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Oxidation of Alkenes with H_2O_2 by an in-Situ Prepared Mn(II)/Pyridine-2-carboxylic Acid Catalyst and the Role of Ketones in Activating H_2O_2

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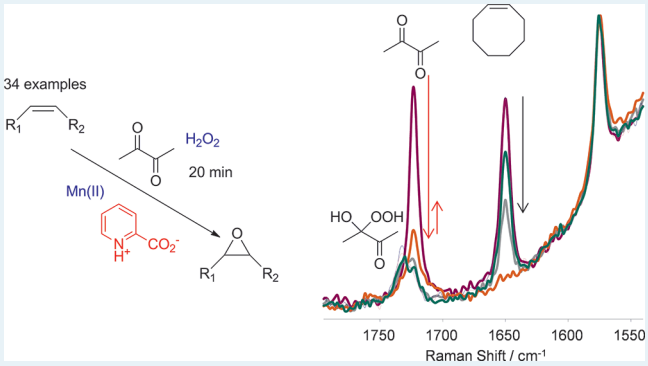
Supporting Information

ABSTRACT: A simple, high yielding catalytic method for the multigram scale selective epoxidation of electron-rich alkenes using near-stoichiometric H_2O_2 under ambient conditions is reported. The system consists of a Mn(II) salt (<0.01 mol %), pyridine-2-carboxylic acid (<0.5 mol %), and substoichiometric butanedione. High TON (up to 300 000) and TOF (up to 40 s^{-1}) can be achieved for a wide range of substrates with good to excellent selectivity, remarkable functional group tolerance, and a wide solvent scope. It is shown that the formation of 3-hydroperoxy-3-hydroxybutan-2-one from butanedione, and H_2O_2 in situ, is central to the activity observed.



KEYWORDS: *manganese, epoxidation, cis-dihydroxylation, hydrogen peroxide*

INTRODUCTION

The central role played by epoxides and (*cis*-)diols in all areas of synthetic organic chemistry, from total synthesis and materials science to bulk chemicals production,[1] places the development of new methods for olefin oxidation at the center of efforts to increase sustainability and reduce the environmental footprint of processes.[2] In this regard, considerable efforts have focused on replacing methods based on scarce and potentially toxic metals such as chromium, ruthenium, and osmium with metals such as iron, titanium, manganese, tungsten, and molybdenum. In addition to using environmentally benign and abundant metals, substituting terminal oxidants—in particular, oxone, NaOCl, iodosylbenzenes, and *m*CPBA,[3]—with more atom economic oxidants such as O_2 and especially H_2O_2 is a major challenge.

Ideally, catalytic oxidation methods based on efficient, safe, and readily applicable "off the shelf" components (i.e., in situ preparation) are desirable for the oxidation of alkenes with H_2O_2 for practical, economic, and environmental reasons. Their relatively low toxicity and cost and the often high turnover numbers (TONs) that can be achieved position manganese-,[4−6] iron-,[7] tungsten-,[8−12] and molybdenum-based[13] catalysts at the focus of current attention.[3] Notable examples are the "off the shelf" systems based on molybdenum and tungsten oxides developed by Payne,[8] Venturello,[9,10] and Noyori[2,11,12] and co-workers and the methyltrioxorhenium (MTO) system developed by Herrmann[14,15] and others. The tungsten and molybdenum systems have demonstrated remarkably high turnover numbers (>2000) and frequencies (>10 s^{-1}) with H_2O_2 as terminal oxidant. Initial limitations imposed by the acidic conditions resulted in restrictions to their application in the formation of acid-sensitive substrates and other substrates such as styrene, but recently, modified conditions toward addressing this issue have been reported.[16,17] In the case of the MTO systems, good conversion and selectivity can be achieved for a range of alkene substrates, in particular, *trans*-alkenes, albeit with relatively long reaction times (1−20 h).[14,15]

Alkene epoxidation and cis-dihydroxylation with manganese-based catalysts has seen rapid progress in recent years also,[18,19] in particular the recent reports by Lau and co-workers with $(PPh_4)_2[Mn(IV)(N)(CN)_4]$,[20] and with the manganese tri- and tetraaza-macrocycle-based complexes developed by De Vos,[21] Berkessel,[22] Busch,[23,24] Costas,[25,26] and our own groups.[4,27] For methods based on manganese, however, the

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challenge is to activate H_2O_2 using similarly simple in situ prepared catalysts without producing hydroxyl radicals and avoiding strongly acidic or basic conditions.[28] The systems reported by Hage et al. in $NaHCO_3$(aq) buffer[4] and by Burgess and co-workers[5] for the epoxidation of alkenes with $MnSO_4$ and aqueous $NaHCO_3$ with DMF or *t*-BuOH, albeit both requiring excess H_2O_2 (>5 equiv), are among the few in situ-prepared manganese-based procedures available to date.

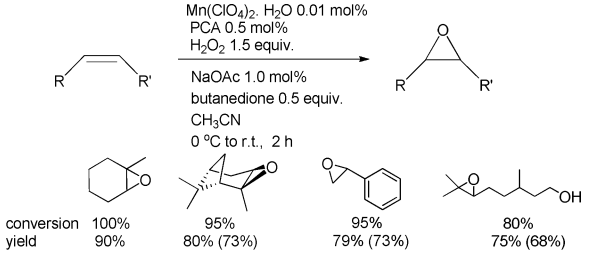
The current challenge, therefore, is to develop methodologies that allow for efficient oxidation of alkenes (in terms of oxidant) with readily available catalyst systems under neutral conditions with good functional group tolerance and selectivity. Recently, we reported such a straightforward method based on a Mn(II) salt (0.1 mol %), pyridine-2-carboxylic acid (PCA, 0.5 mol %), and H_2O_2 (2.0 equiv) for the cis-dihydroxylation of electron-deficient alkenes in acetone in excellent yields and selectivities.[29−31] In addition, the system showed moderate to good activity and selectivity in the epoxidation of electron-rich alkenes.

The system, although effective, raised two important issues. First, the requirement for a ketone to be used as (co)solvent[32] suggested that ketone-hydrogen peroxide adducts are involved in the reaction as a reservoir, to reduce the steady-state concentration of H_2O_2, or that these adducts are, in fact, involved in the oxidation directly. Second, in contrast to the, for example, largely aqueous tungsten-based systems,[8−12] the use of a combination of acetone and H_2O_2 presents a substantial risk of explosion and, hence, may prove unsuitable for routine use, especially on medium and large scale.[33−35] In our earlier report,[29] we demonstrated that in acetonitrile, similar reactivity could be achieved with 5 vol % of 1,1,1-trifluoroacetone, albeit being a ketone that is expensive and generates fluorinated waste. The combination of safety issues, cost, and waste, in addition to solubility considerations and the drive for increased selectivity toward epoxidation of electron rich alkenes, prompted us to explore other solvents and ketones.

Here, we report a general and robust method for the epoxidation of simple and multifunctional alkenes with H_2O_2, catalyzed by a combination of a Mn(II) salt, pyridine-2-carboxylic acid (PCA), and substoichiometric 1,2-diketones, specifically butanedione,[36] in a wide range of solvents (Scheme 1). The use of substoichiometric butanedione is cost-effective and reduces the risks associated with H_2O_2 in combination with organic solvents considerably compared with the original acetone/H_2O_2 combination.[37] Importantly, it enables a broad solvent scope, much higher reaction rates (completion reached within 10−20 min), unprecedented turnover frequencies (up to 40 s^{-1}), and extremely low catalyst loadings (<0.01 mol % Mn(II)) at room temperature. The method is straightforward and provides high selectivity with good to excellent atom efficiency (Scheme 1).

Furthermore, we demonstrate that the ketone used is catalytic in the reaction through the reversible formation of ketone−peroxide adducts. Through mechanistic studies, we show that the primary limitation to the system is the competing oxidation of the ketone additive to carboxylic acids,[37] which eventually leads to a loss in activity. The recognition of the ketone-hydrogen peroxide adduct as the actual oxidant[38] presents considerable potential in the development of a new approach to oxidation catalysis.

Scheme 1. Conversions and Yields (Isolated) Obtained for the Epoxidation of Selected Electron Rich Alkenes[a]



[a]See Supporting Information Table S3 for details. Substrates were 0.5 M final concentration.

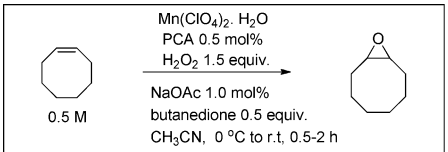
RESULTS AND DISCUSSION

General Reaction Conditions and Optimization. An initial screening of the oxidation of diethylfumarate and cyclooctene using stoichiometric amounts of ketones, with acetonitrile as solvent, identified butanedione[36] as a viable alternative to acetone or 1,1,1-trifluoroacetone in terms of cost, safety/toxicity, and selectivity.

Initial screening showed that, with 0.5 equiv of butanedione, 0.05 mol % Mn(II), and 0.5 mol % PCA, 95% conversion and 53% yield of cyclooctene oxide could be achieved (see Supporting Information (SI) Table S1a). *cis*-Diol and *α*-hydroxyketone byproduct were also obtained. Surprisingly, increasing the amount of butanedione decreased both the conversion of cyclooctene and the yield of epoxide. Higher turnover numbers (TON 9500) and yield (80%) of the desired epoxide product were obtained by decreasing the amount of Mn(II) to 0.01 mol %. Under these conditions, full conversion was achieved within 15 min at room temperature (SI Table S1, entry 3). For *α*-pinene, a similar optimization indicated that the optimum conditions for cyclooctene were generally applicable (see SI Table S1b) for electron-rich alkenes (with regard to electron-deficient alkenes, somewhat different conditions provided the best conversions and yields; see SI Table S2, vide infra).

The dependence of conversion on the concentration of Mn(II) was examined further in the epoxidation of cyclooctene (Table 1). Similar yields (71−74%) were obtained, even when only 0.001 mol % Mn(II) was used. Conversion decreased to

Table 1. Effect of Mn(II) Concentration on the Epoxidation of Cyclooctene[a]



Entry	$Mn(ClO_4)_2.6H_2O$ (mol %)	T.O.N.	Conversion (%)	Yield (%)
1	0.005	19,400	97%	71%
2	0.002	48,500	97%	74%
3	0.001	95,000	95%	72%
4	0.0005	130,000	65%	50%
5	0.0001	300,000	30%	20%

[a]Conversion and yield was determined by Raman and ^{1}H NMR spectroscopy (±3%, see the Supporting Information). Substrates were 0.5 M final concentration.

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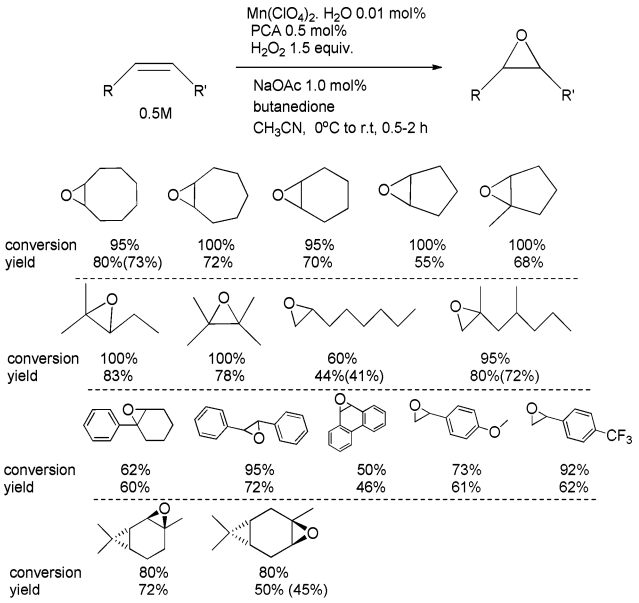
30% with 0.0001 mol % Mn(II); however, this still represents a turnover number of 300 000 with respect to Mn(II).

The concentration of PCA could be reduced to 0.1 mol % with only a slight decrease in yield (see SI Table S1, entry 4). Omission of either Mn(II), PCA or butanedione resulted in a complete loss of activity (SI Table S1, entries 6–8).

Using conditions optimized for cyclooctene directly, the epoxide product of 1-methyl cyclohexene was obtained in high yield (90%), which indicated that with aliphatic alkenes, this system performs well. Both aliphatic and aromatic alkenes were investigated under the reaction conditions optimized for cyclooctene also (Schemes 1 and 2 and SI Table S3). Even

Scheme 2. Conversions and Yields Obtained for the Epoxidation of Electron-Rich Alkenes Using Reaction Conditions Optimized for Cyclooctene[a]



[a]Conversion and yield was determined by Raman and ^{1}H NMR spectroscopy (±3%, see the Supporting Information). Substrates were 0.5 M final concentration. Isolated yields are indicated for selected substrates in parentheses. (For full details for each substrate, see Section 3 of the Supporting Information).

without further optimization, good to excellent conversion was observed for all cyclic alkenes examined, with typically 70% yield of the corresponding epoxide products. From a mechanistic perspective, the notable absence of significant allylic oxidation of cyclohexene indicates that hydroxyl radicals are not involved.[39]

For acyclic alkenes, good conversion was achieved with the highest yields for trisubstituted alkenes: 44% yield of epoxide product was obtained for 1-octene and for the gem-disubstituted alkene, 2,4-dimethyl-heptene, 80% yield of the epoxide product was obtained. Internal di-, tri-, and tetra-substituted alkenes showed higher reactivity in general, with full conversion and 70–83% yield of the epoxide product (Schemes 2 and 9). As for styrene (Scheme 1), a set of aromatic alkenes were selectively oxidized to the corresponding epoxide (Scheme 2). Epoxidation of 2-carene and 3-carene (Scheme 2) showed full diastereoselectivity, as in the oxidation of α-pinene (Scheme 1).

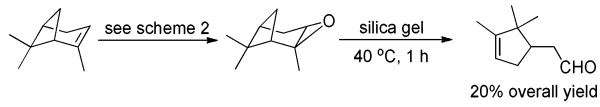
Although the conditions optimized for the oxidation of cyclooctene provide generally good conversions and yields of the epoxide products, for several substrates, such as 1-octene and phenanthrene, incomplete conversion was observed, (Scheme 2). Variation in the concentration of butanedione, catalyst, or H_2O_2 did not lead to improved results. However, by reducing the concentration of the substrate from 0.5 to 0.25 M but holding the concentration of all other components the same as in Scheme 2, higher conversion (90 and 85%, respectively) and yield of epoxide (60 and 68%, respectively) could be achieved. For α,β-unsaturated alkenes (Supporting Information Tables S5), in general lower conversions were achieved, and selectivity was low, with the *cis*-diol product as the major product.

Increasing the reaction to multigram scale for cyclooctene (1.1 to 5.5 g, 10–50 mmol) and *trans*-stilbene (9 g, 50 mmol) afforded essentially the same conversions and yields as on subgram scale (see the Supporting Information, section 5).

Oxidation of Acid-/Base-Sensitive Alkenes. The optimized reaction conditions described above are essentially neutral, which makes the current method especially suitable for acid- or base-sensitive epoxide products, such as α-pinene oxide and styrene oxide. For both these substrates (Scheme 1), excellent conversion and good yields (73% isolated yield) were achieved with the present system.

The natural product α-pinene is an important precursor to the flavor ingredient campholenic aldehyde (Scheme 3), and

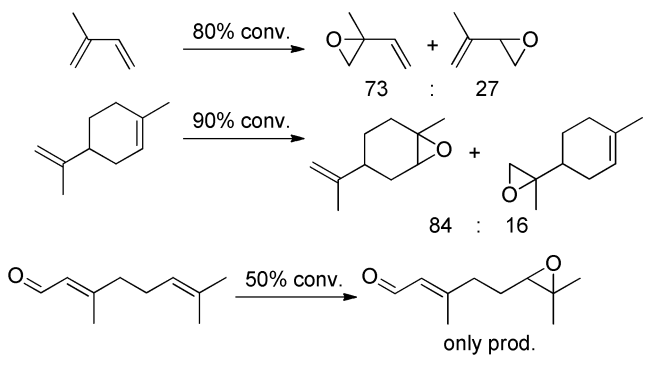
Scheme 3. Oxidation of α-Pinene Followed by in Situ Conversion to Campholenic Acid



the preparation is carried out typically via the epoxide. α-Pinene oxide could be isomerized in situ to campholenic aldehyde with 20% final yield in an overall one-pot reaction by adding SiO_2 with gentle heating (Scheme 3).[40−43] The present system allows the use of silica directly (i.e., without the need to modify it with other metal catalysts), which offers a considerable advantage over other methods.

Oxidation of Conjugated and Nonconjugated Dienes. For nonconjugated dienes, high regioselectivity was obtained compared with conjugated dienes, which showed only modest regioselectivity (see Supporting Information section 5 and Scheme 4). In general, epoxidation of more-substituted double

Scheme 4. Epoxidation of Substrates Containing Progressively Dissimilar Double Bonds[a]



[a]For reaction conditions see Scheme 1 and SOI.

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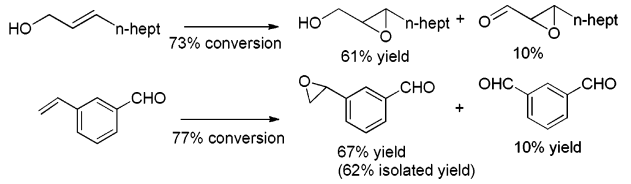
bonds was preferred over less-substituted double bonds. For limonene, selectivity for the epoxidation of the internal alkene was observed. For citral, only one product was obtained; that is, chemoselective epoxidation of the electron-rich alkene without aldehyde oxidation (Scheme 4).

Oxidation of Alkenes Bearing Multiple Functional Groups and Allylic Stereocenters. Selective oxidation of compounds with multiple oxidation sensitive centers, especially alcohols and aldehydes, is a major challenge and is essential in achieving general applicability of any new method.[44−46] Remarkably, for the unprotected homoallylic alcohol *trans*-2-decen-1-ol, the epoxide product was obtained in 61% yield (73% conversion) with only 10% of aldehyde. Indeed, in general, aldehydes and primary alcohols were stable under reaction conditions as shown for a series of bifunctional alkenes. For example, 3-vinyl benzaldehyde afforded the corresponding epoxide with 77% conversion and 66% yield (Scheme 5). *β*-Citronellol showed good selectivity for the epoxide product, and the aldehyde was not observed after the reaction (Scheme 1).

Scheme 5. Oxidation of Aldehyde-, Alcohol-, and Nitrile-Functionalized Alkenes to the Corresponding Epoxide Products[a]



[a]For reaction conditions, see Scheme 1 and the Supporting Information. Yield determined by ^{1}H NMR spectroscopy, isolated yield in parentheses.

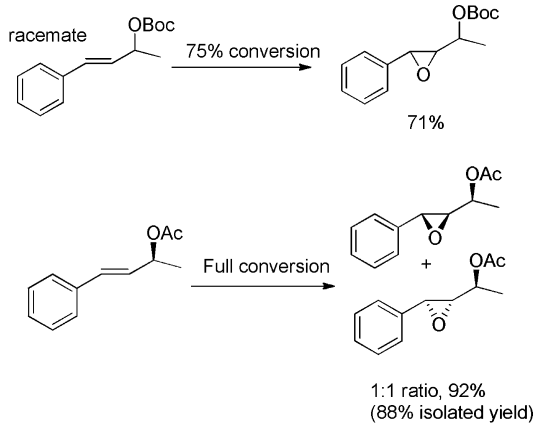
For *N*-phenylcarbonyl-1,2-dihydroquinoline-2-carbonitrile the corresponding epoxide product could be obtained in 65% isolated yield (vide infra, Scheme 7).

Tolerance to protecting groups is a further characteristic of the present system. In the present study, silyl-based protecting groups were found to be unstable to reaction conditions, as expected on the basis of the sensitivity of such groups to H_2O_2. By contrast, hydrolytically sensitive acetyl and *tert*-butoxycarbonyl (Boc)-protected alcohols were found to be stable under reaction conditions (Scheme 6).

Retention of configuration at the chiral center of enantiopure acetyl-protected allylic alcohol[47] (isolated yield of epoxide 88%) upon epoxidation was observed, that is, the epoxide product was obtained as only two of the four possible diastereomers (see the Supporting Information, section 9). This, together with the absence of allylic oxidation in the case of cyclohexene (Scheme 2), provides strong evidence that species such as hydroxyl radicals are not formed in the reaction.

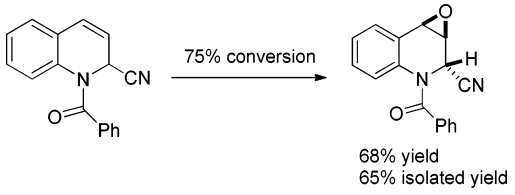
Stereochemical Aspects. Stereochemistry presents a key challenge in modern synthetic chemistry. In the present system, the influence of substrate on the stereochemical outcome of the reaction is evident for cyclic systems, especially terpenoids such as pinene and carenes (Schemes 1 and 2). For *N*-phenylcarbonyl-1,2-dihydro-quinoline-2-carbonitrile (Scheme 7), the corresponding epoxide product was obtained as a single diastereomer, showing that stereochemical control by the substrate can be exerted for cyclic alkenes. This, together with the retention of stereochemistry in protected allylic alcohols,

Scheme 6. Oxidation of Protected Allylic Alkenes to the Corresponding Epoxide Products[a]



[a]For details see Supporting Information, yield determined by ^{1}H NMR spectroscopy, isolated yield in parentheses.

Scheme 7. Oxidation of *N*-Phenylcarbonyl-1,2-dihydroquinoline-2-carbonitrile to the Corresponding Diastereomerically Pure Epoxide Product[a]

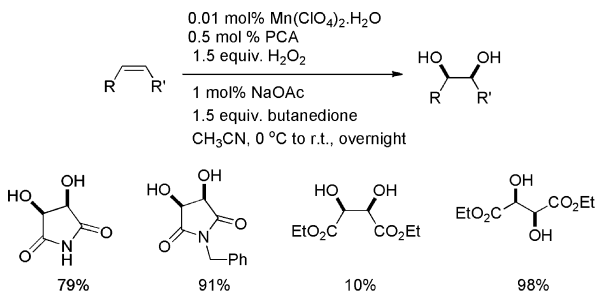


[a]For reaction conditions, see Scheme 1 and the Supporting Information. Yield determined by ^{1}H NMR spectroscopy.

makes the present system a versatile general method for the epoxidation of complex alkenes.

cis-Dihydroxylation of Electron Deficient Alkenes. The catalyzed cis-dihydroxylation of electron-deficient alkenes such as diethylfumarate and succinimide was a major challenge in oxidation chemistry until recently, when we demonstrated that clean conversion and excellent selectivity for the *cis*-diol product could be achieved using acetone as solvent.[29] Under the present conditions using acetonitrile and butanedione optimized for cyclooctene epoxidation, good conversion (74%) and full selectivity was observed for the cis-dihydroxylation of diethylfumarate (Scheme 8 and Supporting Information Table

Scheme 8. Oxidation of Electron Deficient Alkenes to Their *cis*-Diol Products[a].



[a]For details, see Supporting Information section 7. In all cases, only a single product was formed. Yield determined by ^{1}H NMR spectroscopy. Substrates were 0.5 M final concentration.

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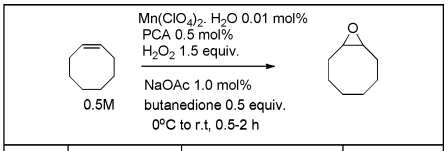
S2). Increasing the relative amount of butanedione from 0.5 equiv to 1.0/1.5 equiv with respect to substrate allowed for full conversion. Surprisingly, an increase in [Mn(II)] to 0.05 mol % resulted in a decrease in conversion (Supporting Information Table S2).

Solvent Dependence and Scope. Although acetonitrile is the solvent of choice in the present study, the ability to use a wider range of solvents is important both for safety and economic reasons and to overcome solubility limitations that may be encountered with certain substrates. Using the conditions optimized in acetonitrile, the solvent scope for the oxidation of cyclooctene and diethylfumarate (which yields the *cis*-diol product exclusively) was examined.[48] In general, in alcohols, good conversion and yields were obtained, albeit slightly lower than obtained in acetonitrile (Table 2). Remarkably, in acetone and butanone, using only 0.01 mol % of manganese(II), conversion was not observed without butanedione within 2 h.

Table 2. Solvent Dependence of the Epoxidation of Cyclooctene[a]



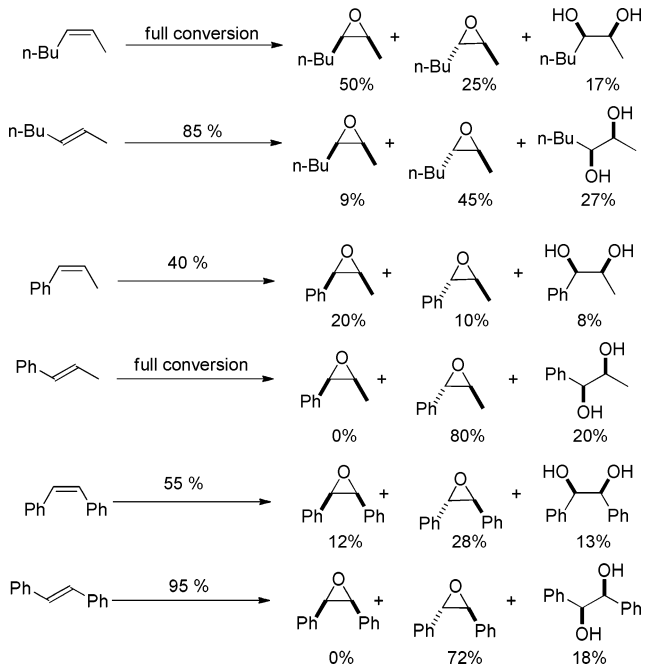
Entry	Solvent	Conversion (%)	Yield (%)
1	Acetone	90	68
2	Butanone	85	58
3	tert-BuOH	65	55
4	CH_3CN	95	80
5	Methanol	90	62
6	Ethanol	70	45

[a]For other solvents, see the Supporting Information for expanded Table S4.

Mechanistic Considerations. Several mechanistically relevant observations can be made on the basis of the substrate scope. The degree of retention of configuration of *cis*-/*trans*-2-heptene (Scheme 9) is relatively low. For *cis*-2-heptene, 75% of the epoxide product was obtained as a mixture of *cis*-2-heptene oxide and *trans*-2-heptene oxide (2:1) (Scheme 9). By contrast, *trans*-2-heptene provided 45% *trans*-2-heptene oxide and only 9% *cis*-2-heptene oxide. This indicates that the epoxidation of alkenes is not a concerted reaction but is, instead, stepwise. It should be noted, though, that the heptane-1,2-diol that was formed as a minor product was in both cases the result of *cis*-dihydroxylation only. Essentially the same results were obtained with both *cis*- and *trans*-1-methylstyrene and *cis*- and *trans*-stilbene.

The absence of significant allylic oxidation (for example, for cyclohexene) indicates that the low retention of configuration observed for 2-heptene is not due to a radical oxidation pathway involving hydroxyl radicals, however. Furthermore, the diastereoselectivity observed for the epoxidation of 1-benzoyl-1,2-dihydro-2-quinolinecarbonitrile and the absence of racemization for (*S*)-4-phenylbut-3-en-2-yl acetate requires that if a stepwise mechanism is involved, then the rate of the step, prior to which rotation can occur, is generally fast.

Scheme 9. Oxidation of *cis*-/*trans*-2-Heptene, 1-Methylstyrene, and Stilbene[a]



[a]For conditions, see Scheme 1 and the Supporting Information. Yields determined by ^{1}H NMR spectroscopy. Note that the trans-dihydroxylation products were not observed in any of the examples.

Role of Ketone in the Catalytic Reaction. Although our initial objective was to find safer alternatives to acetone as solvent, we discovered that butanedione was an active ketone for the manganese catalytic oxidation of alkenes substoichiometrically. Indeed, at low Mn(II) loadings, the requirement for butanedione to be present, even when acetone is used as solvent, indicated that the ketone was involved directly in the reaction and not simply acting as (co)solvent. Furthermore, the full conversion observed with substoichiometric amounts of butanedione means that it is involved in the oxidation directly and is therefore catalytic. Furthermore, the broad solvent scope and the absence of activity when butanedione was omitted, together with the increased activity that allows for the use of low Mn(II) (<0.01 mol %) and PCA (<0.05 mol %) catalyst loadings, with much shorter reaction times than in acetone alone, hinted that hydrogen peroxide/butanedione adducts (i.e., 3-hydroperoxy-3-hydroxybutan-2-one) could be involved. UV/vis and Raman spectroscopic analysis of the reaction mixture confirmed that the diketone reacts immediately (<10 s) with H_2O_2 in a 1:1 ratio, manifested in the decrease and blue shift in both the carbonyl stretch (1722 cm^{-1}) in the Raman spectrum (Figure 1) and the absorption band at 417 nm in the UV/vis absorption spectrum of the reaction mixture (Figure 2).

That the changes observed are due to the formation of a monohydroperoxyacetal (Scheme 10) is supported by the 1:1 stoichiometry required to see a complete loss in the intensity of both the 1722 cm^{-1} Raman band and the 417 nm UV/vis absorption band (Figure 2). With 1 equiv of H_2O_2 with respect to substrate, the 1722 cm^{-1} Raman band and the 417 nm absorption began to recover after ~66% of the H_2O_2 was consumed (i.e., <1 equiv of H_2O_2 with respect to butanedione remained). This is consistent with the formation of 1:1 adduct of H_2O_2 and butanedione (Scheme 10).[49]

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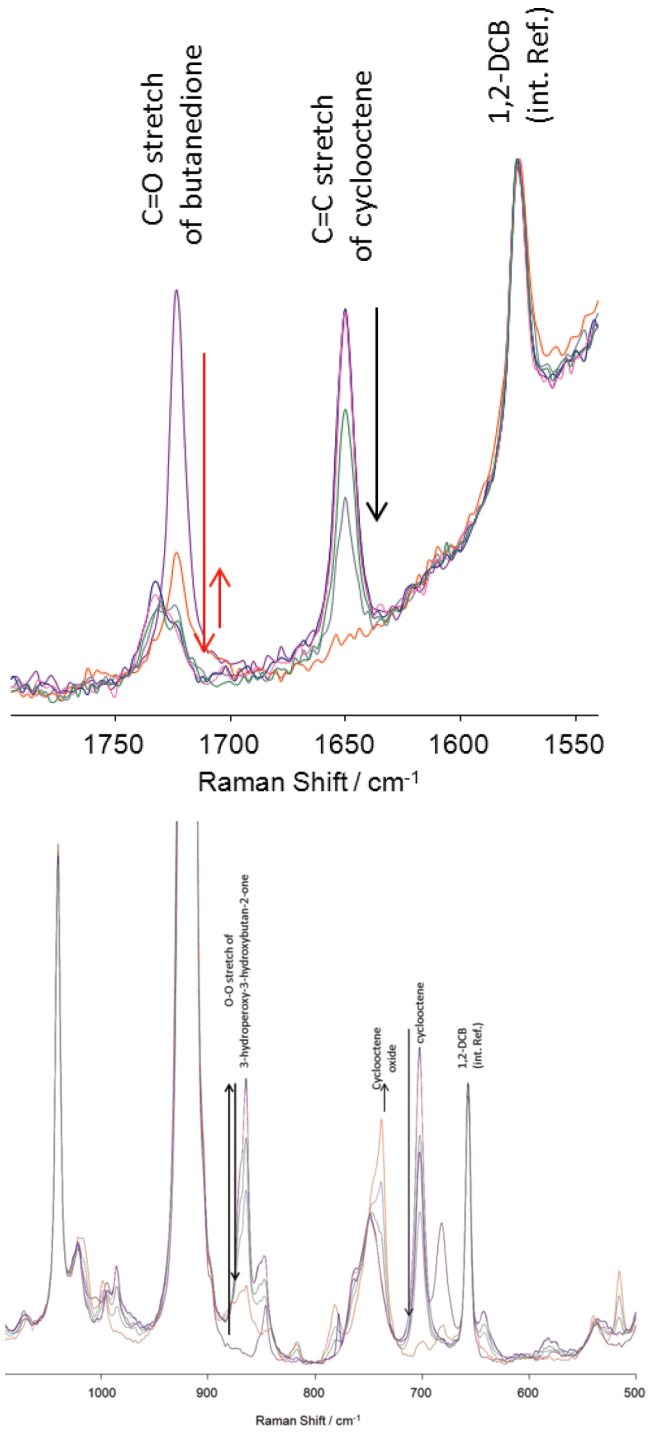


Figure 1. Changes in the Raman spectrum (upper spectrum 1500–1800 cm^{-1} region, lower spectrum 500–1100 cm^{-1} region), λ_{exc} 785 nm, of the reaction mixture during the epoxidation of cyclooctene . The conditions used are those stated in Scheme 3. Spectra at prior to (purple) and t = 1 (blue), 5 (green), 20 (gray), and 30 (orange) min after addition of H_2O_2.

The partial recovery of the diketone is observed by the time the conversion of cyclooctene is complete (i.e., after t > 25 min Figure 3 and 4).

When 1.5 equiv of H_2O_2 was employed with respect to substrate, the recovery of the 1722 cm^{-1} and 417 nm bands of butanedione was ~25%, indicating that decomposition of butanedione was occurring as a competing reaction. The

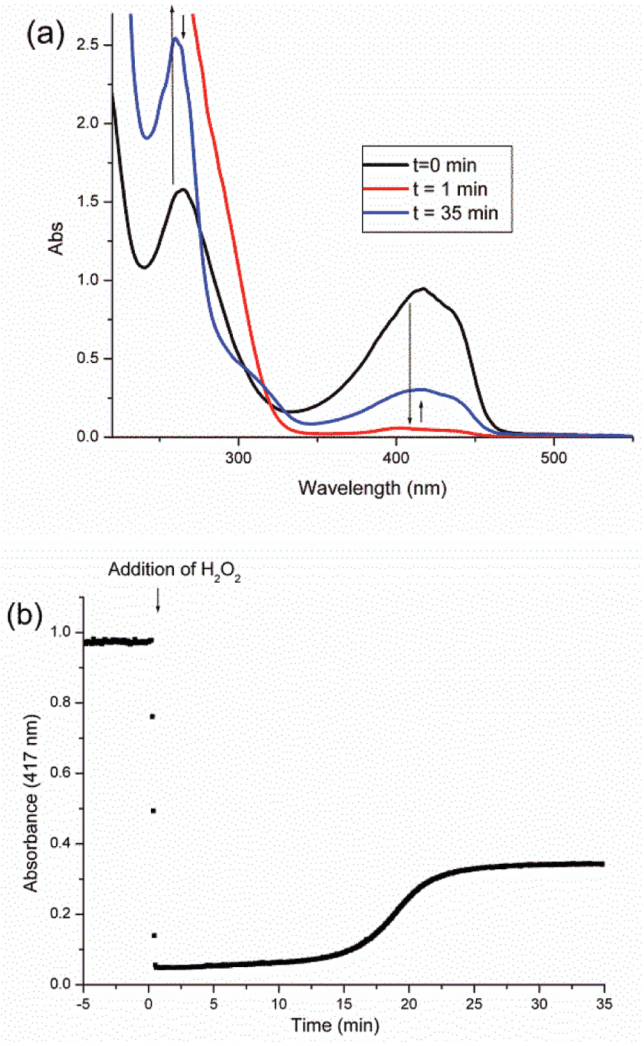
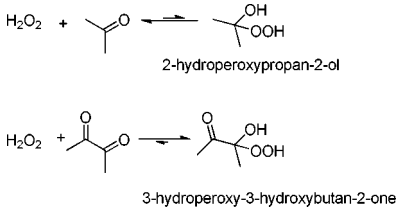


Figure 2. Changes in the (a) UV/vis absorption spectrum of the reaction mixture 1 min after addition of H_2O_2 and after 35 min. (b) Absorbance of the butanedione at 417 nm over time. Conditions used are those stated in Figure 1.

Scheme 10. Reaction between Ketones and H_2O_2



reaction of butanedione with H_2O_2 to form the active peroxy acetal could, in principle, lead to decomposition to acetic acid (Scheme 11).[50–53] The formation of acetic acid was confirmed by ^{13}C NMR spectroscopy (see Supporting Information section 8). In addition, when the loss of butanedione as well as the conversion of cyclooctene are taken into account together, it is apparent that almost all of the H_2O_2 consumed is used in these two processes only. This observation is important because it indicates that the efficiency of the system can be increased by outcompeting the oxidation of the butanedione (i.e., by accelerating the catalytic oxidation of the alkene).

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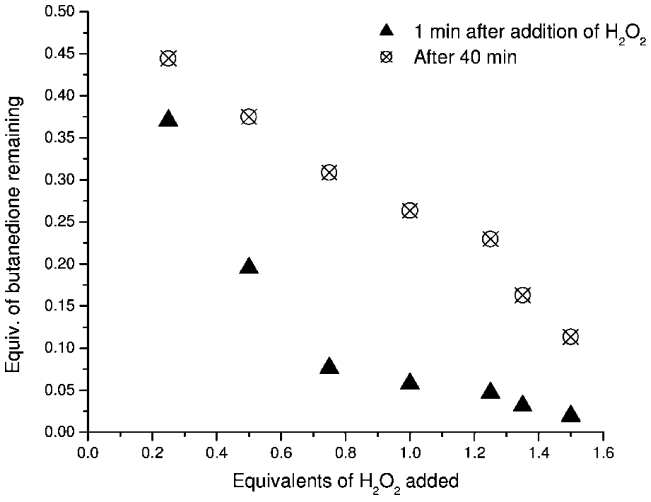


Figure 3. Equivalents of butanedione remaining (determined by monitoring absorbance at 417 nm) 1 min after the addition of H_2O_2 and after 40 min (i.e., after conversion of cyclooctene has stopped), showing the partial recovery of butanedione after the reaction.

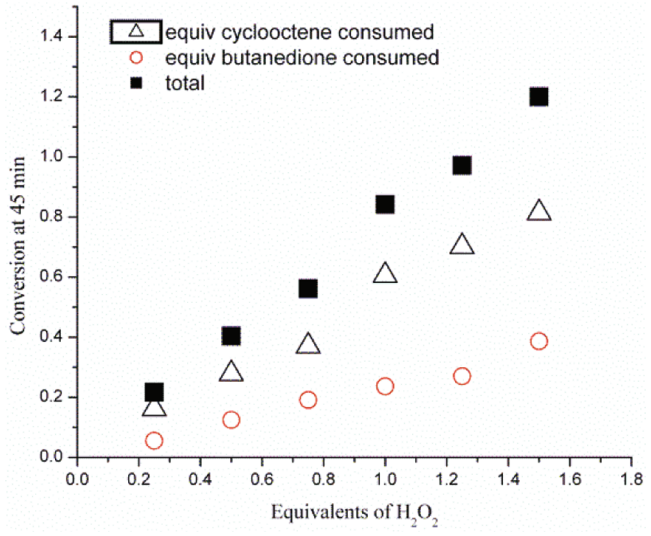
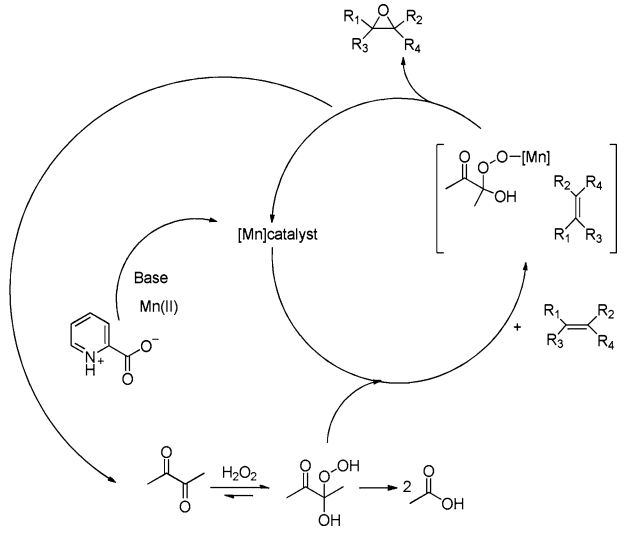


Figure 4. Conversion of cyclooctene and butanedione (expressed as equivalents with respect to cyclooctene) for various equivalents of H_2O_2 measured by Raman spectroscopy (λ_{ex} = 785 nm) and UV/vis absorption spectroscopy, respectively. The total conversion of cyclooctene and butanedione is shown as black squares.

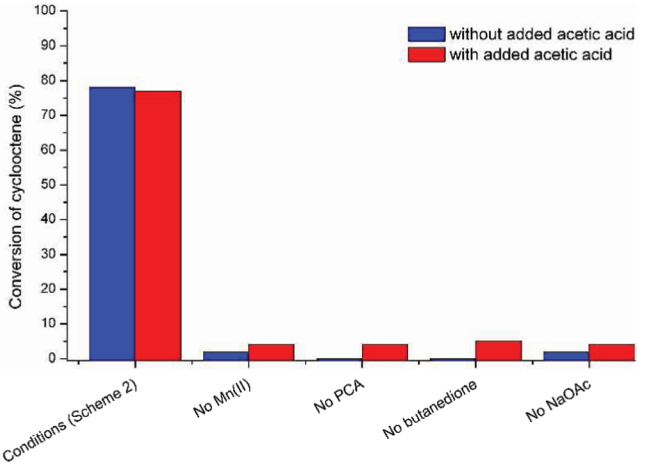
Effect of Acetic Acid on the Catalytic Oxidation of Alkenes. Previously, we demonstrated that the rate of reaction was dramatically reduced in the presence of acetic acid when the reaction was performed in acetone, albeit with relatively little effect on the overall conversion after 24 h.[29] The confirmation that acetic acid forms by decomposition of butanedione in the present system raises a question as to its effect on the conversion and reaction rate. The formation of acetic acid could potentially inhibit the catalytic system in one or more ways, including (i) the loss of butanedione results in reduced activity, since this is required for catalysis; (ii) the acetic acid affects the equilibrium between hydrogen peroxide/butanedione and 3-hydroperoxy-3-hydroxybutan-2-one through reducing the effective nucleophilicity of H_2O_2; and (iii) destabilizing a putative Mn(II)/PCA complex.

Scheme 11. Proposed Mechanism for the Epoxidation of Alkenes



Addition of acetic acid to the reaction (0.05−0.2 equiv with respect to substrate) either before or after addition of H_2O_2 did not affect conversion or yield significantly (Chart 1). This confirms that although acetic acid is formed in significant amounts during the reaction, it does not interfere in the present butanedione-based system.

Chart 1. Effect of Added Acetic Acid on the Catalytic Oxidation of Cyclooctene and the Omission of Individual Components of the Catalyst System on Conversion



The absence of an effect of acetic acid when butanedione is employed is in stark contrast to reactions carried out in acetone.[29] It is possible that under acidic conditions the formation of the hydroperoxy species (Scheme 10) will be affected more in the case of acetone (the equilibrium in this case lies to the left) than in the case of butanedione. Hence, in the latter case, the presence of acetic acid does not affect the availability of the proposed oxidant, 3-hydroperoxy-3-hydroxybutan-2-one, sufficiently to retard the reaction. An alternative hypothesis for the difference in the effect of acetic acid between acetone and butanedione should also be considered, however, in the potential difference in ability of acetate to compete with the peroxyacetal of acetone and of butanedione for

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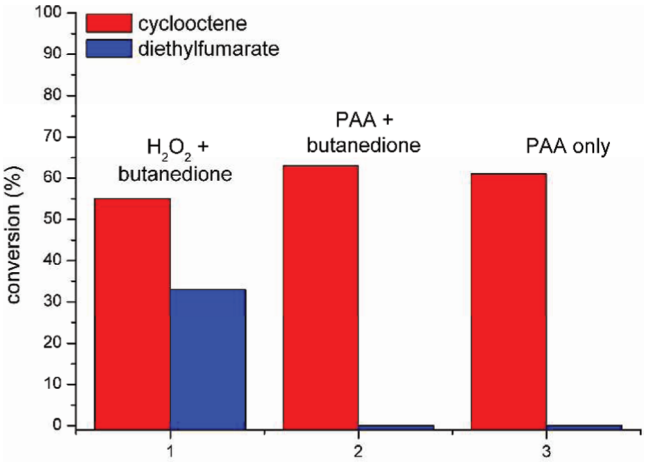
coordination to the manganese catalyst. Regardless of which effect is most important, it is clear that the formation of acetic acid does not lead to catalyst deactivation.

An additional consideration that must be made in regard to the formation of acetic acid is the possibility of subsequent in situ formation of peracetic acid, which is itself capable of oxidizing alkenes.[54] This possibility was investigated in a series of control experiments with cyclooctene and diethylfumarate. Under the present conditions, stoichiometric peracetic acid was found to be effective in the epoxidation of cyclooctene in the absence and presence of butanedione. Importantly, however, no activity in the oxidation of diethylfumarate was observed (Chart 2). Taken together with the absence of activity in the oxidation

Chart 2. Oxidation of Cyclooctene (red) and of Diethylfumarate (blue) with Peracetic Acid in the Presence and Absence of Butanedione under Otherwise Standard Reaction Conditions (see Scheme 3)



of cyclooctene with added acetic acid when butanedione is omitted (Chart 1), this confirms that the in situ formation of peracetic acid does not occur significantly in the present system.

Proposed Mechanism. The reversible reaction of ketones, such as acetone and butanedione, with hydrogen peroxide is expected. Both UV/vis and Raman spectroscopy confirm that in the case of butanedione, the equilibrium lies toward 3-hydroperoxy-3-hydroxybutan-2-one. Indeed, for acetone or butanone,[29] the equilibrium constant for the reaction would be expected to be less than that for butanedione and 1,1,1-trifluoracetone. This can be rationalized on the basis of the increase in electrophillicity due to the electron withdrawing $CH_3(C{=}O)-$ and CF_3- groups, respectively. This, together with the higher catalytic activity observed with the latter two ketones and the lack of activity when the ketone is omitted, suggests that it is 3-hydroperoxy-3-hydroxybutan-2-one that is directly involved in the oxidation of alkenes. This is supported by the decrease in reaction rate observed in acetone when acetic acid was added.[29] In the present case, with butanedione, acetic acid has negligible effect on the reaction rate.

Importantly, the 3-hydroperoxy-3-hydroxybutan-2-one formed in situ does not react directly with alkenes under the current conditions; that is, the omission of PCA or Mn(II) results in no conversion of substrate. This indicates that a Mn(II)/PCA catalyst formed in situ uses the in situ formed 3-hydroperoxy-3-hydroxybutan-2-one as the oxidant (Scheme 11).[38]

Although proposing a detailed mechanism as to the exact mode of action of the manganese catalyst is premature at this stage, the absence of any absorption in the visible region except that of the butanedione during the reaction indicates that the catalyst has a Mn(II) resting state, albeit the absence of an EPR signal indicates that it is not mononuclear Mn(II).[55,56] In addition, the relatively broad solvent scope, including protic and aprotic polar solvents, together with the observed substrate control of selectivity between epoxidation and cis-dihydroxylation indicates that the mechanism for both processes is largely the same. Although we can only guess at the structure of the active catalyst, we can envisage that the peroxy acetal coordinates to a Mn(II) center that bears PCA as a ligand. The observation of incomplete retention of configuration for several substrates (Scheme 9) means that for epoxidation, a stepwise mechanism is likely to be involved, allowing for bond rotation. The absence of products resulting from trans-dihydroxylation for any of the substrates, however, indicates that cis-dihydroxylation is a concerted process or at least that any intermediate has a lifetime less than the bond-rotational time scale.

CONCLUSIONS

In conclusion, a practical, fast, and readily implemented method for selective epoxidation of electron-rich alkenes with H_2O_2 and an in situ-prepared catalyst system was established that can achieve high turnover numbers (up to 300 000). Importantly, the tolerance to other oxidation-sensitive functional groups, the mild conditions (i.e., between 0 °C and room temperature) and solvent scope make this system highly competitive with stoichiometric oxidants such as *m*CPBA. The system is especially suited to epoxidation of electron-rich alkenes and shows good to excellent selectivity in the epoxidation of dienes and bifunctional substrates. In the case of electron-deficient alkenes, the method can show exceptional selectivity and activity in their cis-dihydroxylation. The preliminary mechanistic study has focused on the role of butanedione and indicates that further optimization of the system should focus on overcoming the oxidation of the ketone as a competing reaction.

EXPERIMENTAL SECTION

Materials and Methods. UV/vis absorption spectra were recorded at room temperature in 1 mm path length quartz cuvettes using an AnalytikJena Specord600. Raman spectra were recorded using a Perkin-Elmer Raman Flex equipped with a fiber-optic probe (λ_{exc} 785 nm). For both Raman and ^{1}H NMR spectroscopy, 1,2-dichlorobenzene was employed as internal standard. EPR spectra were recorded using a Bruker ECS-080 spectrometer at room temperature using a liquid cell and at 77 K using 2 mm EPR tubes.

ASSOCIATED CONTENT

Supporting Information

Tabulated data on conversion and yields, NMR analysis, and isolation methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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expected six-line signal, under reaction conditions, no EPR signals were observed at room temperature, indicating that mononuclear Mn(II) is not present in significant amounts.

(56) The absence of evidence for manganese species in higher oxidation states does not preclude the involvement of such species in a catalytic cycle; however, if such species do form, then the rate at which they react must be significantly faster than their rate of formation. A possibility is that the reaction proceeds via an electron transfer-mediated mechanism. See, for example, Piera, J.; Bäckvall, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506−3523.