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Published on Web 09/13/2002

# Manganese-Catalyzed Epoxidations of Alkenes in Bicarbonate Solutions

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Received February 17, 2002

***Abstract:*** This paper describes a method, discovered and refined by parallel screening, for the epoxidation of alkenes. It uses hydrogen peroxide as the terminal oxidant, is promoted by catalytic amounts (1.0−0.1 mol %) of manganese(2+) salts, and must be performed using at least catalytic amounts of *bicarbonate* buffer. Peroxymonocarbonate, $HCO_4^-$, forms in the reaction, but without manganese, minimal epoxidation activity is observed in the solvents used for this research, that is, DMF and $^t$BuOH. More than 30 d-block and f-block transition metal salts were screened for epoxidation activity under similar conditions, but the best catalyst found was $MnSO_4$. EPR studies show that $Mn^{2+}$ is initially consumed in the catalytic reaction but is regenerated toward the end of the process when presumably the hydrogen peroxide is spent. A variety of aryl-substituted, cyclic, and trialkyl-substituted alkenes were epoxidized under these conditions using 10 equiv of hydrogen peroxide, but monoalkyl-alkenes were not. To improve the substrate scope, and to increase the efficiency of hydrogen peroxide consumption, 68 diverse compounds were screened to find additives that would enhance the rate of the epoxidation reaction relative to a competing disproportionation of hydrogen peroxide. Successful additives were 6 mol % sodium acetate in the $^t$BuOH system and 4 mol % salicylic acid in the DMF system. These additives enhanced the rate of the desired epoxidation reaction by 2−3 times. Reactions performed in the presence of these additives require less hydrogen peroxide and shorter reaction times, and they enhance the yields obtained from less reactive alkene substrates. Possible mechanisms for the reaction are discussed.

## Introduction

Aside from dioxygen, hydrogen peroxide is probably the terminal oxidant of choice with respect to environmental and economic considerations.[1−4] Systems for epoxidation that use hydrogen peroxide in conjunction with catalytic amounts of cheap, relatively nontoxic metals, therefore, have the potential to be viable for the large scale production of inexpensive products, as well as for more specialized applications in development, process, and research.

Some of the catalysts developed for the epoxidation of alkenes with hydrogen peroxide are heterogeneous, for example, zeolites[5,6] or hydrotalcites.[7] Others are polyoxometalate salts composed of complex anions often incorporating two or more metals,[8] for example, $(R_4N)_6SiW_{10}Fe(OH_2)_2O_{38}$ (where R = alkyl).[9] There are also several homogeneous coordination complexes that are active. These include porphyrins,[10−22] salens,[23−31] 1,4,7-triazacyclononane (tacn) derived catalysts,[32−41] and iron complexes from tetradentate diamine-dipyridine

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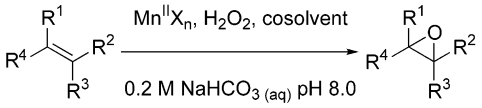
**10.1021/ja025956j CCC: $22.00** **© 2002 American Chemical Society**

ligands.[42−44] Organic catalysts for epoxidation have also been developed, mainly for asymmetric transformations.[45,46] Some selenium,[47−49] arsenic,[50] and organofluorine[51] compounds are surprisingly active and selective catalysts, but they have obvious limitations with respect to large-scale "green" processes. However, the most pertinent category of epoxidation catalysts here are the "soluble metal oxides".

Prominent among simple, soluble metal oxide epoxidation catalysts are systems derived from tungstic acid ($H_2WO_4$), phosphate, and ammonium or phosphonium counterions to act as phase transfer agents.[52−61] Typically, these are formed in situ, but catalytically active complexes such as $(R_4N)_3\{PO_4(W(O)(O_2)_2)_4\}$ have been isolated and even characterized crystallographically. [62] Noyori showed that terminal aliphatic alkenes could be epoxidized by this system at 90 °C without organic solvent by rapid stirring.[63] Acid sensitive epoxides such as phenyl oxirane are not stable to these conditions, however.[63] Herrmann and co-workers found 0.1−1.0 mol % methyltrioxorhenium ($MeReO_3$ or MTO) is an epoxidation catalyst that works in *tert*-butyl alcohol using 30% $H_2O_2$ at room temperature or below.[64,65] The Lewis acidity of the catalyst tends to mediate the ring opening of sensitive epoxides to diols, but Sharpless' group found that pyridine[66] and other basic additives[67−71] accelerate the reaction and protect acid sensitive epoxides from ring opening. The solvents used ($MeNO_2$ or chlorocarbons) are not ideal for process reactions, and there may be problems separating the product from the additive. MTO and tungsten-based catalysts are suitable for large scale epoxidations, but their use tends to be constrained by metal toxicity issues. Other soluble metal oxides have reactivity profiles characteristic of reactions mediated by free hydroxy radicals, that is, "Fenton chemistry".[10,72]

This paper describes the epoxidations of alkenes via a method (reaction 1) that has several attributes. It involves reagents and solvents that have manageable levels of toxicity and proceeds at room temperature with high selectivity for the epoxide product and with catalytic turnovers as high as 6700. Several manganese-




*reaction 1*

(2+) salts can be used, and the cosolvent can be selected from DMF and *tert*-butyl alcohol, whichever is more suitable for the substrate to be epoxidized. [73]

**Critical Role of Bicarbonate in the Reaction System.** Control experiments indicate the desired epoxidation reaction only occurs in the presence of bicarbonate buffer. Attempts to epoxidize 4-vinylbenzoic acid over a period of more than 24 h, with and without 1 mol % $MnSO_4$, in phosphate, triethanolamine, borate, or MOPS (3-{*n*-morpholino}propanesulfonic acid buffer systems, all failed. Further investigations revealed that the epoxidation is *catalytic in bicarbonate*. Table 1 shows reactions for which good yields of epoxides were obtained using only 0.25 equiv of $NaHCO_3$.

The epoxidation of alkenes in the presence of bicarbonate alone is known.[74,75] Richardson[76] has shown that a key aspect of such reactions is that hydrogen peroxide and bicarbonate combine in an equilibrium process to produce peroxymonocarbonate[77−79] (Figure 1). This entity should not be confused with sodium percarbonate, the simple cocrystallite of sodium carbonate and hydrogen peroxide,[80] that does not epoxidize nonactivated alkenes. The equilibrium that results in the formation of peroxymonocarbonate is established in minutes, but epoxidation reactions that rely on this species alone require reactions times

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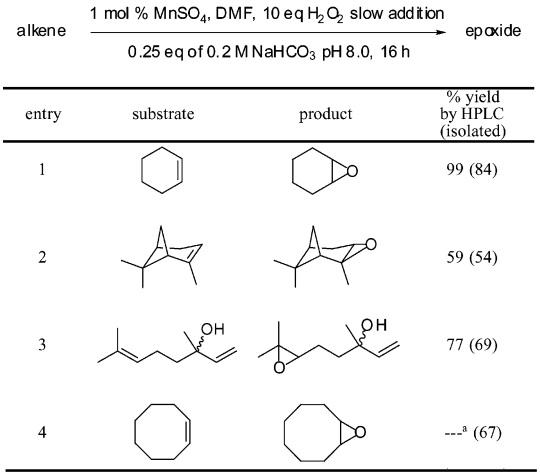
***Table 1.*** Epoxidations of Alkenes Using a Catalytic Amount (25 Mol %) of Sodium Bicarbonate




| entry | substrate | product | % yield by HPLC (isolated) |
|---|---|---|---|
| 1 | | | 99 (84) |
| 2 | | | 59 (54) |
| 3 | | | 77 (69) |
| 4 | | | ---[a] (67) |

[a] Not determined.

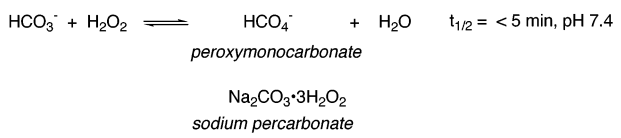






***Figure 1.*** Peroxymonocarbonate and sodium percarbonate.

of 1−2 d. For instance, when 4-vinylbenzoic acid was treated with 10 equiv of $H_2O_2$ in $^t$BuOH and 0.2 M $NaHCO_3$, after 24 h, only a 37% yield of epoxide was obtained. Thus, in the absence of a catalyst, it is epoxidation by peroxymonocarbonate that is rate limiting, not its formation.

The deprotonation of bicarbonate ($pK_a = 10.3$) to carbonate becomes significant at pH values above ~8−9. This deprotonation process should decrease the concentration of bicarbonate in the equilibrium shown in Figure 1, and this reduces the amount of peroxymonocarbonate present. The situation may be further complicated by the deprotonation of the $HCO_4^-$, but this is unlikely to increase the efficiency of the reaction. Consequently, epoxide yields in the manganese-catalyzed reactions would be expected to decrease at elevated pH values if peroxymonocarbonate plays a key role in the process. Figure 2 shows that the epoxide yield does, in fact, decrease from around 95% at pH values less than 8.2 to less than 50% at pH 9.0.

Peroxymonocarbonate in equilibrium with $NaH^{13}CO_3$ and hydrogen peroxide can be observed by $^{13}$C NMR.[76] In the current study, when $NaH^{13}CO_3$ and $H_2O_2$ were here mixed in $^t$BuOH, a new $^{13}$C NMR signal was observed at $\delta$ 158.8 ppm that we attribute to peroxymonocarbonate. A one-dimensional saturation transfer NMR experiment[81] was used to prove that the chemical entity responsible for the peak at $\delta$ 158.8 ppm exchanged with the bicarbonate.

The reaction of $NaH^{13}CO_3$ with $^t$BuO$_2$H in $^t$BuOH was also studied by $^{13}$C NMR to explore the possibility that organic peroxides might enter into a similar equilibrium with bicarbonate and, if they did, that they might be viable epoxidation agents with or without a manganese catalyst. Just as for the formation of peroxymonocarbonate, a new resonance (158.3 ppm) slightly upfield of the bicarbonate signal (160.4 ppm) was established

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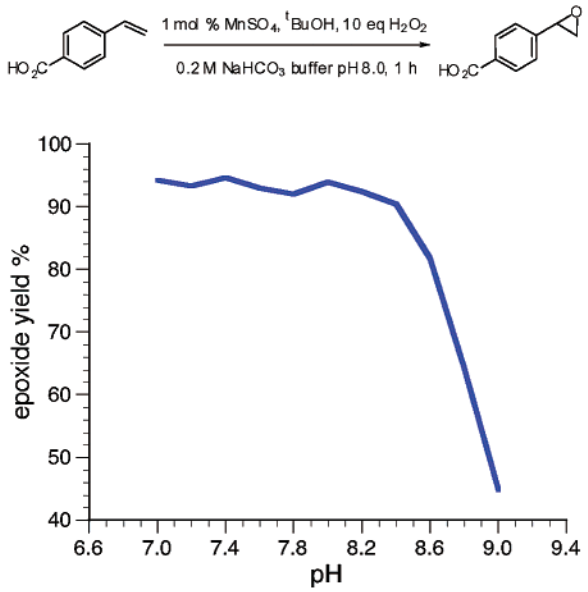
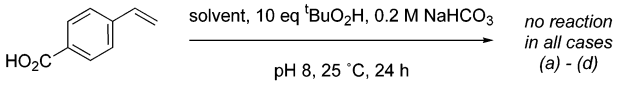


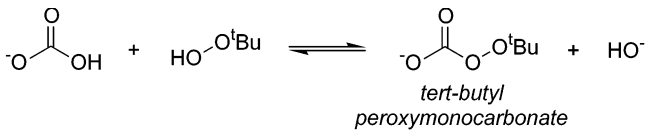

***Figure 2.*** Epoxide yield as a function of pH. 1 mol % $MnSO_4$, 10 equiv of hydrogen peroxide, *tert*-butyl alcohol/water (1:2), reaction time 1 h. Yield determined by HPLC verses an internal standard.




(a) DMF, no catalyst; (b) $^t$BuOH, no catalyst
(c) DMF, 1 mol % $MnSO_4$, (d) $^t$BuOH, 1 mol % $MnSO_4$

***Figure 3.*** Attempted epoxidation reactions using $NaHCO_3$/$^t$BuO$_2$H.

in minutes. Saturation transfer experiments showed the bicar-




bonate resonance exchanged magnetization with the new resonance at 158.3 ppm, consistent with the formation of equilibrium quantities of *tert*-butyl peroxymonocarbonate (reaction 2). Experiments a−d (Figure 3) were used to test combinations of $NaHCO_3$/$^t$BuO$_2$H in potential epoxidation systems. No reaction was observed with or without manganese. It appears from these observations that peroxymonocarbonate esters are not active in the epoxidation reaction.

## Special Character of Mn(2+) in the Catalysis

Parallel screens in a 128-well block were used to screen metal salts for similar epoxidation reactivities to Mn(2+). Figure 4 shows data for the metals in the first transition and some likely candidates in the second and third. Some metal salts gave less epoxide than the background epoxidation by $NaHCO_3$/$H_2O_2$ without catalyst, presumably because of the relatively rapid decomposition of the hydrogen peroxide. Several gave epoxide yields that are comparable to the background level. The third, and most interesting, group, $CrCl_3$, $MnSO_4$, $Mn(OAc)_3$, and $Fe_2(SO_4)_3$, gave between 27 and 94% epoxide yields, but the best of these catalysts was $MnSO_4$. A similar screen using $MnCl_2$, $Mn(OAc)_2$, $MnSO_4$, and $Mn(acac)_2$ showed that there was a negligible difference in the performances of these salts in the

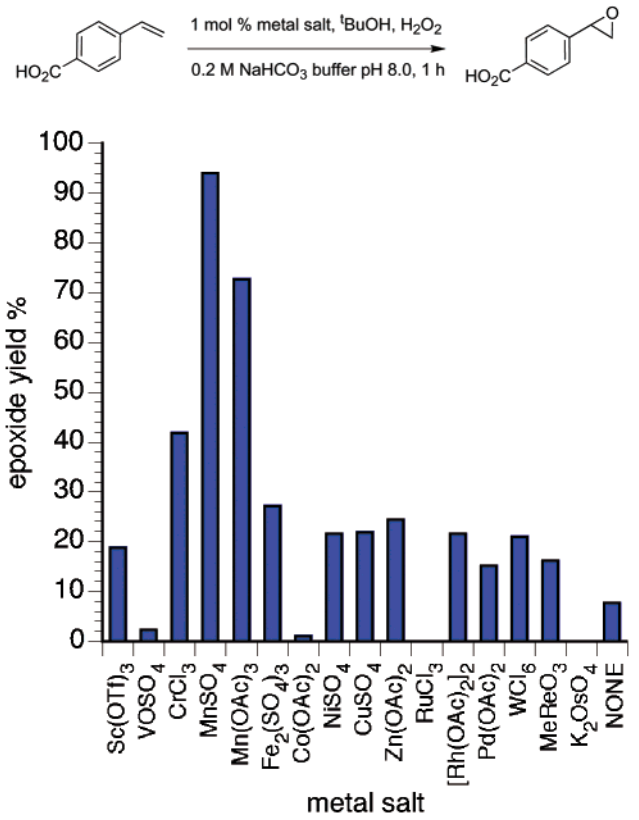



***Figure 4.*** Screen for epoxidation activity with various metal salts. Yield determined by HPLC verses an internal standard (benzoic acid).

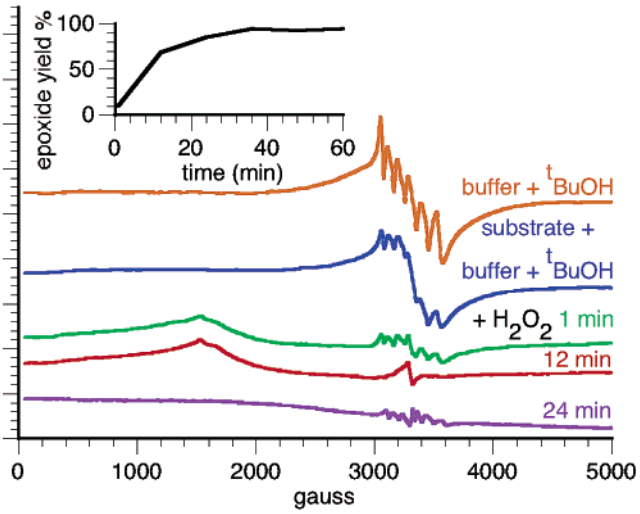



***Figure 5.*** EPR spectra of the reaction mixture prior to the addition of $H_2O_2$ (top) and at times following the addition. Reaction aliquots were also measured for epoxide product (inset). Conditions: 0.2 mM $MnSO_4$, 20 mM 4-vinylbenzoic acid, 100 mM carbonate in 1:2 $^t$BuOH/$H_2O$, 10 equiv of $H_2O_2$. EPR spectra: 9.4 GHz, 7K, 2mW microwave power.

epoxidation reaction. Fourteen different lanthanide(3+) sulfates ($Ln_2(SO_4)_3$; Ln = La, Nd, Gd, Ho, Yb, Ce, Sm, Tb, Er, Lu, Pr, Eu, Dy, Tm) were also screened as a potential epoxidation catalyst in the reaction, but none of these were active.

EPR spectroscopy was performed to observe the Mn component during the epoxidation reaction (Figure 5). The initial solution containing Mn(2+) and bicarbonate buffer gave a six-line pattern centered around $g = 2$, consistent with high-spin $S = {}^5/_2$ Mn(2+) (see the Supporting Information). The addition of substrate alkene causes an increase in line width but no change in hyperfine splittings in the six-line pattern. When the initiation of the reaction by the addition of $H_2O_2$ has occurred, the $g = 2$ signal immediately diminishes in amplitude and a broad signal at $g \approx 4$ grows in. This new $g \approx 4$ signal persists as the reaction progresses (Figure 5, inset), while, at the 12-minute time point, the six-line $g \approx 2$ EPR signal from Mn(2+) is no longer visible. At the end of the reaction (~24 min), the $g \approx 4$ EPR signal is not detected and the six-line $g \approx 2$ EPR signal from Mn(2+) reappears.

EPR signals at $g \approx 4$ are characteristic of high-spin Mn(4+) $S = {}^3/_2$ species having $D > h\nu$, which also have a lower amplitude feature at $g \approx 2$.[82] In addition to the $g \approx 4$ signal, the EPR spectrum from the 12 min time point has a feature at $g \approx 2$ which lacks the six-line hyperfine splitting characteristic of Mn(2+) and may arise in part from the $S = {}^3/_2$ species. The presence of Mn(4+) suggests a two-electron oxidation of Mn(2+) to a high-valent Mn(4+)-oxo species as a potential epoxidation catalyst in the system. Broad signals at low magnetic fields also have been associated with Mn(3+) $S = 2$ states, such as in Jacobsen's Mn-salen catalyst.[83] These two possibilities can be distinguished using parallel-mode EPR spectroscopy ($B_{ext} \parallel B_{mw}$), since the even-spin Mn(3+) systems can give strong signals under those conditions.[84] By contrast with the Mn(3+) catalysts, the Mn(2+)-initiated reaction mixture showed no evidence for a Mn(3+) species on the basis of parallel mode EPR spectroscopy (Supporting Information), providing further evidence that Mn(4+) predominates in the reaction.

### Solvent Effects

All the experiments described so far involve a slightly water-soluble substrate. To accommodate lipophilic substrates, the aqueous components were added slowly, and the buffer concentration was set at 0.2 M $NaHCO_3$ or less. DMF and $^t$BuOH proved to be the best cosolvents. Other solvents such as acetone, acetonitrile, methanol, ethanol and DMSO were inferior, in some cases because they were unstable to the reaction conditions. Several attempts were also made to effect the epoxidation reaction in a biphasic solvent system. Mixtures of aqueous bicarbonate buffer with methylbenzene, dichloromethane, diethyl ether, ethyl acetate, or pentane gave little or no reaction. In separate experiments, a surfactant, Tween 20, was added to these reactions, but this had no significant effect. A phase transfer catalyst, $(n\text{-Bu})_4NCl$, was also added to the methylbenzene, dichloromethane, and ethyl acetate systems, but no epoxidation was observed.

### Additives to Enhance the Reaction Efficiency

Preliminary studies had revealed two disadvantages of the manganese-mediated epoxidation reaction that could be important under some circumstances. First, terminal, monosubstituted, aliphatic alkenes were unreactive. This may be an *advantage* in cases, where selectivity for an internal alkene was required, but that is not always the case. Moreover, our preliminary studies did not encompass 1,1-dialkyalkenes or acyclic 1,2-dialkylalkenes, so it was unclear whether these would react or not. Second,

(82) Saadeh, S. M.; Lah, M. S.; Pecoraro, V. L. *Inorg. Chem.* **1991**, *30*, 8−15.
(83) Campbell, K. A.; Lashley, M. R.; Wyatt, J. K.; Nantz, M. H.; Britt, R. D. *J. Am. Chem. Soc.* **2001**, *123*, 5710−5719.
(84) Campbell, K. A.; Yikilmaz, E.; Grant, C. V.; Gregor, W.; Miller, A.-F.; Britt, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 4714−4715.

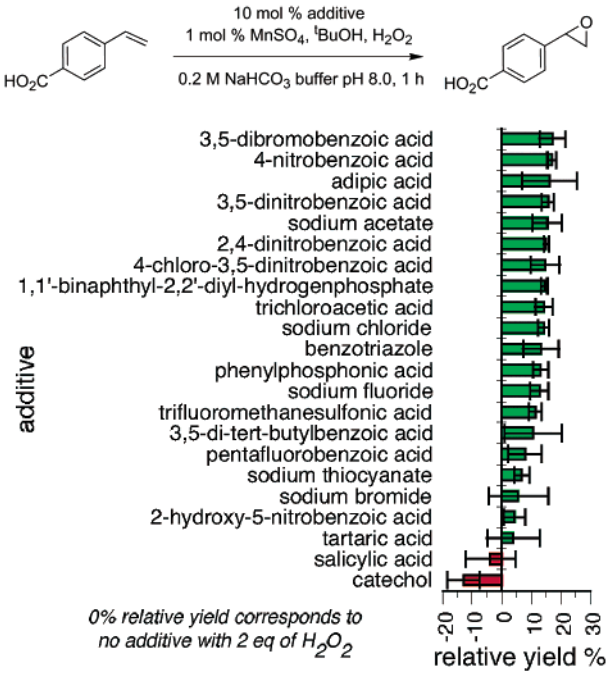



***Figure 6.*** Effects of additives on epoxide yields relative to the process without the additive that gave 85% of the epoxide when 2 equiv of hydrogen peroxide were used. All yields were measured by HPLC relative to benzoic acid as an internal standard.

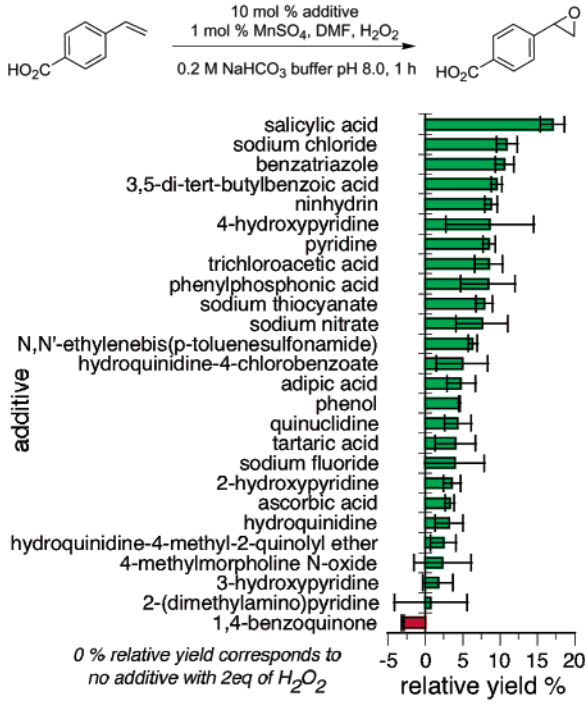



***Figure 7.*** Effects of additives (in triplicate, error bars represent one standard deviation from the mean) relative to the process without the additive that gave 22% when 2 eq of hydrogen peroxide were used. All yields were measured by HPLC relative to benzoic acid as an internal standard.

10 equiv of hydrogen peroxide were required. Hydrogen peroxide is a relatively cheap bulk chemical, but it would be useful to reduce the excess of this reagent in very large-scale reactions from a cost and safety perspective. For these reasons, a series of catalytic additives were screened to test for possible beneficial effects.

Initially, 68 different additives were screened under the reaction conditions indicated in Figure 6 (for $^t$BuOH), and the same ones were also tested for DMF as cosolvent (Figure 7). A 128-well screening block was used throughout. The additives were selected to include both organic and inorganic compounds with a diversity of potentially relevant characteristics. These included acidic and basic functionalities, compounds that could coordinate $Mn^{2+}$ very well (like EDTA) and others that cannot, carboxylates that can bridge metal centers, and compounds with activated carbonyl groups that may react with peroxide anions in situ. In the initial screens (Supporting Information), 6 equiv of hydrogen peroxide were used and the reactions were performed only once. From these screens, a set of additives that gave positive effects on the yields were identified. These were then re-tested, in triplicate, using only 2 equiv of hydrogen peroxide. The purpose of repeating the experiments in triplicate was just to gauge the accuracy of the screen, and the motivation for reducing the amount of hydrogen peroxide was to expose additives that could increase yields significantly from relatively low levels (i.e., from the relatively low yields obtained using only 2 equiv of hydrogen peroxide and no additive). If the additive reduced the yields relative to that of the reaction with no additive, that is a negative relative yield, but if an additive increased the yield that is shown as a positive relative yield.

Of the 68 additives screened using $^t$BuOH as cosolvent, 22 resulted in a yield increase relative to that of the reaction without additive. The 22 additives that increased the yield in the preliminary assay were then screened three more times, but using only 2 equiv of hydrogen peroxide; the yield in the reaction without additive was then 47%, giving more scope for improvement. The averaged data generated from this screen are presented in Figure 6, with error bars representing one standard deviation from the mean. The comparison of Figure 6 with data from the initial screen (Supporting Information) shows that the initial screen was quite reliable, since the absolute values did not change significantly and the relative rankings of the additive effects were much the same in the two sets of experiments. Of these 22 additives, 13 were carboxylic acids or carboxylates. Three of the other nine included a diaryl phosphate, phenyl phosphonic acid, and a sulfonic acid. The more basic additives tended to decrease the yields. The data in Figure 6 show that there is no one particular additive that enhances the epoxide yield more than the others.

The screening strategy described above for $^t$BuOH was repeated using DMF as a cosolvent to test if the effects of additives were similar in this solvent. It became evident early in this phase of the work that they were not. In DMF, salicylic acid caused the maximum yield enhancement (Figure 7). However, we were unable to identify any recurring molecular similarities between the additives that gave yield enhancements: some are acids, some are bases, and some are inorganic compounds. In fact, there were clearer similarities between compounds that inhibit the reaction. Some chelating ligands such as EDTA, bipyridine, and catechol diminished the yields (Supporting Information).

At this stage, there was no basis to suggest that 10 mol % additive (as used in the experiments outlined in Figures 6 and 7) was optimal. This is a typical multivariable problem in catalysis. The ideal conditions cannot be determined with certainty unless all the additives are tested at a comprehensive range of relative concentrations. However, an indication of the

importance of additive concentrations was obtained by retesting the additives that gave positive yield enhancements, but this time, at 0.1, 0.5, 1.0, 2.0, 4.0, 6.0, 10, and 30 mol % levels. These screens were done in triplicate; this resulted in too much data to present effectively in one plot. Instead, the data sets for the best four additives in each cosolvent are shown here in Figure 8a and b (corresponding to $^t$BuOH and to DMF, respectively). Standard deviations for these data were calculated and are given in the Supporting Information.

Of the additive mol % levels tested, 10 mol % was not the best for any of the reactions in $^t$BuOH as cosolvent. The ideal levels were in the 2−6 mol % range, that is, of the same order of magnitude as the catalysts loading. High concentrations of the diacid adipic acid did not increase but actually depressed the epoxide yield. Thus, the mol % additive level is critical in some cases. Sodium acetate (6 mol %) was the best additive/loading identified for the $^t$BuOH cosolvent using 2 equiv of hydrogen peroxide. In DMF, similar trends were observed. Even though the additives were different, the optimal levels in most cases were shown to be in the 4−6 mol % range. In this solvent, the best additive identified was salicylic acid at 4 mol % loading.

The goal of screening additives was to increase the epoxide yields, while decreasing the amount of hydrogen peroxide used. Clearly, these screens enabled that. However, it was also of interest to study, at least in one case per solvent system, the effect of an influential additive on the rate of a typical epoxidation reaction. A kinetic study was, therefore, performed using UV to monitor the progress of the reaction of 4-vinylbenzoic acid in the presence of 1 mol % $MnSO_4$, 6 mol % sodium acetate in 0.2 M $NaHCO_3$/$^t$BuOH. An identical study was performed using 4 mol % salicylic acid in DMF as cosolvent. In both cases, a large excess of hydrogen peroxide was used (750 equiv) to attempt to impose pseudo-first-order kinetics with respect to the substrate. In the $^t$BuOH case, the observed rate constants were $4 \times 10^{-4}$ mol s$^{-1}$ without additive but $8 \times 10^{-4}$ mol s$^{-1}$ in the presence of 6 mol % NaOAc. Thus, the additive approximately doubled the rate of the epoxidation reaction. For DMF without additive, $k_{obs}$ was $7 \times 10^{-4}$ mol s$^{-1}$, but in the presence of 4 mol % salicylic acid, it increased to $2 \times 10^{-3}$ mol s$^{-1}$, that is, just under a 3-fold increase.

### Scope of the Epoxidation Reaction

Seventeen alkenes were studied as epoxidation substrates in the preliminary communication of this work. Data for 10 of these alkenes are shown again in Table 2. The epoxide yields for these particular reactions were very high in most cases.

Table 3 presents a comparison of the epoxidation reactions without and with salicylic acid. The first six alkenes shown are all ones that had been epoxidized in the preliminary study, and the data for those experiments are presented in the "no additive" column. A 10-equiv amount of hydrogen peroxide was used for those experiments. In the presence of 4 mol % salicylic acid, however, these same substrates were epoxidized in higher yields and with only 5 equiv of hydrogen peroxide. In the first entry, even less hydrogen peroxide was used (2.8 equiv), and this seemed to be beneficial.

The last five entries in Table 3 address issues that were not explored previously. For instance, 2,3-dimethylbut-2-ene is the first tetraalkyl-substituted alkene to be studied in this reaction. It was shown that this material is epoxidized in high yields using

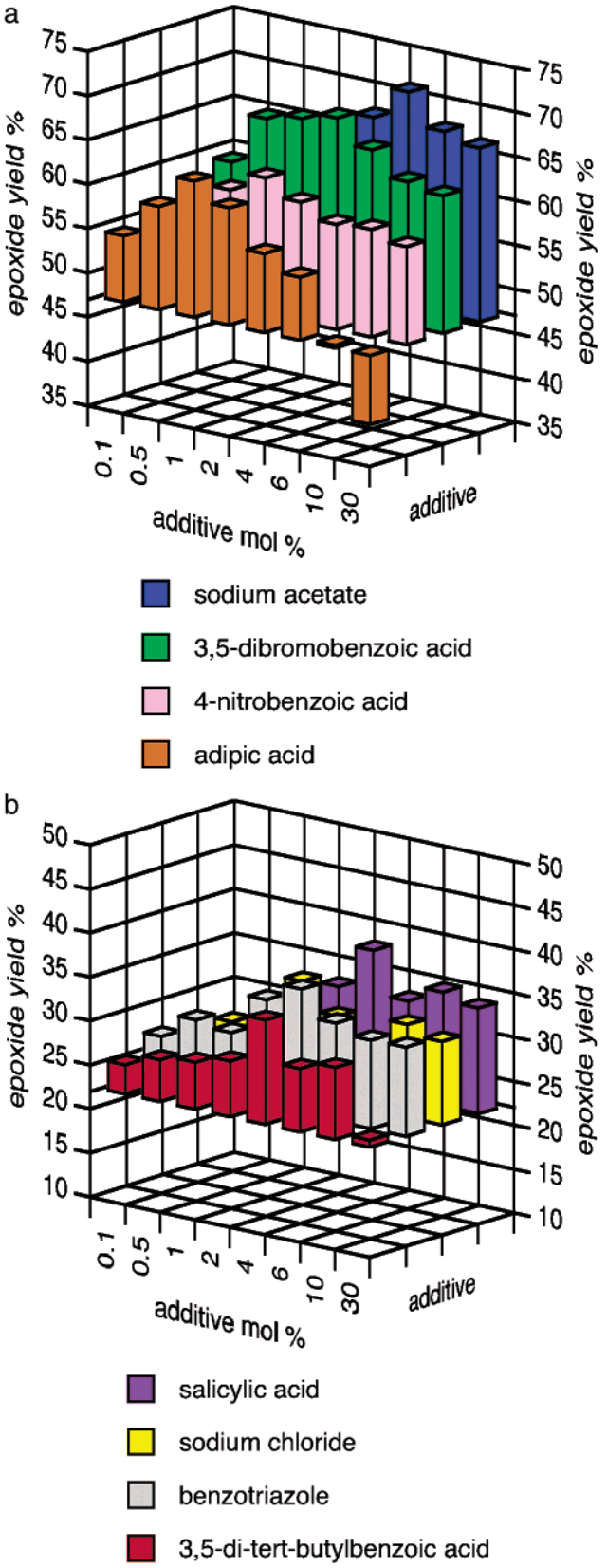
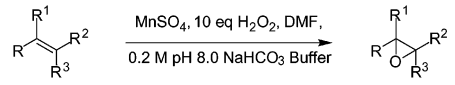
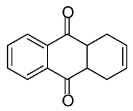
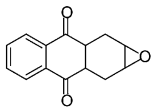
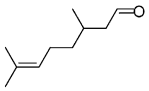
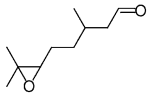
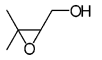
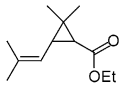
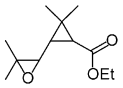
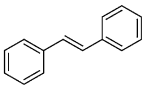
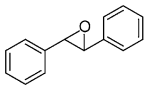
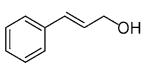
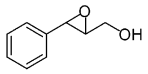
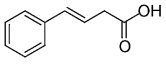
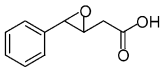
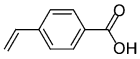
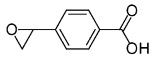
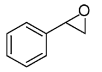
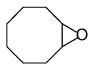



***Figure 8.*** Effects of additives at a range of mol % values in the reactions indicated: (a) for $^t$BuOH as cosolvent and (b) for DMF as cosolvent. A 2-equiv amount of $H_2O_2$ was used. All reactions were repeated in triplicate, and the values shown are the average.

only 5 equiv of hydrogen peroxide in the presence of salicylic acid additive. Dialkyl-substituted alkenes reacted less readily

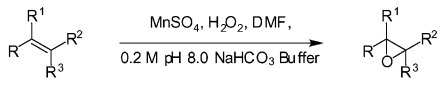
***Table 2.*** Epoxidations of Representative Alkenes without Additives

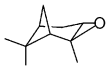
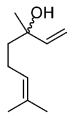
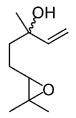



| substrate | product | % yield[a] (iso'd yield) |
|---|---|---|
|  |  | 63[b] |
|  |  | 95 (82) |
|  |  | 98 |
|  |  | 92 |
|  |  | 92 (86) |
|  |  | 78[c] |
|  |  | 78 (64)[d,e] |
|  |  | 94 (89)[d] |
|  |  | 93 (83)[f] |
|  |  | (67)[g] |

[a] Unless otherwise specified, the reactions were performed using 10 equiv. of hydrogen peroxide, 0.01 equiv. of $MnSO_4$ on a 1-mmol scale; yields determined by NMR or GC versus an internal standard. [b] The corresponding anthraquinone (35%) was also observed. [c] *Trans*-3-phenylpropenal was also observed (16%). [d] In place of DMF, $^t$BuOH used. [e] Isolated as the methyl ester. [f] 0.001 equiv. of $MnSO_4$ was used. [g] 1-mol scale.

***Table 3.*** Comparison of Epoxidations of Representative Alkenes without and with Catalytic Salicylic Acid




| substrate | epoxide | no additive | | 4 mol % salicylic acid | |
|---|---|---|---|---|---|
| | | eq $H_2O_2$ | yield[a] (%) | eq $H_2O_2$ | yield[a] (%) |
|  |  | 10 | 99 (84) | 2.8 | 96 |
|  |  | 10 | 59 (54) | 5 | 89 |
|  |  | 10 | 77 (69) | 5 | 91 |
|  |  | 10 | 87 (78) | 5 | (97) |
|  |  | 10 | 96 (95) | 5 | (95) |
|  |  | 10 | 95 (93) | 5 | (95) |
|  | | 10 | 51 | 5 | 81 |
|  |  | 25 | 60 | 25 | 75 |
|  |  | 25 | 54[b] | 25 | 75[c] |
|  | | 25 | 37 | 25 | 51 |
|  |  | 25 | 0 | 25 | 0 |

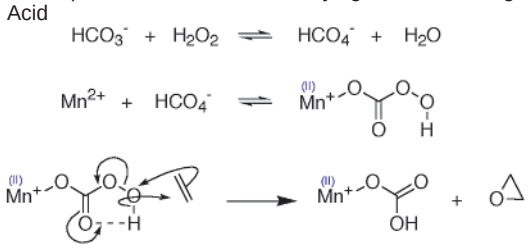
[a] Determined by GC versus dodecane internal standard; yields in parentheses were isolated. [b] Isolated as a 1.00:1.45 *cis/trans* mixture. [c] Isolated as a 1.00:1.10 *cis/trans* mixture.

in these epoxidation processes, so more hydrogen peroxide was used to force the reaction. *Trans*- and *cis*-oct-4-ene were epoxidized to give 75% yields of product when an additive was used. In the absence of additive, the yields were less. For the *Z*-isomer, the reaction was not stereospecific, and near equimolar amounts of the corresponding *cis*- and *trans*-epoxide were formed. The compound 2-ethylbut-1-ene was also epoxidized, though even with additive the product yield was moderate (51%). The terminal alkyl-substituted alkene 1-decene did not react to give epoxide, even in the presence of the additive.

## Conclusions

The work described in this paper has led to a cheap and environmentally compassionate method for epoxidation. High throughput screening enabled us to identify additives that increase the efficiency of the reaction with respect to hydrogen peroxide consumption. Screening and spectroscopic techniques have also allowed us to identify some key features of the reaction that reflect upon its mechanism. Bicarbonate buffer seems to be essential for the epoxidation process, and this led to the implication of peroxymonocarbonate as a key molecular entity. This assertion is supported by the NMR experiments with $NaH^{13}CO_3$ and by the pH dependence of the reaction. The fact

***Scheme 1.*** Epoxidation Mechanism Relying on $Mn^{2+}$ Acting as a Lewis Acid

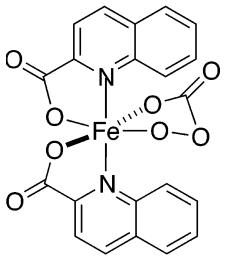


that *tert*-butyl peroxymonocarbonate is *inactive* in the reaction implies that the alkyl substituent somehow blocks the reaction pathway.

Throughout this study, the epoxidation reactions were carried out in open vessels. In the early work, transformations performed under an inert atmosphere were shown to give almost identical product profiles, and in all cases, the reactions tend to be quite clean. This is indicative of a process that does not involve a high concentration of free radicals, particularly not reactive ones such as HO• or HOO•. Radical intermediates *are* implicated in the loss of stereochemistry seen in the epoxidations of *Z*-1,2-diphenylethene and of *Z*-oct-4-ene. However, the radicals involved in these reactions are almost certainly carbon-based ones involved in a stepwise oxygen transfer pathway. For these reasons, we conclude that epoxidation reactions that proceed via HO• or HOO• radicals are not prevalent in this reaction.

Scheme 1 shows one of the simplest mechanisms that can be drawn for the epoxidation process. In this, the manganese acts as a Lewis acid to facilitate cleavage of the O−O bond by stabilizing the carbonate leaving group. However, if it is the prevalent mode of epoxide formation, then the EPR-active species that are generated as the reaction proceeds must be largely irrelevant because the metal is not required to undergo redox processes. Moreover, if it were the predominant pathway, then it is surprising that most of the metal salts that were screened did not have similar activities, because many of them would have comparable Lewis acidities. While this mechanism cannot be excluded, it is less consistent with the experimental data than some other possibilities.

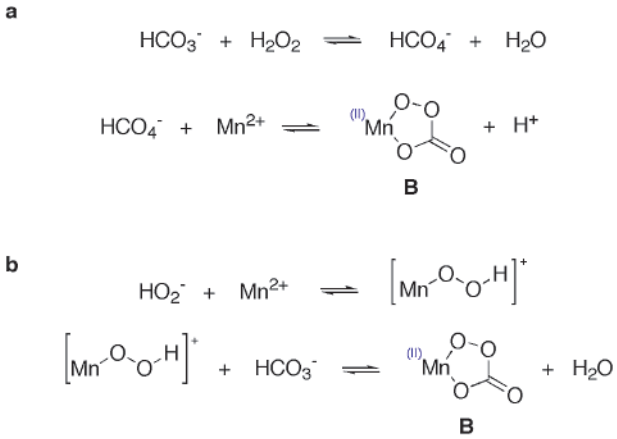
The mechanistic pathways that we regard as most likely all involve manganese $\eta^2$-peroxycarbonate complexes. Peroxycarbonate complexes are not new. Rhodium[85] and platinum[86] peroxycarbonate complexes have been formed and characterized primarily by vibrational spectroscopy. Very recently, the iron-



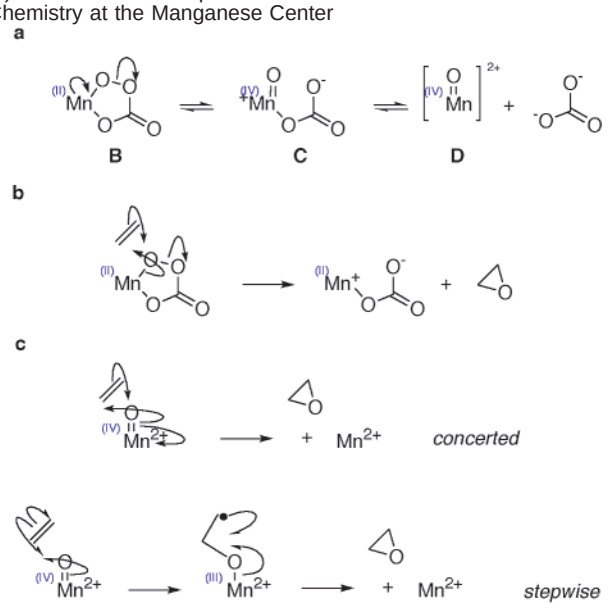
**A**

(3+) peroxycarbonate complex A was isolated and characterized via X-ray crystallography.[87] This complex is unstable in solution above −60 °C. At that temperature or below, it did not epoxidize alkenes, but it would be unwise to infer from this that similar complexes would not do so.

***Scheme 2.*** Formation of the Peroxycarbonate Complex B (a) by the Direct Reaction of Peroxymonocarbonate and (b) by the Reaction of a Peroxy Complex with Bicarbonate



***Scheme 3.*** (a) Three Molecular Species Postulated for Oxygen Transfer, (b) Transfer without Redox at the Mn(4+) Center, and (c) Concerted and Stepwise Processes for *O*-transfer with Redox Chemistry at the Manganese Center



Scheme 2 outlines routes by which a manganese peroxycarbonate complex B could form. One possibility involves the generation of an equilibrium concentration of peroxymonocarbonate, and then coordination of this to Mn(2+). Alternatively, the coordination of peroxide anion to Mn(2+), deprotonation, and reaction of this with bicarbonate would lead to the same intermediate, as indicated. Both routes seem plausible, and they might be operative simultaneously.

The most critical issue of the epoxidation process is the oxygen delivery step. Scheme 3a shows species that could potentially deliver oxygen to the alkene; equilibria of the type shown would account for the presence of Mn(4+) in the reaction. Intermediate B might directly epoxidize alkenes, as shown in Scheme 3b. Alternatively, *O*-transfer from the

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carbonate complex C or the free Mn(4+) oxospecies D could take place, as shown in Scheme 3c. Manganese(4+) complexes have been shown to be viable epoxidation intermediates, and a simple interpretation of the mechanism of these reactions is that a Mn(4+) oxo complex gives the epoxidation reaction.[88−91] They might be presumed to act via the direct addition of the alkene substrate to the oxo ligand with the concerted or sequential formation of the C−O bonds. The latter is similar to the Mn(3+)/Mn(5+) catalytic cycles widely accepted for epoxidations for Mn-porphyrin[92−94] and salen[95,96] complexes. The formation of intermediates B−D would not be possible if *tert*-butyl peroxycarbonate were used (as observed, vide supra).

None of the mechanisms shown in Scheme 3 can be eliminated. Moreover, the mechanisms outlined above are oversimplifications if the active catalyst is di- or oligo-nuclear (attempts to detect higher molecular mass species in ESI-MS of the reactions mixtures, however, were negative). The acquisition of more data to exclude some of these possibilities will be difficult. The system is hard to study because the active catalyst forms in situ, it is not stabilized by organic ligands, kinetic investigations are complicated by the disproportionation of hydrogen peroxide and the possibility of competing pathways, and the paramagnetic properties of some of the compounds in the reaction mixture preclude NMR analyses. However, a stepwise oxygen delivery via intermediates C or D as implied in Scheme 3c seems the least speculative mechanistic proposal based on similarities with Mn-porphyrin[92−94] and -salen[95,96] mediated epoxidations. Stepwise oxygen delivery via *C*-radical intermediates is consistent with *cis*−*trans* isomerization, as observed.

Our efforts to increase the efficiency of hydrogen peroxide usage in these reactions were successful. Screens with additives led to the discovery of simple compounds such as sodium acetate (in $^t$BuOH) and salicylic acid (in DMF) that enhance the rate of the epoxidation reaction. Without a screening process, it would have been extremely difficult to identify beneficial additives. The additives studied could affect the epoxidation process in different ways that this study did not attempt to address. However, it does seem plausible that since two of the most active ones {sodium acetate (in $^t$BuOH) and salicylic acid (in DMF)} are carboxylates, then the catalytically active species might be bridged dimers or oligomers.[97]

Additives are most useful for the epoxidation of less reactive alkenes. The data collected in this study indicate that electron-rich alkenes are most reactive. Thus, the yields of epoxide are high for aryl-substituted alkenes, even without an additive. Higher hydrogen peroxide concentrations and special additives are required to obtain good yields from less reactive substrates such as dialkyl-substituted alkenes. However, the modified procedure, with additive, has other advantages that may justify its use, even with reactive alkenes. The procedure with the additive uses catalytic bicarbonate, less hydrogen peroxide, shorter addition times, and the overall reaction is faster.

The main objective of the work presented here was to show that screening could facilitate the discovery of an experimentally useful epoxidation system. This has been achieved. The cost and the lack of toxicity of Mn(2+) salts compares well with rhenium and tungsten-based catalysts such as $MeReO_3$ and $WO_4^{2-}$. Our catalyst is "ligand free", and this further reduces costs and increases experimental convenience relative to the case of some other reaction types. The solvent systems used ($H_2O$ and DMF or $^t$BuOH) are appropriate for process chemistry, being relatively safe, nonhalogenated, and inexpensive. A major advantage of the featured epoxidation method over virtually all others is that acid sensitive epoxides are not only stable under the reaction conditions but are also easily isolated. Methyltrioxorhenium is also a viable catalyst for preparations of acid sensitive epoxides, provided pyridine or other basic additives are included. However, if the only way to isolate the epoxide from these basic additives is via an acidic workup, then the practical value of that approach is diminished. Conversely, in the work described here, most epoxides are easily isolated via a simple extraction into an apolar solvent (e.g., pentane or diethyl ether) and, in many cases, after removal of the solvent, further purification is unnecessary. It is not essential to use additives in this process, but if they are used, then the favored ones (NaOAc for $^t$BuOH and salicylic acid for DMF) remain in the basic aqueous layer during the extraction.

The system reported here is experimentally and mechanistically distinct from any of the well-known epoxidation systems reported to date. We suspect it will find applications in both research and process chemistry.

**Acknowledgment.** We wish to thank Mr. Steve Silber for help with the presaturation NMR experiments and Dr. Huay-Keng Loke for assistance with the preliminary EPR studies. Financial support for this work was provided by The Robert Welch Foundation. TAMU EPR facilities are supported by the NSF (CHE-0092010). Use of the TAMU/LBMS-Applications Laboratory and Dr. Shane Tichy are acknowledged.

**Supporting Information Available:** NMR spectra for the saturation transfer experiments, additional EPR spectra including control- and parallel-mode experiments, details of the screens using the additives, and full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

JA025956J

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