consistent with that previously reported.[6]

Synthesis of P3



S3 P3 **(SI-11)**

2-(6-oxabicyclo[3.1.0]hexan-3-yl)acetic acid (**P3**):

A solution of **S3** (53 mg, 0.420 mmol) in 8 mL of diethyl ether was cooled to 0 °C. mCPBA (140 mg of 77% maximum purity reagent, 0.625 mmol) was added in a single portion and the reaction was allowed to warm to ambient temperature. After 18 hours, the reaction was concentrated and a crude NMR was taken to reveal and 1:2 ratio of diastereomers. Purification by silica gel flash chromatography (30% → 75% ethyl acetate/hexanes) yielded 53 mg (89%) of **P3** as a mixture of isomers.

Spectral Data for **P3** (major isomer):

^{1}H NMR ($CDCl_3$, 500 MHz, δ): 3.48 (s, 2H), 2.37 (d, J = 7.3 Hz, 2H), 2.30 (dd, J = 13.8, 7.4 Hz, 2H), 2.22-2.15 (m, 1H), 1.35 (dd, J = 13.7, 9.5 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz, δ): 177.48, 56.65 (2C), 38.36, 33.73 (2C), 29.00.

Spectral Data for **P3** (minor isomer):

^{1}H NMR ($CDCl_3$, 500 MHz, δ): 3.51 (s, 2H), 2.55-2.46 (m, 1H), 2.45 (d, J = 7.0 Hz, 2H), 1.99 (dd, J = 14.8, 8.7 Hz, 2H), 1.83 9d, J = 14.8 Hz, 2H).

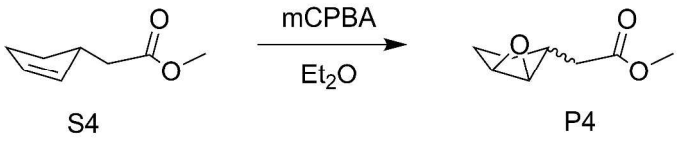
^{13}C NMR ($CDCl_3$, 125 MHz, δ): 177.89, 58.59 (2C), 42.96, 33.35 (2C), 30.39.

Spectral Data for **P3** (major and minor isomers together):

IR (neat, cm^{-1}, υ): 2924, 1705, 1699, 1416, 1305, 1262, 1159.

HRMS (EI, *m/z*): calculated 142.0630 for [M]+, found 142.0508.

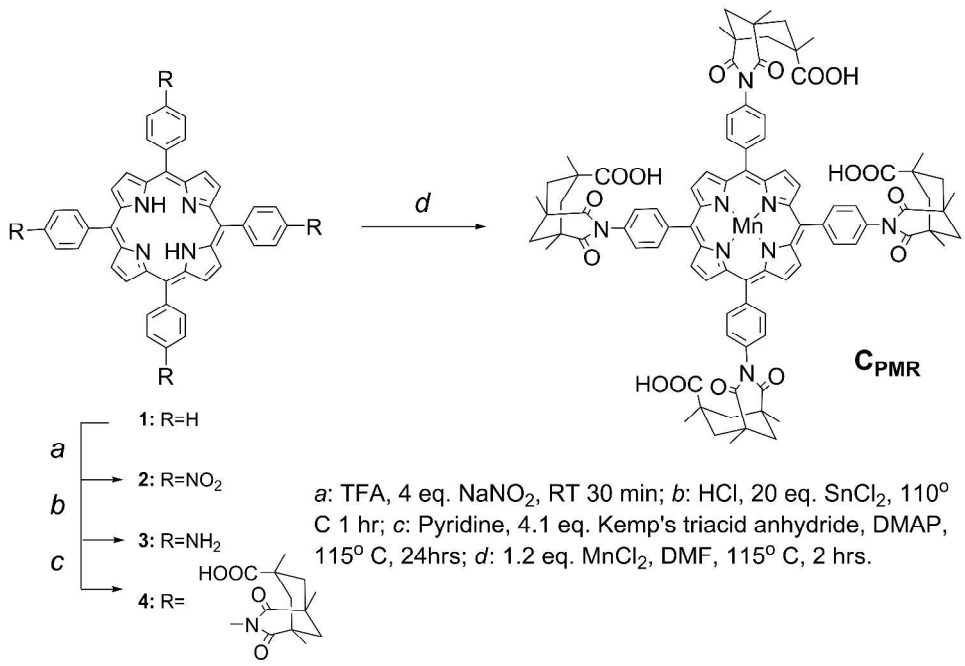
Synthesis of P4



(**SI-12**)

A solution of **S2** (53 mg, 0.420 mmol) in 8 mL of diethyl ether was cooled to 0 °C. mCPBA (140 mg of 77% maximum purity reagent, 0.625 mmol) was added in a single portion and the reaction was allowed to warm to ambient temperature. After 18 hours, the reaction was concentrated and a crude NMR was taken to reveal and 2:1 ratio of diastereomers. The spectral properties agreed with values previously reported.[7]

Catalyst Synthesis



Scheme SI-1. Synthesis of molecular recognition catalyst $\mathbf{C_{PMR}}$.

The porphyrin catalyst (**C2**) was synthesized according to Scheme SI-1. 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine (TPP, **1** /$\mathbf{C_P}$) was converted to 5,10,15,20-(4-Nitro)tetraphenyl-21*H*,23*H*-porphine (**2**) by direct nitration with sodium nitrite in strong acid.**Error! Bookmark not defined.** Four equivalents of $NaNO_2$ were added to a solution of TPP (500 mg) in trifluoroacetic acid. The mixture was stirred for 30 min, and then extracted into dichloromethane. The organic phase was neutralized with a saturated solution of $NaHCO_3$, washed with water, dried over magnesium sulfate and then concentrated under reduced pressure (76% yield). Product **2** was then reduced to 5,10,15,20-(4-amino)tetraphenyl-21*H*,23*H*-porphine (**3**) by refluxing 5 equivalents of tin(II) chloride in HCl under nitrogen for 1 hour (54% yield), and extracted with dichloromethane after adjusting the pH to 8 using ammonium hydroxide. Compound **4** was further converted to **5** by refluxing in pyridine under nitrogen with 4.1 equivalents of Kemp's triacid anhydride chloride and a catalytic amount of N,N dimethylaminopyridine (DMAP, ca. 1 mg) for 24 hours. The progress of the reaction was followed using ESI-MS and TLC (5% methanol in dichloromethane). Porphyrin **5** could be isolated by removing the pyridine under reduced pressure, and purified by flash chromatography using 5% MeOH in dichlormethane (86%). **^{1}H NMR** (400 MHz, DMSO) δ 12.78 (br s, 4H), 8.90 (s, 8H), 8.27 (d, J = 8.1, 8H), 7.62 (d, J = 6.5, 8H), 2.66 (d, 8H), 2.39 (d, J = 13.3, 4H), 1.66 (d, J = 13.1, 4H), 1.47 (d, J = 13.4, 8H), 1.34 (s, 24H), 1.28 (s, 12H), -2.86 (br s, 2H). **HRMS** (ESI+) *m/z* predicted for m^{2+}: 782.8332, found 782.8313.

Alternatively, metalloporphyrin **6** ($\mathbf{C_{PMR}}$) could be obtained by directly adding 1.2 equivalents of $MnCl_2$ dissolved in N,N-dimethylformamide (DMF) to the refluxing solution in the previous step. The mixture was refluxed until the reaction was complete

according to UV-Visible spectroscopy (ca. 2 hours). Metalloporphyrin $\mathbf{C_{PMR}}$ was precipitated by pouring the reaction mixture into a 10-fold excess of cold water, and filtered to give a dark green solid. The solid was then repeatedly dissolved in acetone, filtered, re-precipitated by adding hexane and collected by filtration to remove impurities (80% yield from **5** to $\mathbf{C_{PMR}}$). Diffraction-quality crystals were obtained by cooling a concentrated (>4.5 mM) solution in acetonitrile, but these rapidly desolvated upon removal from the vessel. Figure 1 shows the connectivity of atoms in the the porphyrin which was established from the low resolution X-ray determination of the structure from poorly diffracting crystals (see Supporting Information for crystal data parameters). Paramagnetism in the Mn(III) complex prevented its characterization by NMR. **HRMS** (ESI+) *m/z* predicted (m^+ + H): 1616.5698, found 1616.5681. **Elemental Analysis** Predicted ($\mathbf{C_{PMR}}$ and four water molecules): C 64.34, H 5.20, N 6.76; Found C 64.09, H 5.61, N 6.50.

Terpyridine catalysts $\mathbf{C_T}$[8] was synthesized according to a previously published procedure, and $\mathbf{C_{TMR}}$[9] was made using a modified procedure from that previously reported. The modifications were: (1) LIGAND SYNTHESIS: 'Ligand **2**' was synthesized from aminophenyl terpyridine (200 mg, 0.62 mmol) and Kemp's triacid anhydride chloride (200 mg, 1.25 equiv, 0.77 mmol) in freshly distilled pyridine (15 mL). After refluxing for 48 hours under nitrogen, the mixture was poured into 150 mL 0.05 N HCl and the product extracted with dichloromethane (3x 10 mL). The organic layer was washed with brine, dried with $MgSO_4$ and the solvent removed (CAUTION, trace amounts of pyridine) under reduced pressure. The product was purified by dissolving the remaining

residue in a minimal amount (ca. 5 mL) of dichloromethane, layering with an equivalent volume of pentane, and cooling to -10 °C. A brown solid was collected by filtration (194 mg, 63% yield). (2) CATALYST RECOVERY: Catalyst '**1b**' ($\mathbf{C_{TMR}}$ in this manuscript) was synthesized as described previously,**Error! Bookmark not defined.** but was recovered by removing the solvent under reduced pressure immediately after a dark solid was precipitated with KNO_3. Diethyl ether was added to the resulting solid to form a slurry, which was scraped onto a frit and washed with excessive cold water to remove the white salts. The remaining brown precipitate was collected and dried overnight under vacuum.

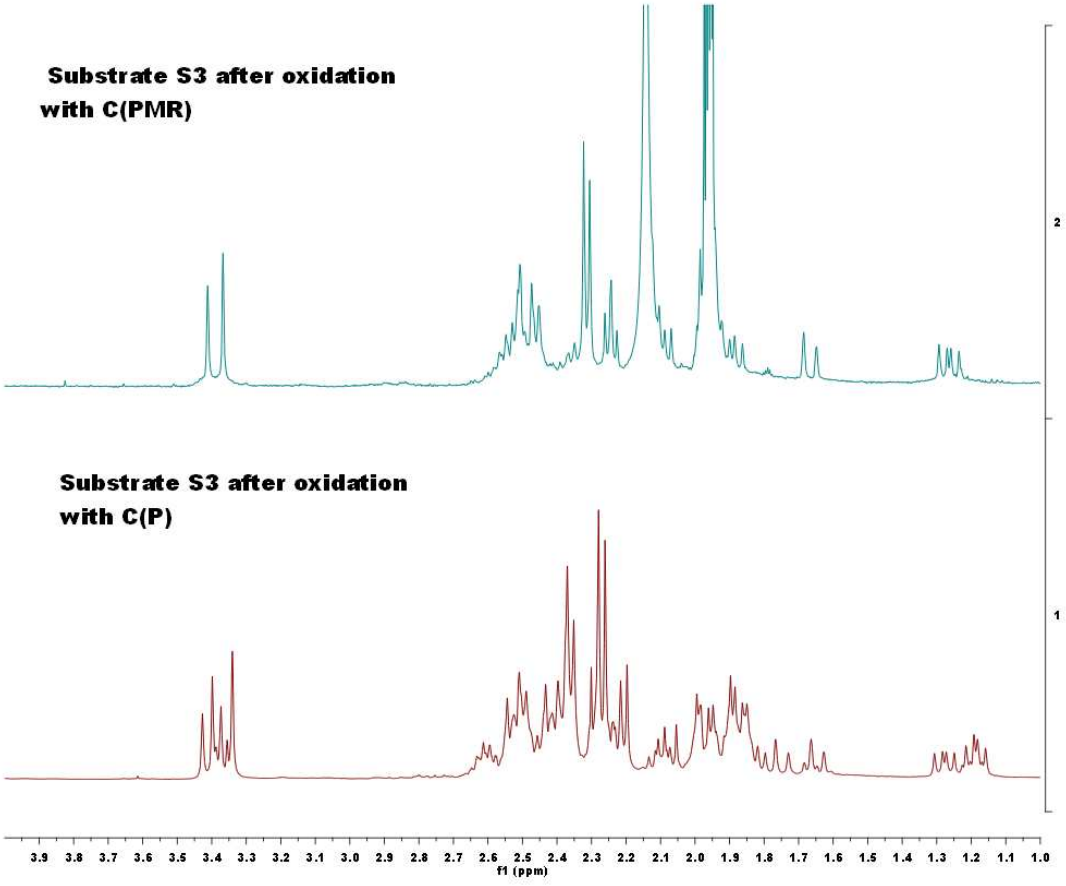
Crystallographic Information for $\mathbf{C_{PMR}}$

All crystals investigated were weakly diffracting and only limited data could be obtained. Crystal data: a = 8.4853(9) Å; b =18.766(2) Å ; c = 20.209(2) Å ; α = 101.299(6)°; β= 89.762(6)°; γ= 99.973(7)°; V = 3106.6(6) Å^3; Z = 1. A triclinic cell was found consistent with a space group of $P\bar{1}$ (No. 2) with the manganese atom on a special position and a nearly centrosymmetric molecule. This requires a disordered chloride bound to the metal at half occupancy. The cell contained a large number of solvent molecules and the data were insufficient to obtain a quality structure. Nevertheless, the connectivity of the molecule could be deduced as shown in the figure.

Example Spectra for Epoxide Mixtures

Relevant portion (4 -1 ppm for clarity) of the NMR spectra of epoxidation mixtures for $\mathbf{C_P}$ (bottom) and $\mathbf{C_{PMR}}$ (top). The spectra show uncontrolled oxidation of substrate S3 on

the bottom, compared with directed oxidation on the top. The mixture resulting from $\mathbf{C_P}$ is complex, and precise yields of epoxide (ca. 3.4 ppm) are difficult to determine.



Supporting Information References

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