

A Cheap, Catalytic, Scalable, and Environmentally Benign Method for Alkene Epoxidations

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This paper reports a simple method wherein manganese (2+) salts, for example, MnSO_4 , catalyze epoxidation of alkenes using 30% aqueous hydrogen peroxide as the terminal oxidant. The reactions are performed by dissolving the substrate and catalyst in DMF or *tert*-butyl alcohol and then slowly adding a mixture of 30% hydrogen peroxide and aqueous 0.2 M sodium hydrogen carbonate buffer. This method has several desirable attributes with respect to cost, simplicity, and environmental factors.

This project emerged from a control experiment performed while screening new, chiral, 1,4,7-triazacyclononane (TACN) complexes as potential asymmetric epoxidation catalysts. High throughput screens in a simple plate apparatus¹ indicated simple manganese (2+) salts, without any organic ligand, mediated the epoxidation *but only in hydrogen carbonate buffer*. There was no epoxidation in buffers based on triethanolamine, 3-[*N*-morpholino]propanesulfonic acid (MOPS), phosphate, or borate.

Alkenes are epoxidized by hydrogen peroxide/ NaHCO_3 in H_2O (for water soluble alkenes) or in acetonitrile/water mixtures.^{2,3} We suspected that the transformations in the presence of manganese (2+) salts were fundamentally different because the reaction times reported for the metal-free system³ were significantly longer than those required in the current study. Moreover, the rates of epoxidation in the metal-free system were known to be significantly slower when *tert*-butyl alcohol was used as the solvent rather than acetonitrile; however, the former solvent was effective in the manganese-containing system.

A set of experiments was performed to test for differences between the metal-free and manganese-containing systems. Figure 1 shows a direct comparison of epoxidation of 4-vinylbenzoic acid under exploratory, unrefined conditions (i.e., hydrogen peroxide added all at once at the beginning of the reaction; *tert*-butyl alcohol solvent). These data showed that the extent of conversion of alkene to epoxide was comparable when 0.1 and 1.0 mol % of manganese sulfate were used. It is less for 0.01 mol % Mn^{2+} , but still much greater than the background conversion that occurred when no metal salt was used.

Epoxidation of *trans*-1,2-diphenylethene was chosen as a model to optimize the conditions. This lipophilic substrate was selected so that solubility issues could be addressed using a relatively difficult case. When the substrate, 10 equiv of 30% hydrogen peroxide, and 1 mol % MnSO_4 , were mixed in 0.2 M NaHCO_3 (pH 8.0) and DMF (1.0:1.4) and the reaction was stirred for 24 h, the yield of the epoxide was only 20%. Precipitation was observed in this experiment, indicating solubility problems. Consequently, slow addition of the aqueous components was investigated to minimize the precipitation, and the yield of product increased. Conversely, increasing the buffer concentration above 0.2 M would be expected to accentuate the insolubility problem, and indeed lower yields were obtained when higher buffer concentrations were used. Finally, a set of conditions were developed wherein a mixture of the buffer and 10 equiv of the peroxide were gradually added over 16 h to a solution of the substrate and catalyst in DMF. These reactions gave 1,2-diphenylethene oxide in 92% isolated yield.

Table 1 summarizes the data obtained using various alkenes. 1-Decene was unreactive under these conditions (GC; entry 1).

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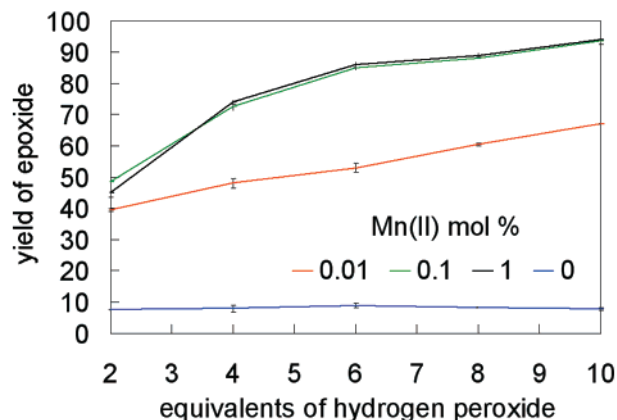
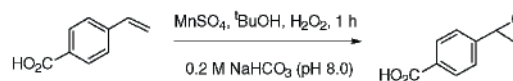


Figure 1. Optimization of the number of the hydrogen peroxide/catalyst stoichiometry. Yield determined by HPLC versus an internal standard. Error bars represent the standard deviation of two trials

Entries 2, 3, and 16 illustrate that disubstituted aliphatic alkenes were reactive, and an excellent yield of cyclohexene oxide was obtained. Oxidation of the tetrahydroanthraquinone (entry 3) gave a significant amount of the corresponding quinone as a major byproduct. No Baeyer–Villiger oxidation was observed for this material or in a control experiment using benzophenone as a substrate (no reaction occurred, data not shown). Entries 4–8 illustrate epoxidations of trisubstituted alkenes. α -Pinene reacted without cyclobutane rupture (entry 4), and citronellal was epoxidized without oxidation of the aldehyde functionality (entry 5; NMR). Similarly, the alcohol functionality of 3-methyl-2-buten-1-ol was preserved in the epoxidation process, and no Payne rearrangement product was observed either (entry 6). Entry 7 tested for the generation of radical character adjacent the cyclopropane in the epoxidation, but no cyclopropane opening was observed. Epoxidation of linalool (entry 8) demonstrated that trisubstituted aliphatic alkenes can be selectively epoxidized in the presence of terminal alkenes. This experiment also implies that the allylic hydroxyl does not activate the terminal alkene via a directing effect. Entries 9–12 illustrate that epoxidations of aryl-substituted alkenes proceed smoothly; qualitatively, the rates of these reactions were observed to be appreciably faster than for aliphatic alkenes. The only complication was that a significant amount of *trans*-3-phenylpropenal was formed in entry 11. Epoxidation of the acid shown in entry 12 was not accompanied by decarboxylation or double bond migration. Some reactions with less catalyst were then attempted since it was evident that aryl alkenes were more reactive than aliphatic ones. Only 0.1 mol % of manganese sulfate was used for the reactions depicted in entries 13–15, and these epoxidations proceeded smoothly. Entries 14 and 15 illustrate that even extremely acid-sensitive epoxides can be formed, and the products are stable under the reaction conditions. The last entry in the table was performed on a 1 mol scale; a detailed procedure for preparation and isolation of 84.5 g of cyclooctene oxide is provided here.⁴

The featured catalytic epoxidation method has numerous attributes. Manganese (2+) salts are cheap, readily available, and relatively nontoxic, and only small amounts (1.0–0.1 mol %) are required. Hydrogen peroxide and sodium hydrogen carbonate are widely used in large-scale production of other chemicals. No halide is involved in the transformation. Slow addition reduces the effective concentration of peroxide and the corresponding risk of explosion. The reaction is run at room temperature in solvents

that are amenable to process chemistry, and no halogenated liquids or ones with low flash points are required. No organic ligands or additives are used, and this facilitates isolation of the desired epoxide.

It is difficult to be certain that the process reported here is completely unprecedented because studies involving transition-metal salts and hydrogen peroxide are so ubiquitous.⁵ However, it is clear that these Mn-catalyzed reactions are much cleaner than Fenton's⁶ and related systems that generate hydroxyl radicals.⁷ Several groups have reported epoxidation reactions using H₂O₂ mediated by TACN–manganese complexes,^{8,9} but the catalysts tend to be relatively inaccessible or require larger excesses of hydrogen peroxide.^{9–11} One of these studies mentions MnCl₂ as a control, and epoxidation activity was detected, but this finding was not exploited.¹⁰ Most importantly, in prior studies of metal-catalyzed epoxidations the special importance of bicarbonate in the media has either not been investigated, realized, or emphasized. Investigations to elucidate the role of bicarbonate are in progress. Our working hypothesis is that percarbonate (HCO₄[−]) formed in situ¹² combines with the manganese to give the active intermediate.

Nearly all of the existing methods for using hydrogen peroxide as an epoxidation reagent have clear disadvantages compared with the one reported here. For instance, most of them involve acidic reagents that tend to decompose the epoxide products.¹³ One notable exception is catalytic methyltrioxorhenium (MTO)¹⁴ buffered with pyridine.¹⁵ However, that procedure features a much more expensive catalyst and media that are explosive or environmentally hazardous, that is, nitromethane or dichloromethane. Moreover, separation of acid-sensitive epoxides from pyridine is likely to be inconvenient for many substrates. On the other hand, the protocol reported here requires 10 equiv of H₂O₂ to drive the reaction to completion, whereas near stoichiometric amounts are used in the MTO/pyridine method. The two procedures are

(4) *Large-Scale Synthesis of Cyclooctene Oxide:* DMF (1.68 L) and MnSO₄ (1.69 g, 0.01 mol) were placed in a 12 L three-neck flask, equipped with a mechanical stirrer and a vent to an oil bubbler. Cyclooctene (110 g, 1.00 mol) was added all at once. The flask was then placed in a water bath at 20 °C (cryocooler). A 3 L two-neck flask equipped with a magnetic stirrer, was charged with 20.6 g of NaHCO₃, 0.123 g of Na₂CO₃, and 1.2 L of H₂O, and the pH of the resulting solution was adjusted to 8.0 with 1 M HCl. The flask was then placed into a water bath maintained at 1 °C and then 1.1 L of 30% H₂O₂ was added all at once. The aqueous solution of buffer/peroxide was then added dropwise to the DMF solution over a period of 36 h via a cannula. **CAUTION!** The reaction exotherms if the buffer/peroxide solution is added too quickly or if heat transfer from the receiving flask is inadequate to maintain the desired temperature. The reaction mixture was extracted into Et₂O (900 mL × 4), washed with brine (900 mL), and dried (Na₂SO₄). The organic fraction was concentrated, and residual DMF was fractionally distilled from it at 5 mmHg. The final product was purified via bulb-to-bulb distillation at 5 mmHg and 57 °C oven temperature, 84.5 g, mp = 53–55 °C. *Small-Scale Epoxidation Procedure:* Similar to the above except that 23 mL of DMF and 17 mL of 0.2 M NaHCO_{3(aq)} were used per 1 mmol of substrate. The aqueous mixture of H₂O₂ and NaHCO₃ was added dropwise over a period of 16 h.

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Table 1. Epoxidations of Representative Alkenes

Entry	Substrate	Product	% Yield ^a (iso'd yield)
1			0
2			99 (84) ^b
3			63 ^c
4			59 (54) ^b
5			95 (82)
6			98
7			92
8			77 (69) ^b
9			87 (78)
10			92 (86)
11			78 ^d
12			78 (64) ^{e,f}
13			94 (89) ^e
14			93 (83) ^g
15			96 (95) ^g
16			95 (93) ^g
17			(67) ^h

^a Unless otherwise specified, the reactions were performed using 0.01 equiv of MnSO₄ on a 1 mmol scale; yields determined by NMR or GC versus an internal standard. ^b 0.1 mol scale. ^c The corresponding anthraquinone (35%) was also observed. ^d *trans*-3-Phenylpropenal was also observed (16%). ^e BuOH used in place of DMF. ^f Isolated as the methyl ester. ^g 0.001 equiv of MnSO₄ were used. ^h 1 mol scale.

complementary insofar as aliphatic terminal alkenes are epoxidized by MTO/pyridine, whereas selective epoxidation of the nonterminal alkenes in the presence of monosubstituted, aliphatic alkenes is possible in the Mn-catalyzed reactions. In summary, the epoxidation protocol presented here has the potential to fulfill unmet needs in exploratory syntheses and large-scale reactions.

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Supporting Information Available: Outlines of optimization procedures, pilot kinetic study to show dependence of reaction rate on manganese concentration (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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