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Non-Heme Manganese Complexes Catalyzed Asymmetric Epoxidation of Olefins by Peracetic Acid and Hydrogen Peroxide

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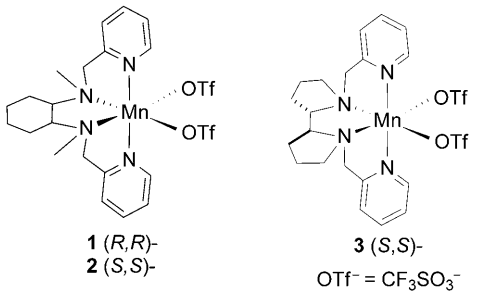
Abstract: Chiral non-heme aminopyridine manganese complexes catalyze the enantioselective epoxidation of olefins with peracetic acid or hydrogen peroxide with moderate to high yields and *ee* valuess up to 89% (peracetic acid, AcOOH) and 84% (hydrogen peroxide, H_2O_2), performing as many as 1000 turnovers.

Keywords: asymmetric oxidation; enzyme models; homogeneous catalysis; hydrogen peroxide; manganese

The discovery of efficient and atom-economic catalyst systems for asymmetric epoxidation is an important objective of catalytic chemistry.[1] Since the breakthrough of the groups of Jacobsen and of Katsuki who pioneered the manganese-salen-catalyzed enantioselective oxidations of unfunctionalized olefins,[2] no manganese-based catalyst systems achieving comparable levels of efficiency and stereoselectivity at the same time has been reported. In 2003, Stack and co-workers published the aminopyridine [Mn(II)[(*R,R*)-bpmcn]$(CF_3SO_3)_2$] complex **1** (Scheme 1) which catalyzed the epoxidation of various alkenes with peracetic acid in high yields (90–99%) and demonstrated an efficiency (TON up to 1000) one order of magnitude higher than that of the manganese-salen catalysts; however, the enantioselectivity of the reaction was not scrutinized.[3] Since then, various related manganese complexes with N_4 donor ligands have been published.[4] Remarkably, Sun and co-workers reported the highly enantioselective epoxidation of α,β-enones (in 70–89% *ee*) using 1 mol% of manganese aminopyridine-type catalysts and 6 equiv. of H_2O_2,[4e] while Costas and co-workers epoxidized (non-stereoselectively) a number of alkenes with H_2O_2 in high yield using 0.1 mol% of the catalyst in CH_3CN/AcOH solution.[4d,f] Some other manganese-based catalyst systems for non-enantioselective oxidations with H_2O_2 have been reported.[5]



1 (*R,R*)-
2 (*S,S*)-

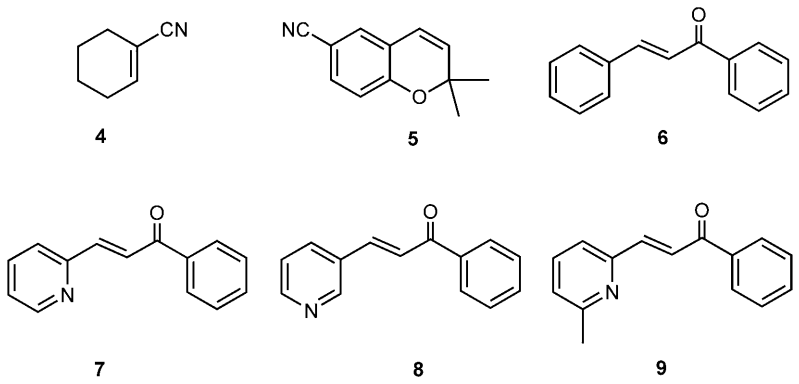
3 (*S,S*)-

$OTf^- = CF_3SO_3^-$

Scheme 1. Complexes **1**, **2** and **3**.

Recently, we have found that chiral manganese-aminopyridine catalysts can conduct the epoxidation of olefins with different terminal oxidants enantioselectively, and gained experimental evidence in favour of the "third oxidant" $[LMn(IV)O(OX)]^{n+}$ responsible for the asymmetric oxygen transfer.[4g] Now, we report on the enantioselective epoxidations of various types of olefins with peracetic acid and hydrogen peroxide over the catalysts [Mn(II)[(*R,R*)-bpmcn]-$(CF_3SO_3)_2$] (**1**), [Mn(II)[(*S,S*)-bpmcn]$(CF_3SO_3)_2$] (**2**) and [Mn(II)[(*S,S*)-pdp]$(CF_3SO_3)_2$] (**3**) (Scheme 1). Apart from the high efficiency (0.1 mol% catalyst loading), these catalysts demonstrate remarkably high enantioselection for both terminal oxidants used, as well as high conversions and chemoselectivities, using as high as 1.3 equivalents of the terminal oxidant.

Complex **1** was earlier reported and characterized using X-ray crystallography by Stack and co-workers,[2a] **2** being its (*S,S*)-enantiomer.[4g] The tetradentate ligand chosen for the preparation of **3** was first used by White and Chen for the synthesis of a structurally related iron catalyst;[6] **3** features the same *cis*-



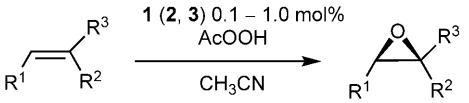
Scheme 2. Olefins used in this study.

α topology as **1** (see Supporting Information and [7]). Some epoxidation results for alkenes **4–9** (Scheme 2) are given in Table 1.

As reported previously,[4g] the enantioselectivity of the epoxidation increased at low temperatures (*cf.* experiments at 0 °C and at −30 °C). The presence of oxygen unaffected the epoxidation.[4g] At 1.0 mol% catalyst loadings, **1**, **2** and **3** gave similar epoxide yields and enantioselectivities, while catalyst **3** performed better than **1** at 0.1 mol% loadings (*cf.* entries 5 and 6, 10 and 11, 16 and 17).[8]

In spite of the remarkable efficiency as well as chemo- and stereoselectivities of the above catalyst systems, peracids are not optimal terminal oxidants from atom economy and environmental points of view. For non-heme iron complexes, H_2O_2 has been used previously as the oxidant, in combination with acetic acid, for epoxidation, *cis*-dihydroxylation,[9] and C–H oxidation reactions.[6] Recently, Sun[4e] and Costas[4f] have applied H_2O_2/AcOH combinations in manganese-based epoxidations. However, the synthetic protocol of Sun exploits 1 mol% loading of the catalyst and requires the use of as high as 6 equivalents of H_2O_2 which is undesirable for preparative syntheses.[10] Given the high stereoselectivities demonstrated by the catalyst systems **1–3**/AcOOH at 0.1 mol% catalyst loadings, we have chosen the synthetic protocol[11]

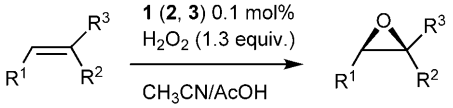
Table 1. Enantioselective epoxidation of olefins by AcOOH.[a]



No.	Substrate	Catalyst[b]	*T* [°C]	Conversion/yield[a]	***ee*** (configuration)
1	**4**	**1** (1.0)	0	71.0/51.8	53[c]
2	**4**	**3** (1.0)	0	48.5/32.8	58[c]
3	**4**	**1** (1.0)	−30	11.0/8.1	67[c]
4	**4**	**3** (1.0)	−30	9.0/6.0	65[c]
5	**4**	**1** (0.1)	−30	0	–
6	**4**	**3** (0.1)	−30	8.6/5.5	64[c]
7	**5**	**1** (1.0)	−30	97.2/90.3	78 (3*S*,4*S*)
8	**5**	**2** (1.0)	−30	98.3/94.3	79 (3*R*,4*R*)
9	**5**	**3** (1.0)	−30	100/93.5	82 (3*R*,4*R*)
10	**5**	**1** (0.1)	−30	0	–
11	**5**	**3** (0.1)	−30	100/90.4	78 (3*R*,4*R*)
12	**6**	**1** (1.0)	0	100/100	82 (2*S*,3*R*)
13	**6**	**3** (1.0)	0	100/100	79 (2*R*,3*S*)
14	**6**	**1** (1.0)	−30	100/100	89 (2*S*,3*R*)
15	**6**	**3** (1.0)	−30	100/100	86 (2*R*,3*S*)
16	**6**	**1** (0.1)	−30	60.6/60.6	88 (2*S*,3*R*)
17	**6**	**3** (0.1)	−30	100/100	88 (2*R*,3*S*)

[a] Epoxide yield and enantioselectivity were analyzed as described in the Experimental Section.
[b] Catalyst loading (mol%) in parentheses.
[c] Optical configuration not assigned.

Table 2. Enantioselective epoxidation of olefins by H_2O_2.[a]



No.	Substrate	Catalyst[b]	*T* [°C]	Additive	Conversion/yield	*ee* (configuration)
1	**4**	**1** (0.1)	−30	AA	94.8/91.3	43[c]
2	**4**	**3** (0.1)	−30	AA	95.4/92.6	54[c]
3	**5**	**1** (0.1)	−30	AA	37.0/37.0	68 (3*S*,4*S*)
4	**5**	**3** (0.1)	−30	AA	73.6/73.6	76 (3*R*,4*R*)
5	**5**	**3** (0.1)	−30	FA	0	–
6	**5**	**3** (0.1)	−30	IBA	50.7/50.7	84 (3*R*,4*R*)
7	**6**	**1** (0.1)	−30	AA	94.3/94.3	78 (2*S*,3*R*)
8	**6**	**1** (0.1)	−30	FA	32.9/32.9	71 (2*S*,3*R*)
9	**6**	**1** (0.1)	−30	IBA	95.4/95.4	80 (2*S*,3*R*)
10	**6**	**3** (0.1)	−30	AA	97.9/97.9	78 (2*R*,3*S*)
11	**6**	**3** (0.1)	−30	FA	4.3/4.3	–
12	**6**	**3** (0.1)	−30	IBA	100/100	82 (2*R*,3*S*)
13	**6**	**1** (0.1)[d]	−30	AA	97.0/97.0	78 (2*S*,3*R*)
14	**6**	**1** (0.1)[d]	−30	IBA	92.5/92.5	80 (2*S*,3*R*)
15	**7**	**3** (0.1)[e]	−30	AA	57.5/57.5	83 (2*R*,3*S*)
16	**8**	**3** (0.1)	−30	AA	42.5/42.5	77 (2*R*,3*S*)
17	**9**	**1** (0.1)[f]	−30	AA	15.6/15.6	72 (2*S*,3*R*)
17	**9**	**3** (0.1)	−30	AA	60.6/60.6	73 (2*R*,3*S*)

[a] Reactions were performed in CH_3CN/acid (0.40 mL/0.08 mL); products were analyzed as described in the Experimental Section; abbreviations: AA = acetic acid, FA = formic acid, IBA = isobutyric acid.
[b] Catalyst loading (mol%) in parentheses.
[c] Absolute configuration not assigned.
[d] 95% H_2O_2 was used.
[e] 0.80 mL/0.08 mL of CH_3CN/AcOH was used.
[f] 0.80 mL/0.16 mL of CH_3CN/AcOH was used.

of Costas (previously used for non-stereoselective epoxidations[4f]).

Some results are presented in Table 2. One can see that for the oxidation with H_2O_2, the stereoselectivities were generally somewhat lower than with AcOOH[12] (yet still around 80% *ee* for the epoxidation of chalcone **6** and its heterocyclic counterparts **7**–**9**), the epoxide yields being moderate to quite high (up to 100%) and the absolute configurations remaining the same as with AcOOH. Noteworthy, no or very small side product formation was documented for the H_2O_2 oxidations. The use of concentrated hydrogen peroxide did not significantly affect the epoxide yield and *ee* (*cf.* entries 7, 9 and 13, 14). We note that this is the first example of enantioselective aminopyridine manganese-catalyzed epoxidation with a nearly stoichiometric amount of H_2O_2.

Of particular importance is the nature of the active, oxygen transferring sites. While the situation with AcOOH is more or less clear now,[13] the true epoxidizing agent in aminopyridine manganese/H_2O_2 systems is little studied so far.[4d,f]

Oxomanganese(IV) species can be ruled out since they appeared fairly inactive in olefin epoxidations.[4g] Unlike the aminopyridine iron/H_2O_2 catalyst systems [where the crucial role of the active oxoiron(V) intermediate is established[9c,14]], the existence of an active oxomanganese(V) intermediate seems unlikely based on ^{18}O-labelling data.[15] Additional evidence against the Mn(V)=O active intermediate was obtained in catalytic experiments with formic and isobutyric acids used instead of acetic acid. Indeed, both complexes **1** and **3** displayed differing performance and enantioselectivity depending on the acid additive (isobutyric acid being the best and formic acid the worst additive, Table 2, entries 4–6, 7–9, 10–12), indicating that the acid molecule could be incorporated into the active species. These data argue both against the simple Lewis acid H_2O_2 activation pathway and carboxylic acid-assisted heterolysis of the O–O bond to generate a high-valence active manganese oxo species.[4f] Further mechanistic studies are needed to establish the valence state of manganese and reliably discriminate between manganese oxo, peroxo, acylperoxo or other active species.

Overall, the high chemo- and enantioselectivities of catalysts **1, 2** and **3** are close to those demonstrated by the Katsuki–Jacobsen salen manganese catalysts,[2] the aminopyridine manganese complexes showing a much higher efficiency and capability of using H_2O_2, a

green and atom-economic terminal oxidant. Catalysts **1**, **2** and, particularly, **3** are also more efficient and selective than related aminopyridine iron catalysts,[6,8] which makes chiral aminopyridine manganese complexes challenging protagonists of bio-inspired stereoselective oxidation catalysts of near future. Mechanistic studies aimed at the understanding of the stereoselective oxygen transfer mechanism will be the subject of our further investigations.

Experimental Section

Materials and ^{1}H NMR Spectra

All solvents were of analytical grade and used without purification. 30% aqueous H_2O_2 was either was used as received or concentrated under reduced pressure to obtain a 95% solution. All other chemicals [olefins, (*R,R*)- and (*S,S*)-1,2-cyclohexanediamine, (*S,S*)-2,2′-bispyrrolidine tartrate, 2-picolyl chloride] were commercial reagents. $Mn(SO_3CF_3)_2$, chiral ligands for **1** and **2** and complexes **1**, **2** were prepared as reported.[4g] Chiral ligand for complex **3** was synthesized as described.[6a] Complex **3** was prepared starting from the chiral ligand and $Mn(SO_3CF_3)_2$ according to the procedure for **2**,[4g] and recrystallized from CH_3CN/ether.

^{1}H NMR spectra were recorded in standard 5-mm NMR tubes on a Bruker Avance 400 MHz spectrometer at 400.13 MHz. Chemical shifts were referenced to added tetramethylsilane.

General Procedure for Epoxidations with AcOOH

The procedure for catalytic olefin epoxidation with AcOOH was essentially the same as reported.[4g] Reaction times and oxidant/substrate ratios were the following: **4** and **6**, 2 h, 1.1:1.0 mol/mol; **5**, 0.17 h, 1.25:1.0 mol/mol.

General Procedure for Epoxidations with H_2O_2

In the general procedure for catalytic olefin epoxidation with H_2O_2, to the solution of appropriate manganese complex (0.1 μmol, 0.068 mg) in CH_3CN (0.40 mL) and AcOH (0.08 mL, 1.4 mmol), thermostated at desired temperature, the substrate (100 μmol) was added in one portion, and 130 μmol of 30% aqueous H_2O_2 (dissolved in CH_3CN, total volume 100 μL) were added with a syringe pump over 30 min. The mixture was stirred for 3 h. Then the reaction was quenched with aqueous $NaHCO_3$, the products were extracted (with pentane for **4**–**6** and with Et_2O for **7**–**9**) and analyzed by ^{1}H NMR in the same way as for the epoxidations with AcOOH.[4g] ^{1}H NMR data for the epoxides can be found in the Supporting Information.

Enantiomeric Excess Measurements

The enantiomeric excess values of the epoxide of **4** were analyzed by ^{1}H NMR with a chiral shift reagent $Eu(hfc)_3$. Enantioselective chromatographic resolution of **5**–**9** epoxide enantiomers was performed on a Shimadzu LC-20 chromatograph (**5** epoxide: Chiralcel OJ-H column, *i*-PrOH:*n*-hexane = 30:70, 1.0 mL min^{-1}, 254 nm, $t_{(3R,4R)}$ = 11.0 min, $t_{(3S,4S)}$ = 19.0 min; **6** epoxide: Chiralcel OD-H column, *i*-PrOH:*n*-hexane = 2:98, 1.0 mL min^{-1}, 254 nm, $t_{(2S,3R)}$ = 17.0 min, $t_{(2R,3S)}$ = 18.2 min; **7** epoxide: Chiralpak AD-H column, *i*-PrOH:*n*-hexane = 20:80, 1.0 mL min^{-1}, 220 nm, $t_{(2R,3S)}$ = 11.0 min, $t_{(2S,3R)}$ = 12.7 min; **8** epoxide: Chiralpak AD-H column, *i*-PrOH:*n*-hexane = 30:70, 0.8 mL min^{-1}, 220 nm, $t_{(2R,3S)}$ = 11.4 min, $t_{(2S,3R)}$ = 18.4 min; **9** epoxide: Chiralpak AD-H column, *i*-PrOH:*n*-hexane = 20:80, 0.8 mL min^{-1}, 220 nm, $t_{(2S,3R)}$ = 9.2 min, $t_{(2R,3S)}$ = 10.1 min).

Acknowledgements

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[8] The higher efficiency of catalyst **3** is most likely caused by slower degradation under oxidative and acidic conditions, due to a higher resistance of the bis(pyrrolidine) moiety with respect to the cyclohexanediamine one.

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[10] Apparently, the use of such a high excess of H_2O_2 was necessary because of a pronounced Mn-catalyzed H_2O_2 disproportionation.

[11] Namely, 0.1 mol% of the catalyst, 1.3 equiv. of 30% H_2O_2 and 83:17 v/v CH_3CN/AcOH mixed solvent was used.

[12] The epoxidation of **7** is a remarkable exception: the epoxide was formed in 83% *ee* upon the oxidation with H_2O_2 (Table 2, entry 15), while the epoxidation with AcOOH yielded the epoxide in 57% *ee* and 44.9% yield, using 1.0 mol% of the catalyst **3**.

[13] The oxidations with AcOOH, AlkOOH, ArIO catalyzed by complex **2** were found to proceed *via* the Lewis acid activation of the oxidant molecule by the oxidized catalyst, that is, *via* $[LMn(IV)O(OX)]^{n+}$ active species.[4g]

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[15] Indirect evidence against the Mn(V)=O active species was gained by Costas and co-workers: they have have shown that the intermediates in aminopyridine manganese/H_2O_2 systems do not exchange the oxygen atom with $H_2{}^{18}O$ under the experimental conditions used, as could be expected for oxometal species; on the contrary, the use of $H_2{}^{18}O_2$ led to a high ^{18}O incorporation in the epoxide.[4d,f]

