# Manganese catalysed asymmetric *cis*-dihydroxylation with $H_2O_2$†

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***Received (in Cambridge, UK) 19th May 2008, Accepted 25th June 2008***
***First published as an Advance Article on the web 17th July 2008***
**DOI: 10.1039/b808355j**

**High turnover enantioselective alkene *cis*-dihydroxylation is achieved with $H_2O_2$ catalysed by manganese based complexes containing chiral carboxylato ligands.**

The central importance of chirality to modern chemistry has driven the development of asymmetric reactions and especially enantioselective catalysis.[1] Amongst the many catalysed organic transformations, selective catalytic oxidation, in particular the *cis*-dihydroxylation of alkenes, has proven to be challenging with regard to achieving atom efficiency and selectivity.[2]

The seminal report[3] and subsequent development[2,4] of the osmium catalysed asymmetric *cis*-dihydroxylation (AD) of alkenes by Sharpless and co-workers have proven to be invaluable to synthetic organic chemistry. However, the cost and toxicity of the osmium based AD systems, prevents their widespread industrial application.[5] This has provided a strong driving force to the identification and development of economically viable and environmentally benign methods based on first row transition metals and $H_2O_2$.

Recently we have demonstrated that highly efficient and selective *cis*-dihydroxylation of alkenes with $H_2O_2$ can be achieved with manganese based catalysts.[6] Taken together with the recent discovery of highly enantioselective AD of, especially, *trans*-alkenes by iron(II) based catalysts, by Que and co-workers, albeit with very low turn over numbers,[7] so far these findings indicate that the goal of high turnover 1st row transition metal based AD methods may be within reach.

Herein, we describe the development of the first manganese based catalyst system for asymmetric *cis*-dihydroxylation (AD) of alkenes with $H_2O_2$. With 0.4 mol% catalyst loading the enantioselective *cis*-dihydroxylation of 2,2′-dimethylchromene proceeds with full conversion and high selectivity towards the *cis*-diol product with enantiomeric excess of up to 54% and with high turnover.

In our earlier reports[6] we described the *cis*-dihydroxylation and epoxidation of alkenes with $H_2O_2$ catalysed by bis-μ-carboxylato bridged dinuclear manganese(III) complexes (*i.e.* $[Mn^{III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(tmtacn)_2]^{2+}$, where tmtacn is *N*,*N*′,*N*″-trimethyl-1,4,7-triazacyclononane, Fig. 1). For the substrate cyclooctene, over 2000 turnovers towards the *cis*-diol could be achieved and catalyst loadings below 0.1 mol% have been used successfully with near complete efficiency in the consumption of $H_2O_2$. The selectivity towards either *cis*-dihydroxylation or epoxidation can be tuned through the carboxylato ligand employed ($RCO_2^-$), *e.g.* 2,6-dichlorobenzoate or 2-hydroxybenzoate, respectively. The catalyst becomes more active with increased electron deficiency of the carboxylic acid and, importantly, the selectivity towards *cis*-dihydroxylation is highest with sterically demanding carboxylato ligands.

Our identification of carboxylato bridged $Mn^{III}_2$ complexes as the active catalyst species,[6] taken together with the results of Bolm,[9] Sherrington[10] and co-workers, where enantiomeric excesses of up to 60% were achieved for alkene epoxidation using related manganese complexes based on chiral tmtacn type ligands,[11] prompted us to explore the use of readily available chiral carboxylic acids in achieving AD.[12] Chiral carboxylic acids hold a distinct advantage over synthetically challenging chiral versions of the tmtacn ligand in that the catalytically active *bis*-μ-carboxylato $Mn^{III}_2$ complex can be formed[6] *in situ* by reduction of **1**[13] $\{[Mn^{IV}_2(\mu\text{-}O)_3(tmtacn)_2]^{2+}\}$ with $H_2O_2$ in the presence of the carboxylic acid of interest, which facilitates optimising the ee (Fig. 1, ESI Table S1†).

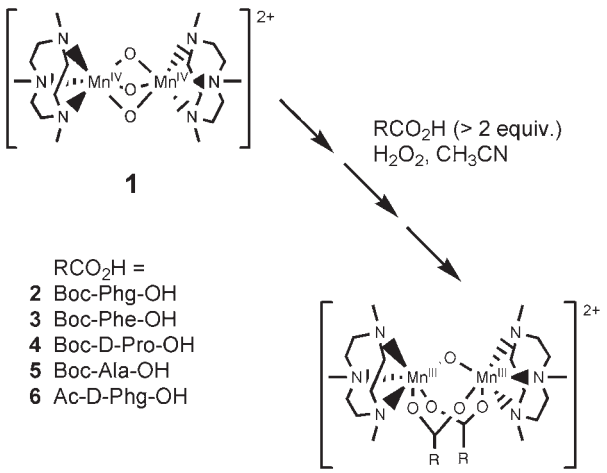


**Fig. 1** *In situ* conversion of **1** to $[Mn^{III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(tmtacn)_2]^{2+}$ by reduction with $H_2O_2$ in the presence of $RCO_2H$. Complexes **2–6** were prepared independently also (see ESI†).

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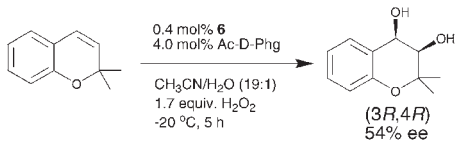
† Electronic supplementary information (ESI) available: Synthesis and characterisation of all complexes and compounds, experimental procedures, NMR analysis, discussion of analysis methods. See DOI: 10.1039/b808355j




**Scheme 1** Asymmetric *cis*-dihydroxylation (AD) of chromene with $H_2O_2$ catalysed by the system **6**/Ac-D-Phg.[8]

A series of twenty four chiral carboxylic acids were selected (see ESI, Fig. S1†) containing a stereogenic centre α to the carboxylic acid. The substrate scope[6a] for the system **1**/$RCO_2H$ shows that the highest selectivity and activity towards *cis*-dihydroxylation are obtained with electron-rich *cis*-alkenes and hence the prochiral *cis*-alkene 2,2-dimethylchromene, one of the more challenging substrates in the osmium catalysed AD,[4] was selected as substrate to identify chiral carboxylic acids suitable for inducing enantioselectivity (Scheme 1).

Overall, chiral carboxylic acids, which contain a phenyl or naphthyl group attached directly to the stereogenic carbon atom show similar ee (13–20%) with substrate conversion generally higher than 60% (Table S1,† Scheme 2). The *N*-carbamate protected amino acids provided an enantiomeric excess of *ca.* 30% (Table S1†). Those acids lacking an aromatic group at the stereogenic centre showed good substrate conversion albeit providing low enantiomeric excess for the *cis*-diol product.

The *cis*-diol product is the major product in all cases and the *cis*-/*trans*-diol ratio[8] is generally good (typically varying between 2.7 and 4.3, see ESI for detailed discussion†). The highest *cis*-/*trans*-diol ratio (7.0) is observed for (1*S*)-(+)-ketopinic acid (Table S1†) and this indicates that steric bulk close to the carboxylic acid functionality favours *cis*-dihydroxylation over the epoxidation of cyclooctene. Thus, based on preliminary screening, it can be concluded that the system **1**/carboxylic acid is effective for catalytic AD of chromene where the carboxylato ligand is functionalised with an aromatic group at the stereogenic carbon atom and that the other atom attached to the stereogenic carbon is, preferably, a protected amine. The combination of **1** with acetyl protected D-phenylglycine (Ac-D-Phg) provided the highest substrate conversion (99%) and ee (38%) of the 3*R*,4*R*-*cis*-diol.

The AD of 2,2-dimethylchromene with $H_2O_2$ catalysed by the independently prepared and characterised (see ESI†) complex $[Mn^{III}_2(\mu\text{-O})(\mu\text{-Boc-phenylglycine})_2(tmtacn)_2]^{2+}$ (**2**, 0.4 mol%)/Boc-phenylglycine (25 mol%) was examined to confirm that the

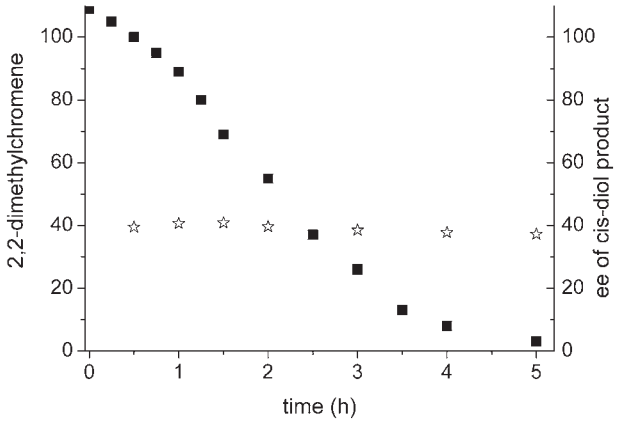
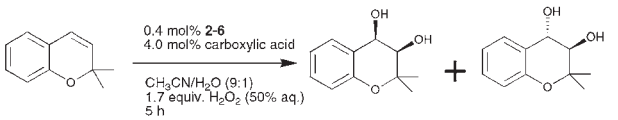



**Fig. 2** Enantioselective *cis*-dihydroxylation of 2,2-dimethylchromene by **2** (1 mM, 0.4 mol%) and Boc-phenylglycine (62.5 mM, 25 mol%) in $CH_3CN$–$H_2O$ (9:1) at 0 °C. Conversion of substrate as function of time (filled squares), ee of the *cis*-diol as function of time (open stars).




**Scheme 2** Asymmetric dihydroxylation (AD) of chromene with $H_2O_2$ catalysed by the system **1–6**/$RCO_2H$.[8]

μ-bis-carboxylato $Mn^{III}_2$ complexes were formed *in situ*. $[Mn^{III}_2(\mu\text{-O})(\mu\text{-}N\text{-Boc-phenylglycine})_2(tmtacn)_2]^{2+}$ (**2**) and complexes **3–6** were prepared as described earlier (see ESI†). Almost complete conversion of 2,2-dimethylchromene was observed and the corresponding *cis*-diol was obtained with 37% ee (Table 1, entry 1). Importantly the ee of the *cis*-diol remains constant over the entire course of the reaction (Fig. 2). Decreasing the amount of Boc-Phg-OH from 25 to 4 mol% resulted in a somewhat lower yield, however the ee was unaffected (entry 2). The conversion and ee of the *cis*-diol product are essentially the same as observed with *in situ* formation of **2** from **1**/Boc-Phg-OH by pretreatment with $H_2O_2$ (entry 5). As expected Boc-D-Phg-OH in place of Boc-Phg-OH provides the same enantioselectivity but for the opposite enantiomer (Table S1†).

With Boc-phenylalanine (Boc-Phe-OH), Boc-D-proline (Boc-D-Pro-OH) and Boc-alanine (Boc-Ala-OH) and their respective complexes **3–5** (see ESI†), *cis*-dihydroxylation of 2,2′-dimethylchromene proceeded (Table 1) as with the complexes formed *in situ* (Table S2†).[15]

**Table 1** Manganese catalysed AD of 2,2-dimethylchromene[a]

| Entry | Catalyst/carboxylic acid (mol%) | Conv. (%)[b] | ee (%) *cis*-diol[cd] | *cis*/*trans*[e] ratio[c] |
|---|---|---|---|---|
| 1 | **2**/Boc-Phg (25) | 97 | 37 | 4.1 |
| 2 | **2**/Boc-Phg (4) | 85 | 36 | 5.3 |
| 3 | **2**/Boc-Phg (4)[f] | 41 | 44 | 4.3 |
| 4 | **2**/— | 48 | 36 | 7.7 |
| 5 | **1**/Boc-Phg (4)[g] | 80 | 35 | 1.8 |
| 6 | $Mn^{II}(ClO_4)_2{\cdot}6H_2O$/Boc-Phg (25) | 0 | — | — |
| 7 | **3**/Boc-Phe (4) | 80 | 2.5 | 1.2 |
| 8 | **4**/Boc-D-Pro (4) | 50 | 12[h] | 1.4 |
| 9 | **5**/Boc-Ala (4) | 75 | 4.7 | 2.4 |

[a] At 0 °C in $CH_3CN$–$H_2O$ (9 : 1), see ESI for details.† [b] Determined by GC. [c] Determined by HPLC. [d] Absolute configuration (3*S*,4*S*) by comparison with reported optical rotation.[14] [e] This ratio provides an indirect estimation of the *cis*-diol/epoxide selectivity of the reaction (see ESI†); the ee of the *trans*-diol was in each case <8%. [f] In $CH_3CN$. [g] Catalyst treated with $H_2O_2$ prior to addition of substrate (see ESI†). [h] (3*R*,4*R*) configuration.

**Table 2** Temperature dependence of the AD of 2,2,-dimethylchromene[a]

| Entry | Catalyst/carboxylic acid (mol%) | Temp. (°C) | ee (%) *cis*-diol | Conv. (%) |
|---|---|---|---|---|
| 1 | **1**/Boc-Phg (25)[b] | 20 | 28 (3*S*,4*S*) | 88 |
| 2 | **2**/Boc-Phg (25) | 0 | 37 (3*S*,4*S*) | 97 |
| 3 | **2**/Boc-Phg (25)[c] | −20 | 47 (3*S*,4*S*) | 51 |
| 4 | **1**/Ac-D-Phg (25)[b] | 20 | 38 (3*R*,4*R*) | 99 |
| 5 | **1**/Ac-D-Phg (4)[d] | 0 | 42(3*R*,4*R*) | 80 |
| 6 | **6**/Ac-D-Phg (4)[c] | −20 | 54 (3*R*,4*R*) | 55 |
| 7 | **6**/ Ac-D-Phg (4)[e] | 0 | 50 (3*R*,4*R*) | n.d. |
| 8 | **6**/ Ac-D-Phg (4)[f] | 0 | 42 (3*R*,4*R*) | n.d. |

[a] See procedure A (ESI†). [b] See procedure B (ESI†). [c] Reaction performed in $CH_3CN/H_2O$ (19 : 1 v/v). [d] Pre-treatment of the catalyst with $H_2O_2$. [e] 30% $D_2O_2$. [f] 30% $H_2O_2$; n.d. not determined.

At 0 °C with **6**/Ac-D-Phg the *cis*-diol product was obtained in 42% isolated yield and 41% ee. The use of $D_2O/D_2O_2$ facilitated the recording of the $^1$H NMR spectrum of the reaction mixture at the end of the reaction. Almost complete conversion of the alkene substrate was observed and furthermore, only the *cis*-diol and (a minor amount of the) *trans*-diol products were observed (see Fig. S2 ESI†).

The temperature dependence of the enantioselectivity shows an increase in ee with reduction in temperature (Table 2). For example, the ee of (3R,4R)-chromene-diol is 38%, 42% and 54% when the reaction catalysed by the system **1**/Ac-D-Phg-OH is performed at 20 °C, 0 °C and −20 °C, respectively (Table 2, entries 4, 5 and 6).[16] In our earlier report[6b] we demonstrated that the activity and the *cis*-diol/epoxide selectivity of the system **1**/$CCl_3CO_2H$ was unaffected by the use of $D_2O_2/D_2O$. However, in the AD of chromene the use of $D_2O_2$ with the system **6**/Ac-D-Phg-OH results in a significant increase in enantiomeric excess (from 42 to 50% ee, Table 2, entries 7 and 8).

In conclusion, we have demonstrated the AD of 2,2-dimethylchromene with $H_2O_2$ catalysed by dinuclear manganese complexes. The reactivity and selectivity is readily tunable by variation of the carboxylic acid employed. The preference of the present $[Mn^{III}_2(\mu\text{-}O)(\mu\text{-}RCO_2)_2(tmtacn)_2]^{2+}$ catalyst systems towards electron-rich *cis*-alkenes limits the scope of the system. However, the high turnover numbers and efficiency achievable, the tunablity of the system and its use of $H_2O_2$ as the terminal oxidant demonstrate that a sustainable and synthetically useful method for the 1st row transition metal catalysed AD is now within reach.

The present system constitutes the first manganese based catalyst for the enantioselective *cis*-dihydroxylation of alkenes. Taken together with the recent report of AD by Que and coworkers[7] where iron based catalysts demonstrate activity in the AD of *trans*-alkenes, the present system forms an excellent basis on which to build on a range of selective and economically and environmentally acceptable 1st row transition metal catalysed AD methods.

We thank the Dutch Economy, Ecology, Technology (Grant EETK01106) program for financial support. We thank Prof. J. Reedijk and Dr J. G. Roelfes for valuable discussions and suggestions.

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16 A further decrease in temperature to below −20 °C results in the freezing out of the water present in the reaction mixture, which reduces the activity of the catalyst significantly.