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Remarkable increase in the rate of the catalytic epoxidation of electron deficient styrenes through the addition of Sc(OTf)₃ to the MnTMTACN catalyst

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The effect of Lewis acids on the catalytic activity of $[Mn_2(\mu - O)_3(TMTACN)_2](PF_6)_2$ in the epoxidation of styrenes using hydrogen peroxide as the oxidant has shown that the addition of Sc(OTf)_3 at low catalytic loading results in a very significant increase in the efficiency of the catalyst and a reduction of the reaction time to only 3 minutes in most cases.

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The development of efficient methods for the selective epoxidation of alkene substrates continues to be an area of considerable contemporary interest due to the high value of epoxides in synthesis.¹ Within the broad field, ^{1d, 2} much effort has focussed on the development of catalytic systems using high-valent manganese and iron complexes³ and the environmentally benign hydrogen peroxide (and peracetic acid) as the oxidant. Many early efforts were directed towards the application of manganese catalysts of the facially coordinating ligand 1,4,7-trimethyl-1,4,7-triazacyclononane (TMTACN) after the disclosure of **1** ([Mn₂(u- $O_3(TMTACN)_2](PF_6)_2)$ as a highly potent bleach activator in domestic laundry applications.⁴ Its application in the epoxidation of the challenging substrate styrene gave the corresponding epoxide product with good yield using from 1.3 to 100 equivalents of H_2O_2 , but its application frequently required the use of a solution of H_2O_2 in acetone to prevent unwanted catalase-like decomposition of the oxidant.⁵ Additionally the use of a variety of co-catalysts and co-ligands e.g. glyoxylic acid methylester methyl hemiacetal/oxalate,⁶ supported benzoic acid,⁷ carbonate buffer (pH 9)⁴ in solvents such as methanol⁴ or acetonitrile^{6, 7} was found to be beneficial although typically these also involved moderately long reaction times of 5-24 hours for the epoxidation of styrene substrates.⁸ Subsequently reports have appeared of other manganese-based systems capable of effecting styrene epoxidation with reaction times as low as 5 minutes,⁹ although these use peracetic acid as the terminal oxidant. The development of efficient manganese-based systems employing hydrogen peroxide as the oxidant remains an enduring challenge in the field.

A major recent development in the area of oxidative catalysis has been the discovery, principally by Fukuzumi, Nam and co-workers, that the addition of Lewis acids (LA) to high valent metal-oxo species results in a significant increase in their activity, modulating and increasing the oxygen atom transfer effectiveness.¹⁰ Given previous proposals that the active species generated from **1** may be a high-valent manganese-oxo complex,¹¹ we speculated that its activity might be favourably modulated through the use of LA additives.

Initially we investigated the influence of scandium(III) triflate as the LA on the activity of 1 in the epoxidation of styrene in acetonitrile solutions in the presence of acetone, according to the procedure of De Vos and Bein.⁵ However, the additive had no effect on the formation of the styrene oxide under these conditions and results were similar with and without the LA with long reaction times (20-60 min.) and low selectivity for styrene epoxide over 1-phenylethane-1,2-diol, 4, (see ESI). Mixtures of acetonitrile with other solvents, including THF, DCM, MeOH were also tested, but none of them proved to be effective and conversions and epoxide yield were moderate to low even in the presence of guite large amounts of Sc(OTf)₃ (Table 1, entries 1-4). A remarkable enhancement in activity was observed when freshly distilled acetonitrile was used as the reaction solvent, with complete styrene conversion and excellent epoxide selectivity being observed after 3 minutes (Table 1, entry 8). The level of loading of the LA proved critical to catalytic activity and efficacy with complete styrene conversion only observed after 3 minutes in the reactions with 1 mol% and 0.5 mol% of Sc(OTf)₃ (relative to the manganese content in 1); a very slightly lower conversion with high epoxide selectivity was also observed when a 0.25 mol% loading of Sc(OTf)₃ was used (Table 1, entry 6) although the reproducibility of the reaction proved best with a 0.5 mol%

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loading. Very low catalytic activities and epoxide yields were detected in reactions with 0.1 mol%,[§] 5 mol%, and 10 mol% Sc(OTf)₃. Applying a larger amount of LA than 0.5 mol% gave a mixture of products with low epoxide selectivity, and in the presence of 10 mol% of the LA the activity of catalyst was significantly reduced, with much longer reaction $\mathsf{times}^{\$\$}$ required for significant substrate conversion to be observed, and different product selectivity being observed (see ESI). The use of different amounts of 1 with the optimal 0.5 mol% Sc(OTf)₃ was also tested, but 100% conversion was only observed when 1 mol% of 1 was utilised. Similarly, optimisation of the amount of H_2O_2 showed that 10 equivalents were optimal and although 5 and 2 equivalents were also effective, substrate conversion was slower. $^{\$\$\$}$ In addition to the reagent loadings, the reaction time also proved to be very important. If the optimal reaction time of 3 minutes was prolonged it resulted in a decrease in epoxide yield and selectivity due to further oxidation to give a complex and intractable mixture of products including diol, 4, aldehyde, 5, and keto alcohol, 6 (see ESI). For example, after 3 minutes under these conditions the styrene epoxide yield was 91%, but this reduced to 85% for a 5 minute reaction and to only 81% after 7 minutes.



Scheme 1. Optimised reaction conditions for the epoxidation of styrenes (R = H, EWG, EDG)

This system is an extremely potent oxidant and typically used internal standards such as anisole, biphenyl and substituted toluenes all underwent oxidation during the reaction. For example, biphenyl, which was more stable in the reaction medium, underwent a slight oxidation reaction but anisole was completely oxidised after 5 minutes. Therefore, to avoid inaccuracies, the internal standard was added at the end of the reaction after decomposition of unreacted hydrogen peroxide by the quenching agent, and the reaction mixture was filtered through silica and magnesium sulfate. A range of typically used hydrogen peroxide quenching reagents were tested and although triphenylphosphine gave the shortest quenching time (1 min.) its oxidation product overlapped with reagents and reaction products in the HPLC chromatogram; manganese dioxide was ineffective due to the long quenching times required (10-12 min.) and silver powder proved to be the most effective (1-2 min.).7b

Table 1. The influence of $Sc(OTf)_3$ and solvents on the efficacy of ${\bf 1}$ in the epoxidation of styrene using H_2O_2 as the oxidant.

Entry	Sc(OTf)₃	30%w/w Conversion [%]		Epoxide yield
	[mol%]	H_2O_2 in	after 3 min. ^a	[%] after 3
		solvent		min.ª
1	1	Acetone	60 ^b	60
2	1	MeOH	50	50
3	1	THF	10	10
4	1	DCM	28	27
5	0.1	MeCN	30	29
6	0.25	MeCN	97	95
7	0.5	MeCN	100 ^b	91 (85, 81) ^c
8	1	MeCN	100	82
9	2.5	MeCN	13	13
10	5	MeCN	17	7
11	10	MeCN	14 ^d	3 ^d

^a reaction conditions: to the solution of 1 mol% of 1, 0.1-10 mol% of Sc(OTf)₃ and 0.5 mmol of styrene in MeCN (2 mL), 10 equiv. of 30% v/v H_2O_2 in 3 mL of the solvent listed was added and the reaction was stirred for 3 min. at rt; the conversion and yields were calculated using biphenyl as the internal standard, ^b see ESI Fig. ES5, ^c epoxide yield achieved respectively after 5 and 7 min. in parenthesis, ^d results obtained after 5 min.

With optimal conditions for Sc(OTf)₃ in hand, a number of other LA's were also tested under identical conditions (Fe(OTf)₃, Zn(OTf)₂, Mg(OTf)₂ and Yb(OTf)₃). Some activity was observed for Mg(OTf)₂ as the co-catalyst (5% epoxide yield after 5 min) but Zn(OTf)₂ and Yb(OTf)₃ were found to be ineffective. Of the salts tested, only Fe(OTf)₃ showed similar activity to $Sc(OTf)_3$ and in the presence of 0.5 mol% $Fe(OTf)_3$ and 1 mol% 1, complete styrene conversion was observed after 5 minutes with 92% yield. Nonetheless, the addition of Sc(OTf)₃ produces a much more potent catalytic system as after the optimal reaction time of 3 minutes only 40% substrate conversion was observed for Fe(OTf)₃. The influence of the different metal triflate additives on the UV-Vis spectra of 1 is depicted in Fig. 1 and shows a strong relationship with catalytic activity. Only the addition of metal triflates that were effective co-catalysts caused a change in the UV-Vis spectrum of 1.

Moreover, the UV-Vis spectra initially recorded for $1/Sc(OTf)_3$ and $1/Sc(OTf)_3$ /styrene were essentially the same but differed from that of 1, whereas the spectrum of the reaction mixture after 1 minute displays bands that are comparable to previously described Mn^{IV} species¹² (see ESI, Fig. ES3). However, the EPR spectra obtained at 100K after 1 and 3 minutes clearly indicate the presence of a Mn^{II} species with a characteristic 6-line signal being observed (Fig. ES4).

It has previously been reported that **1**, which is EPR silent at 77K, is first transformed to a mixed-valence Mn^{III} - Mn^{IV} dimer^{4, 12b} that displays a characteristic 16-line EPR spectrum and that this is then converted to a Mn^{II} species. We have observed no evidence of such a mixed valence intermediate indicating that either the reaction proceeds via a different pathway in the presence of Sc(OTf)₃ or that this intermediate is only transiently formed due to the rapid reaction rate and is consequently not observable. Page 3 of 4

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After optimal reaction conditions had been established for styrene we investigated their efficacy in the epoxidation of a number of substituted styrenes, which are shown in Table 2. This clearly indicate that the best results were obtained for para-substituted styrene substrates with electron-withdrawing groups (entries 1-6) for which yields of up to 99% of the epoxide could be obtained. 3-NO2-styrene also underwent complete conversion but in lower yield (entry 7). 4-Methoxy substituted styrene was completely unsuited as a substrate, appearing to undergo polymerisation (see ESI) as has been previously reported in the presence of the Lewis acids Yb(OTf)₃ and $B(C_6F_5)_3$, although the polymerisation times in these cases were significantly longer than those employed herein. Other styrenes that were para-substituted with electron donating groups reacted much more quickly, but less selectively, than those with electron withdrawing groups, forming other overoxidised products affecting epoxide yield and selectivity. This effect was confirmed in the competitive oxidation of a mixture of 4-methyl- and 4-nitro-substituted styrenes, which gave a crude reaction mixture containing 4-methylstyrene oxide as the major product (yield 51%), with 3-nitrostyrene oxide (yield 15%). In contrast, 2,4,6-trimethylstyrene reacted sluggishly, requiring 7 minutes for a 61% yield of epoxide with incomplete substrate conversion, presumably due to the steric effect of the ortho-methyl groups. Furthermore, the system also appears to be sensitive to both alkene substitution pattern and geometry (entries 11-14) and whilst an α -methyl substituent was well-tolerated, both β -*cis*-methyl and β -*trans*-methyl styrene were less reactive and selective, with the epoxides formed in lower yields with slightly longer reaction times also required. Although trans-stilbene was not a suitable substrate, due to its insolubility in acetonitrile, cis-stilbene gave incomplete substrate conversion even after a prolonged reaction time of 7 minutes and gave a mixture of isomeric trans- and cis-epoxides.

Table 2. Epoxidation of substituted styrenes using H_2O_2 in the presence of 0.5mol% Sc(OTf)_3 and 1 mol% MnTMTACN

Entry	Substituted	Time ^ª	Epoxide yield [%]
	styrene	[min.]	
1	4-F	3	99
2	4-Cl	3	94
3	4-Br	3	95
4	4-NO ₂	3	99
5	4-AcO	3	96
6	4-CN	5	93
7	3-NO ₂	3	79
8	4-Me	3	61
9	2,4,6-triMe	7 ^b	61 (conv. 85)
10	4-MeO	3	-
11	α-Me	3	92
12	β- <i>trans</i> -Me	5	trans-epoxide 77
13	β- <i>cis</i> -Me	4	trans-epoxide 19,
			cis-epoxide 63
14	cis-stilbene	7 ^b	trans-epoxide 16,
			cis-epoxide 12. (conv. 80)

^a Reaction time after which the complete conversions were reached; ^b Despite using an extended time for these substrates 100% conversion was not observed.





In order to probe the mechanism of the optimised reaction conditions we applied them to the epoxidation of trans-1phenyl-1(2-phenylcyclopropyl)-ethylene, 7, a well-established radical clock (Scheme 2). We performed the reaction in MeCNd₃ which was monitored by HPLC and NMR spectroscopy. This clearly showed the formation of epoxide 8 during the first minute of the reaction which was then quickly converted to dihydropyran 9, as has previously been reported in the presence of protic acids (see ESI).¹³ Control experiments showed that on the timescale of the reaction epoxide 8 was not converted to 9 using only $Sc(OTf)_3$ or 1. No products resulting from cyclopropane ring-opening could be identified, indicating that the reaction does not proceed via a radical pathway. This, allied to the fact that the ratio of cis- and transepoxide products formed for β -cis-methyl styrene and cisstilbene are constant throughout the reaction, would suggest the involvement of a two-step epoxidation process presumably involving a high valent Mn-oxo species and cationic intermediates.

In summary, we have developed an exceptionally potent catalytic system for the efficient conversion of electron deficient substituted styrenes through the addition of $Sc(OTf)_3$ to **1** using the environmentally benign oxidant hydrogen peroxide. Preliminary mechanistic studies appear to indicate a cationic pathway for the reaction and further investigations are currently ongoing in our laboratories.

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Notes and references

§ In the presence of 0.1 mol% LA after 3 min. yield of styrene oxide reached 29%, whereas, without LA in acetone only 32% after 40 min.

§§ In the oxidation of 4-F-styrene complete conversion was observed after 40 min., whereas for styrene 100% conversion occurred after 60 min.

§§§ In the presence of 2 equiv. of H_2O_2 moderate conversion (50-60%) was obtained after 5-7 min.; in the presence of 5 equiv. of H₂O₂ very high conversions were reached (95% after 3 min.), however, addition of 10 equiv. of H_2O_2 gave better reproducibility with the same epoxide selectivity. In the absence of substrate considerable catalase-like decomposition of H2O2 still occurs; this is significantly reduced in the presence of substrate.

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