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## Manganese Catalysis

Oxidation of Vicinal Diols to  $\alpha$ -Hydroxy Ketones with  $\text{H}_2\text{O}_2$  and a Simple Manganese CatalystFrancesco Mecozzi,<sup>[a]</sup> Jia Jia Dong,<sup>[a]</sup> Pattama Saisaha,<sup>[a]</sup> and Wesley R. Browne\*<sup>[a]</sup>

**Abstract:**  $\alpha$ -Hydroxy ketones are valuable synthons in organic chemistry. Here we show that oxidation of vic-diols to  $\alpha$ -hydroxy ketones with  $\text{H}_2\text{O}_2$  can be achieved with an in situ prepared catalyst based on manganese salts and pyridine-2-carboxylic acid. Furthermore the same catalyst is effective in

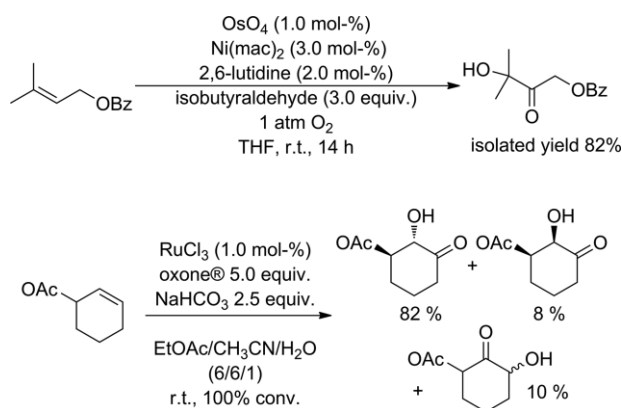
alkene epoxidation, and it is shown that alkene oxidation with the  $\text{Mn}^{\text{II}}$  catalyst and  $\text{H}_2\text{O}_2$  followed by Lewis acid ring opening of the epoxide and subsequent oxidation of the alkene to  $\alpha$ -hydroxy ketones can be achieved under mild (ambient) conditions.

## Introduction

Acyloin building blocks are ubiquitous structural motifs in both biologically active natural products and drugs, and represent highly versatile synthons. Despite their proven value, only a limited number of general approaches to their synthesis are available. Acyloin condensation<sup>[1]</sup> is perhaps the best known and catalytic versions, employing, e.g., lanthanum,<sup>[2]</sup> titanium,<sup>[3]</sup> or  $\text{Cs}_2\text{CO}_3$  with N-heterocyclic carbenes, have appeared recently that provide access to various regioisomers.<sup>[4]</sup> Enolate oxidation<sup>[5,6]</sup> (a two-step procedure with enolate generation followed by oxidation of the enol double bond, typically with *m*-CPBA) enables non-stereoselective C–O bond formation also. Palladium catalysts with cyclic guanidine ligands<sup>[7]</sup> have been used in the racemic transition-metal-catalysed  $\alpha$ -hydroxylation of ketones,<sup>[8–10]</sup> and polymeric  $\{[\text{Cu}(\text{bpy})(\text{BF}_4)_2(\text{H}_2\text{O})_2]_n(\text{bpy})\}_n$  (bpy = 4,4'-bipyridine) catalysts have been employed for the  $\alpha$ -oxygenation of ketones with molecular oxygen.<sup>[11]</sup> The requirement for pre-enolization of the substrates limits the scope of these latter approaches, however. The metal free radical keto-oxygenation of alkenes using hydroxamic acids followed by  $\text{H}_2$  hydrogenation, was reported recently by Schmidt and Alexanian.<sup>[12]</sup>

Ketohydroxylation of olefins and monooxidation of vicinal diols,<sup>[13,14]</sup> represent an important alternative approach, with the earliest examples making use of stoichiometric  $\text{KMnO}_4$ <sup>[15]</sup> or  $\text{NaOCl}$ <sup>[16]</sup> under mildly acidic conditions. Mukaiyama et al. reported the earliest catalytic version, combining co-catalytic

$\text{OsO}_4$  and a  $\text{Ni}^{\text{II}}$  complex to oxidize allylic ethers and terminal alkenes directly to  $\alpha$ -hydroxy ketones.<sup>[17,18]</sup> Recently, Plietker has employed catalytic  $\text{RuO}_4$  (from  $\text{RuCl}_3$  with Oxone<sup>TM</sup>) in the ketohydroxylation of olefins (Scheme 1) and monooxidation of vicinal diols.<sup>[19–23]</sup> The same transformation via a boronic acid catalyzed protocol, in water, employing dibromoisocyanuric acid (DBI) as terminal oxidant or via electrochemical oxidation<sup>[24]</sup> was reported recently also.



Scheme 1. Catalytic oxidation of allylic ethers to  $\alpha$ -hydroxy ketones reported by Mukaiyama et al.<sup>[17]</sup> and ketohydroxylation of olefins reported by Plietker et al.<sup>[19]</sup>

A key challenge therefore is to access  $\alpha$ -hydroxy ketones from 1,2-diols and alkenes using environmentally benign atom efficient oxidants (e.g.,  $\text{H}_2\text{O}_2$ ) and non-toxic/scarcely catalysts. Here, we describe a catalytic method for the preparation of  $\alpha$ -hydroxyketones employing an in situ prepared manganese catalyst and  $\text{H}_2\text{O}_2$  as terminal oxidant with good to excellent selective monooxidation of vicinal diols. The method shows relatively limited further oxidation (e.g., to diketone products, Baeyer–Villiger oxidation and C–C bond cleavage).

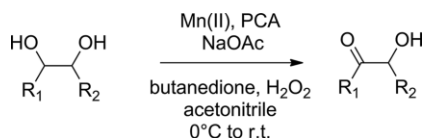
The catalyst, prepared in situ from a  $\text{Mn}^{\text{II}}$  salt and pyridine-2-carboxylic acid (PCA) (Scheme 2), was developed by our group earlier for the oxidation of olefins to epoxides and *cis*-diols,<sup>[25–28]</sup> and more recently for the oxidation of secondary

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alcohols to ketones and C–H bond oxidation.<sup>[29]</sup> This methodology employs the atom-economic oxidant H<sub>2</sub>O<sub>2</sub> and shows excellent solvent scope, including alcohols and acetone, as well as, acetonitrile, under essentially pH neutral conditions. It was noted, however, that in the oxidation of alkenes to epoxides and diols, occasionally minor amounts of the corresponding  $\alpha$ -hydroxyketones were formed by oxidation of the primary products.<sup>[25,28]</sup> These data prompted us to explore this catalytic system in regard to the selective mono-oxidation of diols to  $\alpha$ -hydroxy ketones given its efficiency for secondary and benzylic alcohol oxidation (up to 90 % yields). We show here that, for a broad range of 1,2-diols, selective conversion to the corresponding  $\alpha$ -hydroxy ketone product can be achieved with limited further oxidation under ambient conditions and with reaction times of less than 30 min using a non-scarce/toxic catalyst system. Furthermore we show that in the case of cyclic diols, *trans*-1,2-diols are more reactive than their *cis*-isomers which, together with the absence of significant further oxidation and rearrangements, points to the involvement of a selective oxidising species.



Scheme 2. Oxidation of 1,2-diols to  $\alpha$ -hydroxy-ketones with H<sub>2</sub>O<sub>2</sub> and an in situ prepared catalyst based on Mn<sup>II</sup>, pyridine-2-carboxylic acid (PCA) and butanedione.

## Results and Discussion

Cyclic, linear and benzylic diols were submitted to the oxidative conditions applied earlier in secondary alcohol oxidation<sup>[29]</sup> providing good to excellent selectivity and conversion even

without further optimization of the reactions conditions (Scheme 3). The catalyst was prepared in situ by mixing Mn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O, PCA and a base (NaOAc) in acetonitrile with butanedione [(sub)stoichiometric with respect to the substrate].

### Oxidation of Cyclic Diols

The oxidation of cyclic vicinal diols was examined with a focus on the relative rate of reaction of *cis*- and *trans*-diols and the effect of ring size on conversion and selectivity.

Conditions optimized earlier for the oxidation of alkenes<sup>[28]</sup> were applied in the oxidation of *cis*-1,2-cyclohexandiol (Scheme 3 and Figures S1–7) providing the corresponding  $\alpha$ -hydroxy ketone with 63 % conversion using 1.5 equiv. of H<sub>2</sub>O<sub>2</sub> and near complete conversion was achieved with 3 equiv., with minor amounts (ca. 5 %) of further oxidation products (e.g., aldehyde due to C–C bond cleavage). Similar results were obtained with its stereoisomer *trans*-1,2-cyclohexandiol.

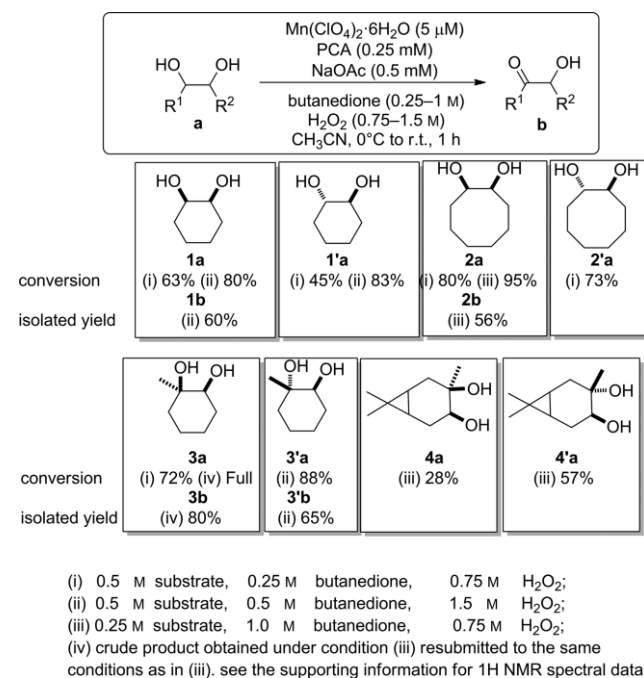
*cis*- and *trans*-cyclooctanediols (**2a**, **2'a**, Scheme 3, and Figures S8–16) are converted into the corresponding  $\alpha$ -hydroxyketones as major products, with minor amounts of cyclooctanediol obtained also. Full conversion and increased selectivity was observed by <sup>1</sup>H-NMR spectroscopy upon a reduction in the substrate concentration and increase in the concentration of butanedione, and despite its volatility the  $\alpha$ -hydroxyketone was obtained in 56 % yield after column chromatography.

*cis*- and *trans*-methyl-cyclohexane-diol (**3a**, **3'a**, Scheme 3 and Figures S18–28) bear only one secondary alcohol moiety and show 72 % and 88 % conversion, respectively, with 3.0 equiv. H<sub>2</sub>O<sub>2</sub>. The absence of side products in the <sup>1</sup>H NMR spectrum of the reaction mixture indicates that cationic or radical intermediates that lead to rearrangements are not formed. In the case **3'a**, 2-methyl-2-hydroxycyclohexanone was obtained in 65 % isolated yield following an aqueous workup to remove unreacted diol. On 10 mmol scale, the  $\alpha$ -hydroxyketone was obtained from *trans*-methyl-cyclohexane-diol in 55 % isolated yield after purification by column chromatography. In the case of the *cis* isomer, **3a**, careful removal of solvent and resubmission of the crude product containing unreacted **3a** resulted in an increase in conversion and 80 % isolated yield (Scheme 3).

The reactivity of *cis*- and *trans*-3-carene-diol (**4a**, **4'a**, Scheme 3 and Figures S29–36) was markedly different with 28 % and 57 % conversion to the desired  $\alpha$ -hydroxyketone, respectively, but with negligible amounts of other products in each case.

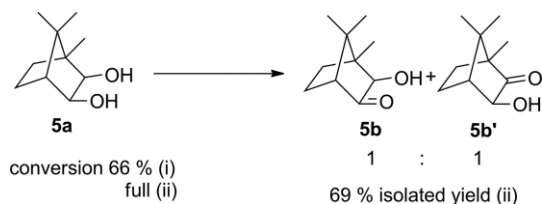
In the case of cyclopentane-1,2-diols, conversion to  $\alpha$ -hydroxy ketones is observed for both *cis*- and *trans*-diol (with the latter showing greater reactivity), however, in contrast to other cyclic substrates as observed earlier by Plietker<sup>[21]</sup> also, the selectivity was poor and multiple by-products were obtained. The increased tendency towards further oxidation for both cyclooctane-1,2-diols and cyclopentane-1,2-diols compared with the cyclohexane-1,2-diols, indicates that ring strain may play an important role in the selectivity obtained.

Camphene diol (Scheme 4 and Figures S39–45) was converted (66 %) to a 1:1 mixture of regioisomers of  $\alpha$ -hydroxy



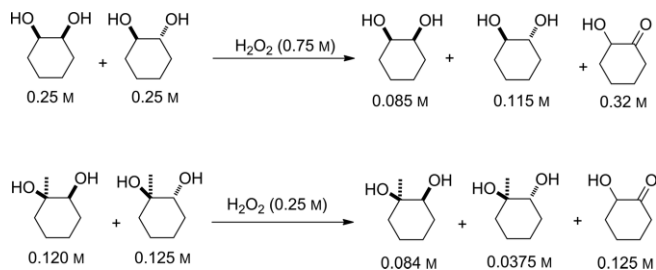
Scheme 3. Oxidation of cyclic 1,2-diols to  $\alpha$ -hydroxyketones.

ketones with 1.5 equiv. of  $\text{H}_2\text{O}_2$ , without significant further oxidation. Notably, full conversion was observed, with high selectivity with respect to the further oxidation products, when the substrate concentration was decreased to 0.25 M, and the two regioisomers were obtained in 69 % combined isolated yield.

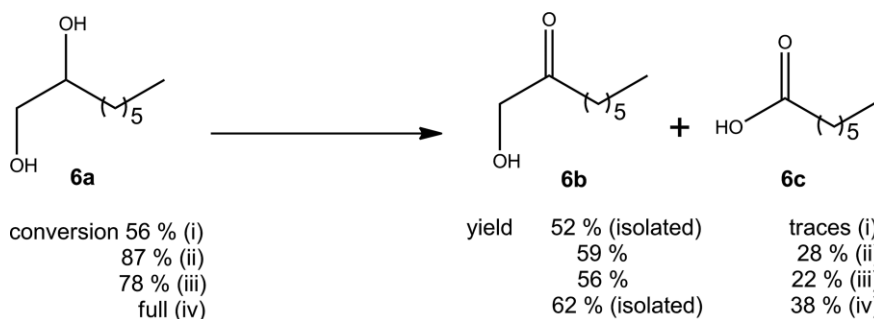


Scheme 4. Oxidation of camphene diol. Reaction conditions: (i) 0.5 M camphene diol,  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), 0.25 M butanedione, 1.5 M  $\text{H}_2\text{O}_2$  in acetonitrile. (ii) as for (i) except with 0.25 M camphene diol (0.5 mmol scale).

A competition reaction between *cis*- and *trans*-1,2-cyclohexanediol (Scheme 5 and Figures S45) demonstrates that the former undergoes oxidation more readily than the latter. Similarly, oxidation of a mixture of *cis*- and *trans*-methylcyclohexane-1,2-diol (10:9.5 initial ratio, by  $^1\text{H-NMR}$  spectroscopy) showed a greater extent of conversion (final substrate ratio 10:4.4) of the *trans*-isomer. These data indicate that oxidation of axial C–H bonds occurs less readily than at equatorial C–H bonds. The difference in reactivity between isomers can be rationalized by considering that although the methyl group has a more dominant steric influence than the hydroxyl group in



Scheme 5. Competition between *syn*- and *anti*-diols under oxidation conditions with 0.5 mmol of each diol in both cases. Reaction conditions:  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), 0.25 M butanedione in acetonitrile 0 °C to room temp. 1 h.



Scheme 6. Oxidation of octane-1,2-diol. Reaction conditions: (i) octane-1,2-diol (0.5 M, 1 mmol),  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), butanedione (0.25 M),  $\text{H}_2\text{O}_2$  (0.75 M) in acetonitrile, 0° to room temp., 1 h. (ii) as for (i) except with  $\text{H}_2\text{O}_2$  (1.5 M). (iii) as for (i) except with octane-1,2-diol (0.25 M, 0.5 mmol),  $\text{H}_2\text{O}_2$  (1.5 M) and butanedione (0.5 M). (iv) Crude product following condition (iii) resubmitted to the same conditions as in (iii). See supporting information for  $^1\text{H}$  NMR spectroscopic data.

*cis*-methylcyclohexane-1,2-diol, the methyl will be forced into an axial position and hence raise the ground state energy. Since the product is in each case the same then the reaction is expected to be faster for the *cis*- than *trans*-methylcyclohexane-1,2-diol.

### Oxidation of Linear Aliphatic Diols

Whereas ring strain is an important factor for cyclic vicinal diols, for terminal linear diols selectivity between primary and secondary alcohol oxidation is of concern. Previously, we demonstrated<sup>[29]</sup> that the present catalytic system shows a strong preference for secondary, and especially benzylic, alcohol oxidation over primary alcohol oxidation. Hence it was anticipated that a preference for formation of 1- $\alpha$ -hydroxy-2-ketones would be observed for linear aliphatic 1,2-diols.

Under standard conditions 56 % conversion of 1,2-octanediol [Scheme 6(i) and Figures S46–55] was observed with a 52 % of the corresponding  $\alpha$ -hydroxyketone isolated yield following column chromatography to remove unreacted diol. The conversion was increased to 87 % conversion with 3.0 equiv.  $\text{H}_2\text{O}_2$  [Scheme 6(ii)], albeit with increased formation of heptanoic acid together with other overoxidation products, as confirmed by negative mode ESI mass spectrometry (vide infra). Reducing the initial concentration of substrate by 50 % [Scheme 6(iii)] resulted in an increase in conversion but also an increase in the extent of further oxidation to heptanoic acid. Resubmission of the crude product to the same reaction conditions [Scheme 6(iv)] resulted in full conversion and the  $\alpha$ -hydroxy ketone was obtained in 62 % yield after basic workup to remove the acid product. Analysis of the crude reaction mixture negative mode ESI-MS (Figure 1) shows other oxidation products in addition to heptanoic acid (129  $m/z$ ). The signals at 145  $m/z$  and 143  $m/z$  pertain to the starting material and  $\alpha$ -hydroxyketone, respectively. The signal at 159  $m/z$  is assigned to  $\alpha$ -hydroxy-octanoic acid indicating that the terminal alcohol is susceptible to oxidation also. The signals at 157 and 113  $m/z$  correspond to the  $\alpha$ -keto-octanoic acid and its decarboxylation product, respectively. Notably hexanoic acid is not observed confirming that C–C bond cleavage takes place between the 1<sup>st</sup> and 2<sup>nd</sup> carbon only.

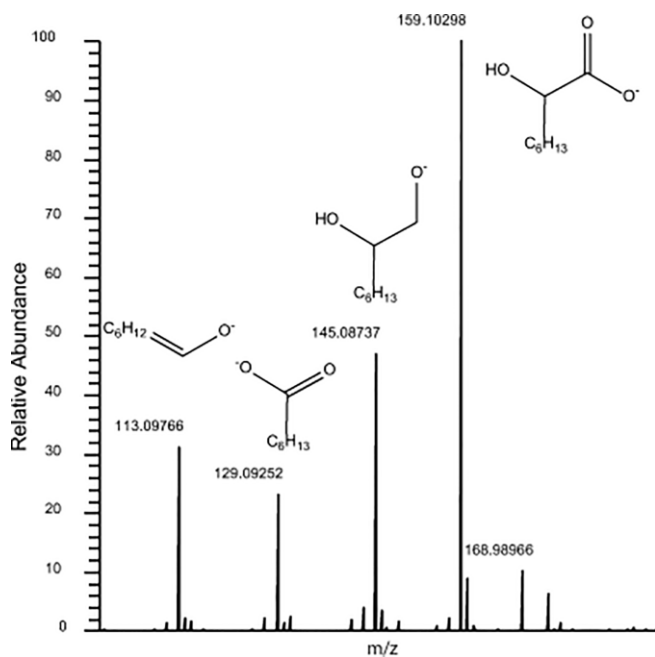
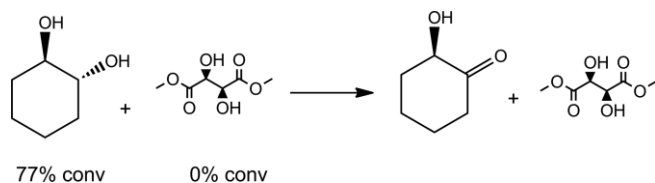


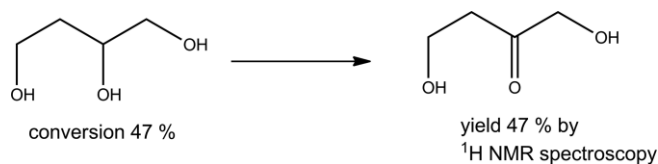
Figure 1. Negative mode ESI mass spectrum of crude product mixture obtained from the oxidation reaction of 1,2-octandiol [Scheme 6(iv)].

As expected, based on the excellent selectivity and yield observed earlier<sup>[25]</sup> in the *cis*-dihydroxylation of diethylfumarate, the product dimethyl-*D,L*-tartrate does not show significant conversion (Figures S56–57). Catalyst inhibition can be excluded because the oxidation of *trans*-1,2-cyclohexandiol (Scheme 7 and Figure S58) proceeds with 77 % conversion in the presence of dimethyl-*D,L*-tartrate.



Scheme 7. Oxidation of *trans*-cyclohexandiol (0.25 M) in presence of dimethyl-*D,L*-tartrate (0.25 M). Reaction conditions:  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), butanedione (0.25 M),  $\text{H}_2\text{O}_2$  (0.75 M) in acetonitrile, 0 °C to room temp., 1 h. See supporting information for  $^1\text{H}$  NMR spectroscopic data.

Selectivity between both primary and secondary alcohols, and between 1,2- and 1,3-diols was explored in the oxidation of butane-1,2,4-triol (Scheme 8 and Figures S59–60). 47 % conversion was observed with formation of the  $\alpha$ -hydroxyketone as the sole product by  $^1\text{H}$  NMR spectroscopic analysis of the

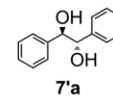
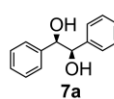
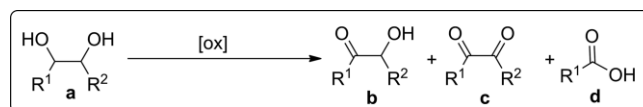


Scheme 8. Oxidation of butane-1,2,4-triol (0.5 M),  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), butanedione (0.25 M),  $\text{H}_2\text{O}_2$  (1.5 M) in acetonitrile, 0 °C to room temp., 1 h. See supporting information for  $^1\text{H}$  NMR spectroscopic data.

crude reaction mixture. A similar result was obtained in a 1:1 mixture of  $\text{CH}_3\text{CN}$  and MeOH.

### Oxidation of Aryl Diols

The catalyst system was shown earlier to be particularly active in the oxidation of benzylic alcohols.<sup>[29]</sup> Both (*R,R*)-(+)-hydrobenzoin and *meso*-hydrobenzoin underwent 48 and 62 % conversion under standard conditions with 1.5 equiv. of  $\text{H}_2\text{O}_2$  [Scheme 9(i) and Figures S61–71]. For both substrates, conversion increased to 75 % and full, respectively, with 3.0 equiv. of  $\text{H}_2\text{O}_2$  [Scheme 9(ii)]. In contrast to aliphatic diols, for aromatic diols the extent of further oxidation and C–C bond cleavage to yield the corresponding benzoic acid products increases with substrate conversion. Hydrobenzoin(s), in which both alcohol groups are at benzylic positions are expected to be susceptible to further oxidation to the corresponding diketone and C–C bond cleavage to yield carboxylic acids.<sup>[30]</sup> A decrease in the concentration of substrate while holding the concentration of all other reagents constant resulted in an increase in conversion and selectivity in the oxidation of (*R,R*)-(+)-hydrobenzoin [Scheme 9(iii)]. For *meso*-hydrobenzoin [Scheme 9(iii)] doubling the amount of  $\text{H}_2\text{O}_2$  used lead to a result comparable to that obtained when the initial concentration of substrate was used and under these conditions an isolated yield of 72 % of  $\alpha$ -hydroxy ketone product **7b**, both on 5 mmol (1.1 g) and 15 mmol (3.2 g) was obtained. The acidic products were removed by basic work-up, while the diketone byproduct (yellow powder) was removed with  $\text{CH}_2\text{Cl}_2$  or  $\text{Et}_2\text{O}$  washing. Overall the limited extent of oxidation of the product to the corresponding carboxylic acid is remarkable given the propensity of benzoin to undergo oxidative carbon–carbon bond cleavage.<sup>[31,32,30]</sup>



conditions	(i)	(ii)	(iii)
conversion	48%	75%	73%
yield of <b>7b</b>	43%	67%	68%
yield of <b>7c</b>	5%	6%	4%
yield of <b>7d</b>	0%	2%	1%

conditions	(i)	(ii)	(iii)
conversion	62%	full	full
yield of <b>7b</b>	59%	78%	74%**
yield of <b>7c</b>	3%	20%	24%
yield of <b>7d</b>	0%	2%	2%

\*\*isolated yield 72%

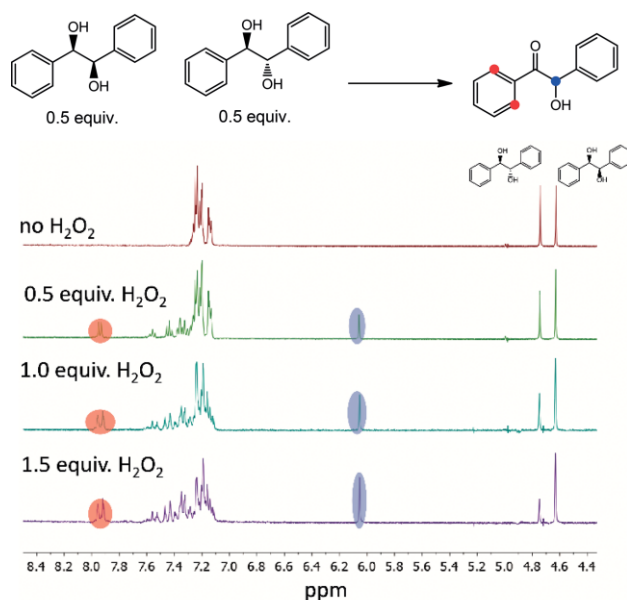
Scheme 9. Dependence of oxidation of (*R,R*)-(+)-hydrobenzoin and *meso*-hydrobenzoin on concentration of substrate and  $\text{H}_2\text{O}_2$ . Reaction conditions: (i) Substrate (**7a/7'a**, 0.5 M, 1 mmol),  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), butanedione (0.25 M),  $\text{H}_2\text{O}_2$  (0.75 M) in acetonitrile, 0 °C to room temp., 1 h. (ii) as for (i) except 1.5 M  $\text{H}_2\text{O}_2$ . (iii) as for (i) except 0.25 M substrate and 1.5 M  $\text{H}_2\text{O}_2$ . See supporting information for  $^1\text{H}$  NMR spectroscopic data.

In several examples discussed above, an increase in conversion was achieved by a decrease in substrate concentration. This increase builds a peculiar characterisation of the catalytic system, which, as shown earlier, shows a zero order depend-

ence on substrate concentration since the rate-limiting step is the reaction between the effective terminal oxidant (3-hydroperoxy-3-hydroxy-butan-2-one, formed within a few seconds of mixing  $\text{H}_2\text{O}_2$  with butanedione) and the catalyst. Hence the reaction rate is unaffected by changes in substrate concentration and the duration over which the reaction proceeds is limited (typically ca. 20 min) by the loss of  $\text{H}_2\text{O}_2$  and/or consumption of butanedione.<sup>[28]</sup> These mechanistic aspects have two consequences in regard to the present study. Firstly, the oxidation of substrate competes with the oxidation of butanedione itself thereby limiting the reaction time to the time taken to consume all butanedione. Secondly, the final ratio of products etc. after the reaction reflects directly the rates at which each substrate is oxidised w. room temp. butanedione. Furthermore it should be noted that butanedione undergoes oxidation to acetic acid also. However, provided the substrate is more reactive than butanedione and the primary oxidation product is less reactive than butanedione, then the conversion can be increased by reducing the initial concentration of substrate without a significant loss in selectivity.

As for cyclic aliphatic diols, there is influence of stereochemistry on the relative reactivity of hydrobenzoin isomers. (*R,R*)-(+)-hydrobenzoin was oxidized more rapidly than *meso*-hydrobenzoin. The difference in reactivity of the substrates was explored through competition experiments, using a limiting amount of hydrogen peroxide under otherwise standard conditions (Scheme 10). It is evident that, since nearly equal amounts of the two substrates were present, the *meso*-hydroxybenzoin is formed from the diastereomer (*R,R*)-(+)-hydrobenzoin. The relative conversions are consistent with conversions for each substrate on their own [vide supra (Scheme 9 and Figures S72–74)]. These data further support the conclusion the active oxidising reagent is selective.

1-Phenyl-1,2-ethanediol underwent 60 % conversion (Scheme 11 [i] and Figures S75–81), with 50 % yield of the  $\alpha$ -hydroxyketone (oxidation at the secondary alcohol) and 5 % of benzoic acid. Benzaldehyde was not observed in the crude reaction mixture. Increasing the number of equiv. of  $\text{H}_2\text{O}_2$  (Scheme 11, [ii]) resulted in a significant increase in oxidation to benzoic acid, whereas reducing the initial amount of substrate by 50 % with respect to standard conditions (Scheme 11 [iii]) resulted in both substantially improved conversion and selectivity, and, after column chromatography, 70 % isolated yield

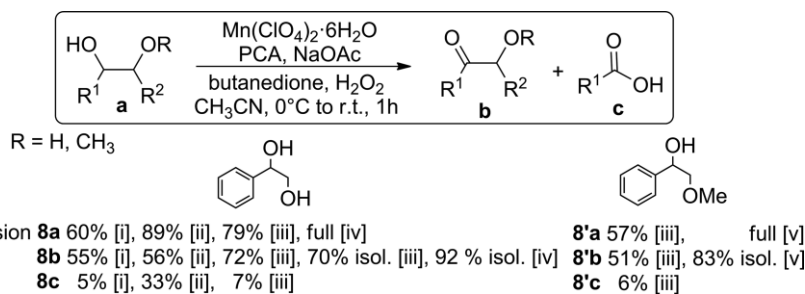


Scheme 10. Competition in the oxidation of (*R,R*)-(+)-hydrobenzoin and *meso*-hydrobenzoin shows that *meso* benzoin undergoes oxidation to a greater extent than (*R,R*)-(+)-hydrobenzoin. Reaction conditions: hydrobenzoin (1:1, *R,R*/*meso*, 0.25 M each),  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), 0.25 M butanedione, 0 to 0.75 M  $\text{H}_2\text{O}_2$  in acetonitrile at room temp.

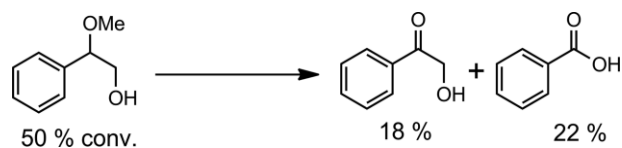
of the  $\alpha$ -hydroxyketone product. Alternatively, resubmission of the crude product to the same reaction conditions (but with only 0.15 equiv.  $\text{H}_2\text{O}_2$ , Scheme 11 [iv]), resulted in full conversion and, after basic workup, 92 % yield of the  $\alpha$ -hydroxyketone product.

For 2-methoxy-1-phenylethan-1-ol, good selectivity was achieved with 57 % conversion, and again resubmission of the crude product to the same reaction conditions (Scheme 11 [v] and Figures S82–83) provided the  $\alpha$ -hydroxyketone product in 83 % yield.

In the case of 2-methoxy-2-phenylethanol (Scheme 12 and Figures S84–85) 50 % conversion was obtained with benzoic acid and 3-hydroxy-acetophenone obtained in an approximately equal ratio (determined by  $^1\text{H-NMR}$  spectral analysis of the crude reaction mixture). The data indicate that benzylic alcohols are much more susceptible to oxidation than terminal alcohols even when protected as ethers.

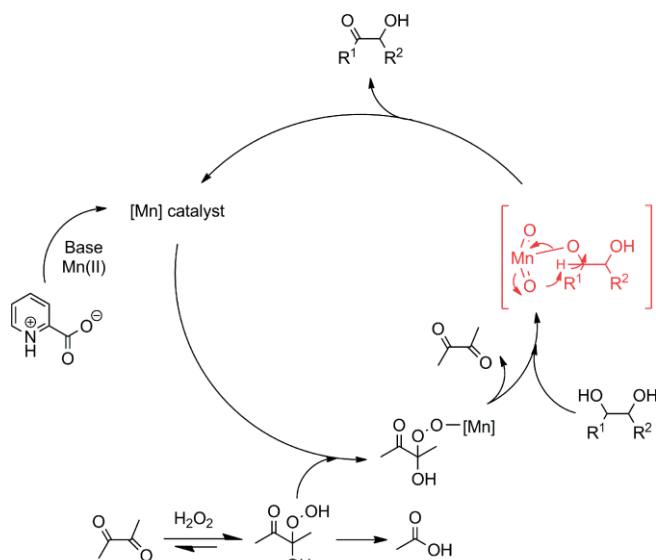


Scheme 11. Oxidation of benzylic diols. Reaction conditions: [i] substrate **8a/8'a**, 0.5 M, 1 mmol,  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), butanedione (0.25 M),  $\text{H}_2\text{O}_2$  (0.75 M) in acetonitrile, 0 °C to room temp., 1 h. [ii] as for [i] except with  $\text{H}_2\text{O}_2$  (1.5 M). [iii] as for [ii] except substrate (0.25 M), butanedione (0.5 M). [iv] Crude product from [iii] resubmitted to the same conditions as in “[iii]” but with  $\text{H}_2\text{O}_2$  (0.025 M) [v] Crude product from [iii] resubmitted to the same conditions as in “[iii]”.



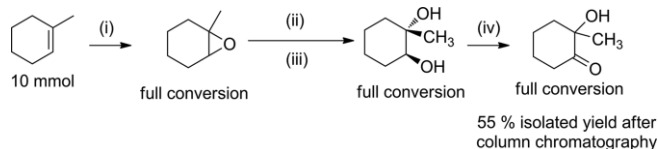
Scheme 12. Oxidation of 2-methoxy-2-phenylethanol. Reaction conditions: 0.5 M 2-methoxy-2-phenylethanol,  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), 0.25 M butanedione, 1.5 M  $\text{H}_2\text{O}_2$  in acetonitrile at room temp.

Although many mechanistic aspects of the reactions involving this catalytic system are clear, the precise structure of the catalyst and the nature of the interaction with the substrate is not yet apparent (Scheme 13). The selectivity of the catalyst indicates that it is likely to be a  $\text{Mn}^{\text{IV}}$  oxido complex, however whether the catalyst reacts hydrogen atom abstraction or deprotonation of a  $\text{Mn}=\text{O}$  ester for example is unknown. The Scheme below shows the known aspects regarding the overall reaction mechanism.



Scheme 13. Mechanism for oxidation showing formation of 3-hydroxy-3-hydroperoxy-butan-2-one from butanedione and  $\text{H}_2\text{O}_2$  and the reaction of this compound with the manganese catalyst to form a reactive intermediate, which reacts with the diol to yield the  $\alpha$ -hydroxyketone product. The structure in red is proposed based on analogy only with permanganate oxidations.

As a final point, the tolerance of the catalytic system demonstrated earlier<sup>[33,34]</sup> in oxidation of alkanes and alkenes in regard to solvent is seen also in the present case. The oxidation of 1-



Scheme 14. Oxidation of 1-methyl-cyclohex-1-ene to 2-methyl-2-hydroxy-cyclohexanone. Reaction conditions: (i) 0.5 M 1-methyl-cyclohex-1-ene,  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), 0.25 M butanedione, 0.75 M  $\text{H}_2\text{O}_2$  in acetone at 0 °C to room temp. (ii) addition of  $\text{Fe}(\text{ClO}_4)_3$  (0.01 mol-%) overnight, (iii) aqueous workup, (iv) 0.5 M crude product,  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (5  $\mu\text{M}$ ), PCA (0.25 mM), NaOAc (0.5 mM), 0.25 M butanedione, 1.5 M  $\text{H}_2\text{O}_2$  in acetone at 0 °C to room temp.

methyl-cyclohex-1-ene proceeds with full conversion to give the corresponding  $\alpha$ -hydroxyketone in 55 % isolated yield over three steps in acetone on a 10 mmol scale (Scheme 14). The oxidation of the alkene to the epoxide was followed by iron(III) catalyzed epoxide ring opening and a short aqueous workup. The *cis*-diol obtained was then oxidized to the  $\alpha$ -hydroxyketone in acetone.

## Conclusions

In the present contribution we show that a simple manganese based catalyst with  $\text{H}_2\text{O}_2$  as terminal oxidant can be applied to the oxidation of diols to their corresponding  $\alpha$ -hydroxyketones. The method shows selectivity for benzylic and secondary positions over primary positions in 1,2-diols as expected considering earlier studies in the oxidation of alcohols. It is notable that although further oxidation to the diketone and cleavage products is observed in some cases the primary product is generally the acyloin. Taken together with the stability of substrates bearing groups sensitive to rearrangements upon formation of carbocation and radical intermediates, the data imply a selective oxidising species (e.g. a high valent manganese complex). The use of a 1<sup>st</sup> row transition metal based (non-scarce/toxic) catalysts with  $\text{H}_2\text{O}_2$  under mild conditions opens a new and versatile route towards an equally versatile class of intermediates.

## Experimental Section

All reagents were of commercial grade and were used as received unless stated otherwise. Hydrogen peroxide was used as received (Acros Chemicals) as a 50 wt.-% solution in water; note that the grade of  $\text{H}_2\text{O}_2$  employed can affect the outcome of the reaction; lower conversion is observed especially in the case of  $\text{H}_2\text{O}_2$  solutions stabilized with sequestrants.  $^1\text{H}$  NMR (400.0 MHz) and  $^{13}\text{C}$  NMR (100.59 MHz) spectra were recorded on a Varian Avance 400. Chemical shifts are relative to the following:  $^1\text{H}$  NMR,  $\text{CDCl}_3$  ( $\delta$  = 7.26 ppm) and  $\text{CD}_3\text{CN}$  ( $\delta$  = 1.94 ppm).  $^{13}\text{C}$  NMR,  $\text{CDCl}_3$  ( $\delta$  = 77 ppm) and  $\text{CD}_3\text{CN}$  ( $\delta$  = 118 ppm). Raman spectra were recorded at 785 nm with a RamanFlex (Perkin-Elmer) spectrometer equipped with a fibre optic probe (Inphotonics).

**Caution!** The drying or concentration of solutions that potentially contain  $\text{H}_2\text{O}_2$  should be avoided. Prior to drying or concentrating, the presence of  $\text{H}_2\text{O}_2$  should be tested for using peroxide test strips followed by neutralization on solid  $\text{NaHSO}_3$  or another suitable reducing agent. When working with  $\text{H}_2\text{O}_2$ , suitable protective safeguards should be in place at all times due to the risk of explosion.

**Caution!** Although used as a food additive, butanedione has been implicated in certain lung diseases upon prolonged exposure to its vapours. It should be handled in a properly ventilated fume hood, and exposure to vapours should be avoided.

**Typical Procedure for Catalytic Oxidations:** The substrate (1 mmol) was added to a solution containing  $\text{Mn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  and PCA in acetonitrile. NaOAc (aqueous, 0.6 M), butanedione (0.5 mmol) and acetonitrile (amount depending on that of the substrate) were added to give a final volume of 2 mL and a final concentration of the substrate of 0.5 M (unless stated otherwise). The solution was stirred in an ice/water bath before addition of  $\text{H}_2\text{O}_2$

(50 wt.-%). Reaction progress was monitored in situ by Raman spectroscopy.<sup>[27]</sup> Conversion was verified by <sup>1</sup>H NMR spectroscopy by dilution of a part of the reaction mixture in CD<sub>3</sub>CN. Spectra were assigned by comparison with authentic samples. Product isolation typically involved addition of brine (10 mL) and extraction with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub> (anhydrous), and filtered, and the dichloromethane removed in vacuo. In the case of hydrobenzoin(s), the diketone product is selectively removed after evaporation of CH<sub>2</sub>Cl<sub>2</sub>, by washing the resulting powder with small amounts of Et<sub>2</sub>O to remove the yellow byproduct. 1,2-Dichlorobenzene, which has a negligible effect on the reaction, was employed as internal standard for Raman and <sup>1</sup>H NMR spectroscopy where necessary. Reaction monitoring with Raman spectroscopy focused primarily on the intensity of the C=C and C=O stretching bands between 1550 and 1800 cm<sup>-1</sup> (e.g., at 1724 cm<sup>-1</sup> for butanedione), between 600 and 900 cm<sup>-1</sup> relating to the C=C and C=O bending modes (682 cm<sup>-1</sup> for butanedione), and the O–O stretching mode of H<sub>2</sub>O<sub>2</sub> at 870 cm<sup>-1</sup>.<sup>[27]</sup>

**Oxidation of 1-Methyl-cyclohex-1-ene to 2-Methyl-2-hydroxycyclohexanone in Acetone:** 1-Methyl-cyclohex-1-ene (10 mmol, 960 mg) was added to a 5.0 mL of acetone with Mn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (5 μM), PCA (0.25 mM), 0.167 mL of NaOAc (aqueous, 0.6 M) and 0.435 mL of butanedione (5 mmol) were added to give a final volume of 20 mL and a final concentration of the substrate of 0.5 M. The mixture was cooled in an ice bath and H<sub>2</sub>O<sub>2</sub> (170 μL, 15 mmol) was added dropwise while stirring. The reaction is allowed to reach room temp. Conversion was verified after 30 min by <sup>1</sup>H NMR spectroscopy reaction after which Fe(ClO<sub>4</sub>)<sub>3</sub> (35.4 mg, 0.01 mol-%) was added and the reaction mixture was stirred overnight at room temperature. Conversion was verified by <sup>1</sup>H NMR spectroscopy followed by aqueous workup (brine/CHCl<sub>3</sub>) of the reaction mixture. The layers were separated and the aqueous layer extracted with CHCl<sub>3</sub> (2 × 10 mL). The combined organic layers were dried with anhydrous MgSO<sub>4</sub> and the solvent was evaporated in vacuo. The crude product was submitted to the same reaction conditions as in the first step, except 30 mmol of H<sub>2</sub>O<sub>2</sub> was added to ensure complete conversion. Conversion after 30 min was verified by <sup>1</sup>H NMR spectroscopy and mixture was added to 100 mL of CHCl<sub>3</sub> and 100 mL of saturated aqueous NaCl. The layers were separated and the aqueous layer extracted with CHCl<sub>3</sub> (2 × 10 mL). The combined organic layers were dried with anhydrous MgSO<sub>4</sub> and filtered, and the solvent evaporated in vacuo. The crude product was purified by column chromatography (Silica gel, Pentane/Et<sub>2</sub>O = 8:2) to give an isolated yield of 55 % (670 mg).

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**Keywords:** Earth-abundant metals · Oxidation · Manganese · Hydroxyl ketone · Homogeneous catalysis · Hydrogen peroxide

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