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A Broad Substrate-Scope Method for Fast, Efficient and Selective Hydrogen Peroxide-Epoxidation

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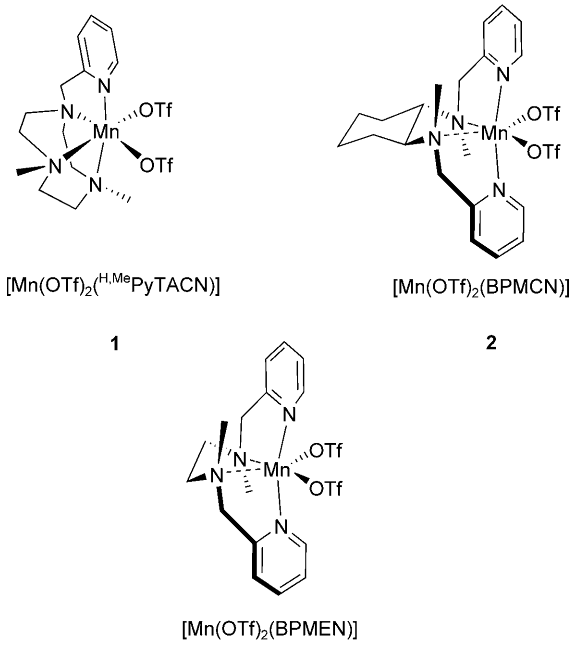
Abstract: The efficient epoxidation of a broad range of olefins using hydrogen peroxide (H_2O_2) as the oxidant has been accomplished by a manganese catalyst that exhibits an uncommon chemoselectivity.

Keywords: catalysis; chemoselectivity; epoxidation; hydrogen peroxide; manganese



Scheme 1.

Olefin epoxidation is an important reaction because epoxides are valuable compounds amenable for a number of subsequent transformations.[1] In addition, chemoselective epoxidations constitute an ongoing challenge in synthetic organic chemistry.[2] Because of environmental, atom-economy, cost and safety considerations, activations of H_2O_2 by first-row transition metal complexes constitute very attractive epoxidation technologies.[3] Furthermore, careful design of transition metal catalysts can also open the door to distinct chemo- and stereoselectivity patterns. However, the combination of hydrogen peroxide with transition metal complexes is often unpredictable as disproportionation and free-radical types of processes can compete with and/or dominate the metal-based epoxidation. Selected examples of H_2O_2-epoxidations catalyzed by Mn[4] and Fe[5] complexes have attracted much interest, but the search for environmentally benign epoxidation methods exhibiting broad substrate scope remains a challenge. In this work we report our advances towards this goal and describe a novel method for the fast, efficient and selective epoxidation of a broad range of olefins with H_2O_2 using small loadings of a manganese catalyst.

We recently reported that [Mn(OTf)$_2$(^{H,Me}PyTACN)] (OTf=CF_3SO_3) (**1**) (Scheme 1) is a robust, efficient and selective catalyst for the epoxidation of a broad range of olefins using peracetic acid as oxidant.[6] We considered that peracetic acid bears important drawbacks such as poorer atom economy than H_2O_2, is more expensive, and commercial solutions are very acidic, limiting their use in the epoxidation of acid-sensitive substrates. Because of that, we sought to extend this chemistry to the use of H_2O_2 (Table 1). Initial attempts to epoxidize 1-octene with H_2O_2 (1.2 equiv.) in the presence of **1** (0.1 mol%) resulted in the immediate evolution of O_2, arising from peroxide disproportionation, and minimum (<1%) epoxide product was obtained. The use of 1.1 equiv. of H_2O_2 in the presence of 1.4 equiv. of acetic acid (with respect to substrate) was also tested because it has been proposed that peracetic acid may be formed *in situ* under these conditions.[7] However, low epoxi-

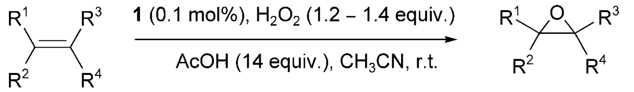
Table 1. Effect of the addition of acetic acid in the epoxidation of 1-octene by **1**/H_2O_2.[a]

Entry	Equiv. Acetic Acid	Conv.[b]	Yield[c]
1	0.05	20	17
2	1.4	27	27
3	7	63	63
4	14	90	90

[a] *Reaction conditions:* 1-octene (1.66 mmol) in CH_3CN (15 mL), **1** (1.66 μmol), acetic acid (0.083–23.3 mmol, 0.05–14 equiv.), and H_2O_2 32% dissolved in CH_3CN 1:1 (v:v) (1.83 mmol, 1.1 equivalent with respect to substrate) added at 0 °C in 30 min. Cat:H_2O_2:olefin ratio = 1:1100:1000.

[b] Substrate conversion into products.

[c] Epoxide yield determined by GC.



Scheme 2.

dation activity was observed (27% epoxide yield). Importantly, the increase of the acetic acid load promoted the epoxidation activity, and upon addition of 14 equiv. of CH_3CO_2H, high substrate conversion was achieved. The corresponding epoxide was now obtained in a rewarding 90% yield (Table 1).

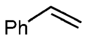
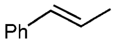
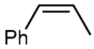
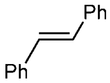
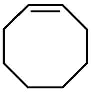
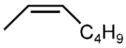
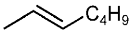
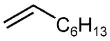
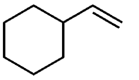
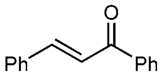
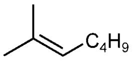
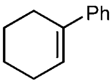
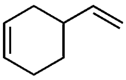
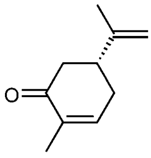
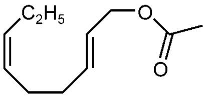
To test the versatility of the method (Scheme 2), it was applied to a series of substrates (Table 2). A broad spectrum of olefins was rapidly epoxidized (< 90 min, TOF > 1700 turnovers·h^{-1}) in good to excellent conversions and yields. Examples include aromatic (entries 1–6), aliphatic (entries 7–9) and terminal aliphatic olefins (entries 10 and 11). The epoxidations of electron-deficient (entry 12) and electron-rich trisubstituted olefins (entries 13 and 14) were also accomplished with good to excellent yields and selectivity. Overall, the efficiency and selectivity of these reactions resemble those where peracetic acid is employed as oxidant, and are significantly faster. Particularly remarkable aspects are also the small excess of H_2O_2 required, and the high turnover numbers attained by the catalyst (810–4500 TN). Noteworthy, very acid-sensitive substrates such as stilbenes and 1-phenyl-1-cyclohexene (entries 5, 6, and 14), which are not suitable for the peracid system,[6] can also be epoxidized in good to excellent yields in the present reaction conditions. In addition, epoxidation of aromatic and aliphatic *cis*-olefins was also highly stereospecific even in the case of highly sensitive *cis*-stilbene (entry 6).[9] No *cis*-dihydroxylation products were found in any of the reactions tested.[10]

We have also tested the activity of the catalyst when its loading was reduced to 0.02 mol%. Under these conditions, epoxidation of styrene with H_2O_2 (1.2 equiv.) affords the corresponding epoxide in 90% conversion/90% yield, reaching 4500 turnovers (Table 2, entry 2). By comparison, the same experiment was performed using peracetic acid (1.2 equiv.) as oxidant, affording substrate conversion of 40% and epoxide yield below < 10%. That suggests that the less acidic conditions of the hydrogen peroxide/acetic acid method allow for the survival of both the catalyst and the products formed.

An excellent regioselectivity of the **1**/H_2O_2/CH_3CO_2H system was also demonstrated by performing the monoepoxidation of the terminal olefin site of R(−)-carvone (99% yield, entry 16) and the monoepoxidation of the *cis*-olefin site of 4-vinylcyclohexene to afford the corresponding 4-vinylcyclohexane 1-epoxide (83% yield, entry 15). Furthermore, the *cis*-olefinic site in the *trans*-2-*cis*-6-nonadienyl ester (entry 17) was selectively epoxidized to furnish the 2-*trans*-olefin 6-monoepoxide product in 95% yield. Additional chemoselectivity tests were performed by doing competition experiments between pairs of olefins ([cat.]/[H_2O_2]/[olefin A]/[olefin B] = 1:100:1000:1000). These experiments show that *cis*-2-heptene is epoxidized 5 times faster than *trans*-2-heptene (lower discrimination compared to peracetic acid system, *cis/trans* = 9).[6] On the other hand *cis*- and *trans*-β-methylstyrene are epoxidized at roughly equal rates (*cis/trans* = 0.9). Finally, much to our surprise, *trans*-stilbene is epoxidized 6 times faster than *cis*-stilbene (*cis/trans* = 0.17), indicating a higher preference for the *trans*-olefin than that observed in the peracetic acid case (*cis/trans* = 0.5). This selectivity for aromatic *trans*-olefins is remarkable, since most of the systems described so far showed a major reactivity for aromatic *cis*-olefins,[3a] and there is no precedent to our knowledge of the reversal of *cis/trans* selectivity upon epoxidizing aliphatic or aromatic olefins.

For comparative purposes, we also studied the activity of manganese complexes $[Mn(OTf)_2(bpy)_2]$, $[Mn(OTf)_2(BPMCN)]$ **2**, and $[Mn(OTf)_2(BPMEN)]$ **3** under the novel reaction conditions (0.1 mol% catalyst, 1.2 equiv. H_2O_2, 14 equiv. CH_3CO_2H). These complexes have showed a very high epoxidation activity in combination with peracetic acid,[11] and could eventually represent a synthetically less elaborate catalyst than **1**. Preliminary tests showed no epoxidation of 1-octene when $[Mn(OTf)_2(bpy)_2]$[12] was tested as catalyst and it was not further explored. On the other hand **2** afforded good epoxide yields in the oxidation of aliphatic olefins, and good stereoretention was observed (Table 2). However, serious difficulties were evidenced when aromatic and electron-deficient substrates were employed. Preliminary experiments also showed that the activity of **3** is significantly reduced with respect to that of **2**.[13] Therefore, while the versatility exhibited by **1** is rather unique, the new method-

Table 2. Epoxidations of different substrates using catalysts **1–2**, H_2O_2 and CH_3CO_2H.[a]

Entry	Substrate	Cat. (mol%)/H_2O_2 (equiv)/*t* (min)[b]	Conv. (yield) Catalyst **1**	Conv. (yield) Catalyst **2**
1		0.1/1.2/60	100 (94)	89 (77)
2		0.02/1.2/60	90 (90)	–
3		0.1/1.2/5	91 (91)	31 (31)
4		0.1/1.2/5	100 (94[c])	83 (78)
5		0.1/1.2/5	100 (95[d]) (92[e])	26 (26)
6		0.1/1.2/5	100 (88[d,f]) (86[e])	36 (28)
7		0.1/1.1/5	100 (95)	100 (97)
8		0.1/1.2/60	100 (83[g])	95 (75)
9		0.1/1.4/5	96 (81)	95 (70)
10		0.1/1.1/60	90 (90)	89 (89)
11		0.1/1.4/5	84 (84)	–
12		0.1/1.4/5	87 (87[d]) (87[e])	61 (53)
13		0.1/1.4/5	100 (89)	100 (87)
14		0.1/1.4/5	100 (96) (90[e])	59 (51)
15		0.1/1.2/60	97 (83[h])	–
16		0.1/1.2/5	100 (>99[d]) (92[e])	–
17		0.1/1.2/5	95 (95[d]) (86[e])	-

[a] *Reaction conditions:* olefin (1.66 mmol), catalyst **1** or **2** (1.66 μmol, 0.1 mol%), AcOH (23.3 mmol, 14 equiv.) in acetonitrile (15 mL), then H_2O_2 32% dissolved in CH_3CN (1:1) (1.83–2.33 mmol, 1.1–1.4 equiv.) added *via* syringe pump over 30 min at 0 °C; GC yields.

[b] Time after total H_2O_2 addition.

[c] 98% *cis*-epoxide.

[d] NMR yield.

[e] Isolated yields.

[f] 90% *cis*-epoxide.

[g] 98% *cis*-epoxide.

[h] 4% diepoxide.

ology applied to **2** opens up a very simple procedure for fast, environmentally benign and efficient stereospecific epoxidation of aliphatic olefins.

First approximation to the possible active species responsible for this chemistry was obtained by competitive epoxidation of styrene *vs.* *p*-substituted styrenes catalyzed by **1**. A Hammett plot analysis provides a $\rho = -1.20$ ($R^2 = 0.99$) which indicates that the active oxidant is an electrophilic species. Furthermore, the difference between the **1**/CH_3CO_3H system ($\rho = -0.67$) and the **1**/H_2O_2/acetic acid system strongly suggests that the active oxidant in the two processes is not the same. Further mechanistic considerations arise from isotopic labelling experiments. The epoxidation reaction of styrene (100 equiv. substrate: 25 equiv. CH_3CO_3H) in the presence of a large excess of $H_2{}^{18}O$ (1000 equiv.) shows no incorporation of ^{18}O into the epoxide indicating that the oxidant does not exchange with water. Moreover, the epoxidation of styrene using $H_2{}^{18}O_2$ shows a high incorporation of ^{18}O into the epoxide (92%), indicating that the peroxide is the main origin of the oxygen atoms incorporated into the oxidized products and excluding the formation of free-diffusing carbon centered radicals. On the other hand, the stereoretention observed in the epoxidation of very epimerization-prone substrates such as *cis*-stilbene is a strong indication that oxygen atom transfer is a concerted process, or alternatively, that it occurs *via* very short time-living intermediates. The sum of all these observations indicate close similarities between the oxidations performed with **1**/CH_3CO_3H and these carried out with **1**/H_2O_2/CH_3CO_2H, although selectivity considerations clearly demonstrate that different reactive species are generated in both cases. These observations are in good agreement with our original proposal that reactions proceed *via* Lewis acid activation of the peroxide *via* an oxidized Mn center.[6,14] Nevertheless, the involvement of high valent manganese oxo species cannot be ruled out. The decisive role of acetic acid in these reactions is intriguing and beyond the scope of this work. However, possible scenarios consider that it enhances the electrophilicity of the peroxide moiety, or alternatively, it assists heterolytic O−O bond cleavage of a manganese peroxide intermediate to generate a high-valent manganese oxo species, which would be the active epoxidation agent. Precedent for the former includes Sharpless' proposal for the Mo- and V-catalyzed epoxidation of olefins by alkyl peroxides.[15] On the other hand, acetic acid-assisted O−O bond lysis has been proposed for iron systems.[5f] Nevertheless, its exact role may not be limited to a single aspect.

In conclusion, the present work describes a novel method for the fast epoxidation of a wide range of olefins using hydrogen peroxide as terminal oxidant and using low loadings of a manganese catalyst. The present H_2O_2/CH_3CO_2H oxidant system imposes milder experimental conditions than commercial peracetic acid[6] offering a broader substrate scope, and lower catalyst loadings. The present system compares well with state-of-the-art epoxidation technologies in terms of product yields, substrate scope, and environmental considerations. Furthermore, the system exhibits quite unusual chemoselectivity properties that allow regioselective monoepoxidation of diolefins, also including a reversal of the *cis*/*trans* selectivity depending on whether aliphatic or aromatic olefins are epoxidized, and finally it exhibits an unusual preference for *trans*-stilbenes. Preliminary mechanistic studies suggest a concerted oxygen atom delivery to the olefin mediated by electrophilic yet distinct active species with respect to the oxidations performed with peracetic acid. Mechanistic studies on these highly active systems and evaluation of the role of different carboxylic acid additives are warranted.

Experimental Section

General Procedures for an Epoxidation Reaction

An acetonitrile solution (15 mL) of the specific olefin (1.66 mmol, final reaction concentration 0.11 M) and **1** (0.11 mM) was prepared in a 25-mL round-bottom flask equipped with a stir bar and cooled in an ice bath. 1.4 mL of acetic acid (23.3 mmol, 14 equiv.) were added directly to the solution. Then, 0.35–0.44 mL of 1:1 v:v acetonitrile:hydrogen peroxide solution 32% (1.83 to 2.33 mmol, 1.1–1.4 equiv.) was added by syringe pump over a period of 30 min. The solution was further stirred at 0 °C for 5–60 min. At this point, the internal standard (biphenyl) was added and the solution was filtered through a basic alumina plug, which was subsequently rinsed with 2 × 1 mL AcOEt. GC analysis of the solution provided substrate conversions and product yields relative to the internal standard integration.

General Procedure for Epoxide Isolation. Epoxidation of *cis*-Stilbene

An acetonitrile solution (15 mL) of *cis*-stilbene (312 mg, 97% pure, 1.66 mmol, final reaction concentration 0.11 M) and **1** (1 mg, 1.66 μmol, final reaction concentration 0.11 mM) was prepared in a 25-mL round-bottom flask equipped with a stir bar and cooled in an ice bath. 1.4 mL of acetic acid were directly added (23.3 mmol, 14 equiv). Then, 0.38 mL of an 1:1 v:v acetonitrile:H_2O_2 solution 32% (1.99 mmol, 1.2 equiv.) was added by syringe pump over a period of 30 min. The solution was further stirred at 0 °C for 5 min. At this point, 50 mL of an aqueous Na_2CO_3 saturated solution were added to the mixture. The resultant solution was extracted with diethyl ether (3 × 50 mL). Organic fractions were combined, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to afford of the product; yield: 280 mg (1.43 mmol 86%). A product sample was dissolved in $CDCl_3$ and analyzed by ^1H NMR analysis as pure epoxide (90% *cis*). For details on the isolation of other epoxide products see the Supporting Information.

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[12] $[Mn(OTf)_2(bpy)_2]$ was prepared *in situ* by mixing equimolar amounts of $Mn(OTf)_2$ and 2,2′-bipyridine in acetonitrile.

[13] Under analogous conditions, the epoxidation of 1-octene and styrene catalyzed by **3** affords the corresponding epoxides in respective 81% yield (81% conversion), 36% yield (36% conversion).

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