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Highly Enantioselective Bioinspired Epoxidation of Electron-Deficient Olefins with H_2O_2 on Aminopyridine Mn Catalysts

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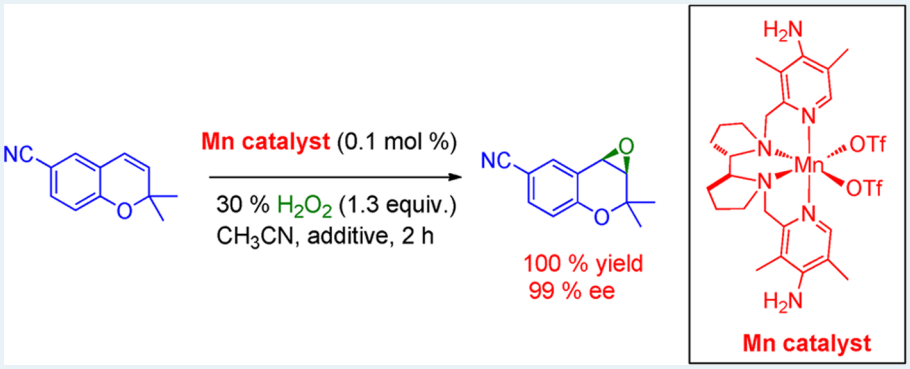
Supporting Information



ABSTRACT: The asymmetric epoxidation of various electron-deficient olefins with H_2O_2 in the presence of a novel family of chiral bioinspired bipyrrolidine-derived aminopyridine manganese(II) complexes $[LM^{II}(OTf)_2]$ is reported. High enantioselectivities (up to 99% ee) and epoxide selectivities (up to 100%), unprecedented for catalysts of this type, have been achieved; the catalysts perform up to 8500 catalytic turnovers. The presence of electron donors in the catalyst structure substantially enhances the enantioselectivity. Isotopic (^{18}O) labeling studies provide evidence of the formation of the oxomanganese(V) active species. Hammett analysis suggests that the enantioselective epoxidation is rate-limited by the transfer of an electron to the $Mn^{V}O$ intermediate, to form a short-lived acyclic (carbocationic) intermediate. In effect, the epoxide stereoconfiguration may be affected by the competition between the rotation around the $C_\alpha-C_\beta$ single bond and the epoxide ring collapse.

KEYWORDS: *asymmetric catalysis, enantioselective, epoxidation, hydrogen peroxide, intermediate, manganese, mechanism*

INTRODUCTION

Olefinic groups are relatively inert functionalities requiring chemical modification (functionalization) prior to use in fine chemical synthesis. Catalytic asymmetric oxidation of olefins provides a powerful synthetic methodology leading to versatile and reactive yet stable intermediates, containing one or two stereogenic centers, that can be involved in further transformations, e.g., via asymmetric ring opening reactions.[1] The first examples of enantioselective epoxidation (of allylic alcohols) were reported in 1977 using chiral molybdenum[2] and vanadium[3] complexes as catalysts, and alkyl hydroperoxides as terminal oxidants. Since the early 1980s, numerous catalyst systems have appeared, relying on either transiton metal-based or purely organic catalysts, the most recognizable ones being Katsuki's[4−7] and Jacobsen's[8−11] manganese−salen-based systems for the epoxidation of unfunctionalized olefins. In recent years, various aspects of metal-catalyzed asymmetric epoxidations have been comprehensively reviewed.[12−25]

Since the milestone discoveries of Katsuki[5−7] and Jacobsen,[8−11] manganese-catalyzed asymmetric epoxidation has remained one of the major protagonists in catalytic asymmetric epoxidations with various oxidants.[15,20−24] In line with growing environmental concerns, Mn-based catalyst systems adopted O_2 and H_2O_2 as greener alternatives to the originally used hypochlorite and iodosylarenes. Major pitfalls of O_2-based systems[26−36] are their potential fire risk (in organic solvents) and the need for organic coreductants (typically, several equivalents of aliphatic aldehyde). In turn, manganese systems using H_2O_2 or its derivatives, reported recently,[37−54] in most cases required several equivalents of H_2O_2 to ensure high levels of substrate conversion. In general, both types of systems were moderately efficient (typically, 10−20 turnovers).[21,25]

Asymmetric epoxidations of electron-deficient olefins have recently attracted wide attention, because the resulting optically active epoxides are valuable precursors of many biologically active organic compounds (Scheme 1).[55−61] Existing catalytic

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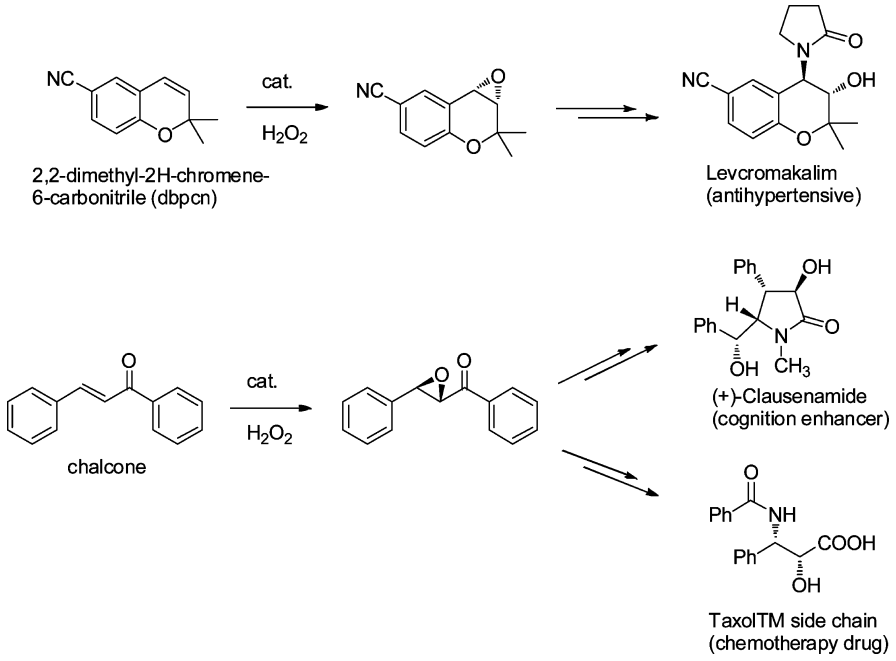
Scheme 1. Examples of Syntheses of Biologically Active Agents via the Asymmetric Epoxidation of Prochiral Electron-Deficient Olefins[55,59−61]

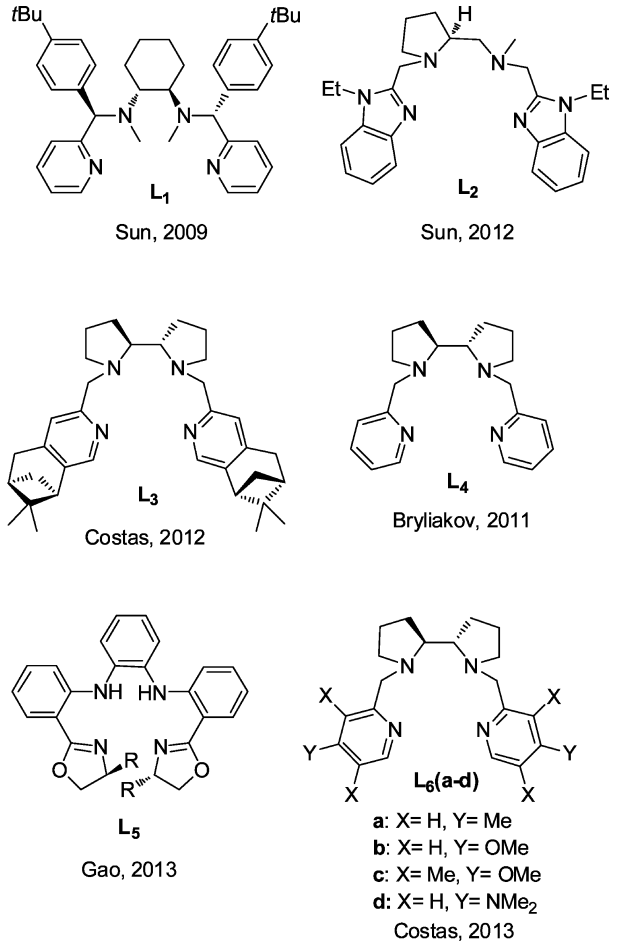


approaches, exploiting either metal-based catalysts or organocatalysts,[19,22,55−58] are mostly focused on the epoxidation of α,β-unsaturated ketones, while efficient general catalytic methods for the enantioselective epoxidation of other types of olefins containing electron-withdrawing groups remain less developed.

In the past five years, asymmetric epoxidation of electron-deficient olefins in the presence of biologically inspired chiral manganese-based catalysts, mimicking the naturally occurring metalloenzymes, has developed and attracted a high level of interest. In 2009, Sun with co-workers reported the epoxidations with H_2O_2 in the presence of a C_2-symmetric chiral aminopyridine manganese catalyst $[\mathbf{L}_1\mathrm{Mn}^{II}(\mathrm{OTf})_2]$ (Scheme 2) and acetic acid, with enantioselectivities up to 89% ee for electron-deficient olefins (in particular substituted chalcones).[62] The same group subsequently reported even higher enantioselectivities (up to 94% ee), along with high yields (from 60 to >90%), achieved through the use of C_1-symmetric manganese triflate complexes $[\mathbf{L}_2\mathrm{Mn}^{II}(\mathrm{OTf})_2]$.[63] Costas with co-workers synthesized a series of pinene-derived ligands of the type $\mathbf{L}_3$, featuring a chiral bipyrrolidine moiety; the corresponding Mn triflate complexes demonstrated high efficiencies (up to 1000 turnovers) and moderate to good enantioselectivities for the epoxidation of various electron-deficient olefins (up to 73% ee).[64] We studied the oxidation of several olefins over various chiral aminopyridine Mn complexes[65−67] and identified $[\mathbf{L}_4\mathrm{Mn}^{II}(\mathrm{OTf})_2]$ [**1** (Scheme 3)] with (*S*,*S*)-bipyrrolidine-derived aminopyridine ligand $\mathbf{L}_4$ as the most efficient and stereoselective one.[66−68]

The presence of the carboxylic acid additive in the structure of the active species at the enantioselective oxygen-transfer step had been documented.[66,67] The epoxidation enantioselectivity increased with increasing steric bulk at the α-carbon, 2-ethylhexanoic acid showing the best results (with enantioselectivities up to 93% ee).[67] More recently, Gao with co-workers reported a "porphyrin-inspired" system exploiting an *in situ*-generated [from $\mathrm{Mn(OTf)_2}$ and ligand $\mathbf{L}_5$] catalyst.[69] In

Scheme 2. Chiral Aminopyridine Ligands Used in Manganese-Catalyzed Asymmetric Epoxidations with H_2O_2



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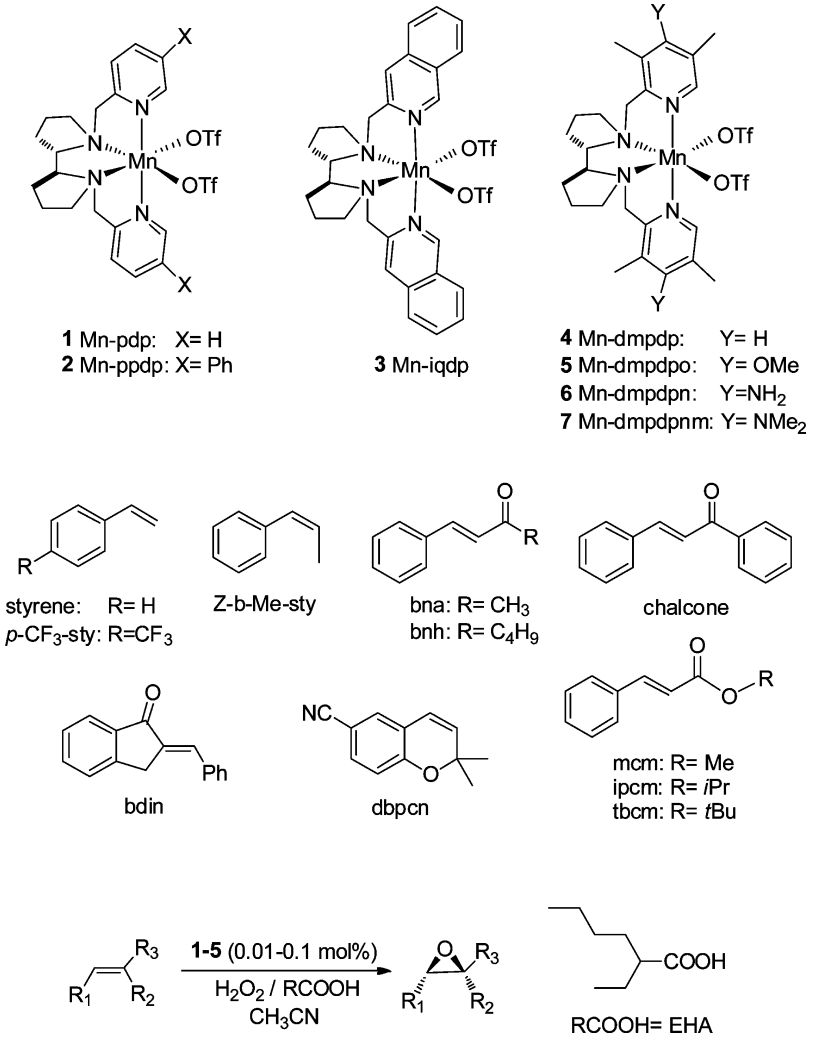
Scheme 3. Manganese(II) Catalysts (1−7) Used in This Study (OTf^- = $CF_3SO_3^-$), Structures of Olefins, and Catalytic Epoxidation with H_2O_2



contrast to the systems mentioned above, Gao's one catalyzed the epoxidation of conjugated alkenes with higher asymmetric inductions and yields, while, e.g., electron-deficient chalcone was epoxidized with only 50% ee. Very recently, Costas and co-workers reported that manganese complexes with ligands $\mathbf{L}_6$, bearing electron-donating substituents, demonstrate high efficiencies [turnover number (TON) of up to 1000] and enantioselectivities [up to 97% ee for dbpcn (cf. Scheme 3)], also distinguishing 2-ethylhexanoic acid as the optimal additive.[70]

In this work, we have undertaken a systematic study of (*S*,*S*)-bipyrrolidine-derived manganese-based catalysts, focusing on the effect of steric and electronic properties of aminopyridine ligands on their performance, and on the discussion of the nature of active species and the mechanism of oxygen transfer. In particular, a series of structurally similar novel catalysts **2**−**7** (Scheme 3) was prepared and characterized by X-ray analysis.[71,72] In **2** and **3**, the accessibility of the metal center was in a way attenuated by a higher level of steric congestion, compared with that of **1**. In turn, electronic properties of the pdp-type ligand frameworks of complexes **4**−**7** were modulated by the introduction of electron-donating substituents. X-ray data indicate the same *cis*-α coordination topology for those octahedral complexes (Figure 1 and the Supporting Information). The catalytic properties of **1**−**7** were screened, with 2-ethylhexanoic acid (EHA) as the additive.

RESULTS AND DISCUSSION

Asymmetric Epoxidations in the Presence of Bipyrrolidine-Derived Manganese Complexes: Probing Steric and Electronic Effects on Epoxidation Enantioselectivity. Steric effects on the epoxidation enantioselectivity (Scheme 3) were tested on catalysts **1**−**3** (Tables 1 and Figure S1 of the Supporting Information). Generally, catalyst **3** bearing isoquinolyl fragments instead of pyridyl fragments showed enantioselectivities slightly higher than or equal to that of parent complex **1**. Apparently, an increased level of steric shielding of the central atom favors a more structurally defined transition, resulting in better stereocontrol. On the other hand, catalyst **2** displayed results inferior to those of **1**; the possible reason for that is the interference of steric and electronic effects (the 3-Ph substituent is a mild electron acceptor). Attempts to further enhance the steric crowd by replacing isoquinolyl moieties of **3** with quinolyl moieties afforded an inactive manganese complex [Mn(qdp)$(OTf)_2$].[73]

We examined the catalytic productivity of Mn complexes **1**−**7** and found that in some cases, catalyst loads of only 0.01−0.02 mol % were sufficient, the reactions proceeding to completion

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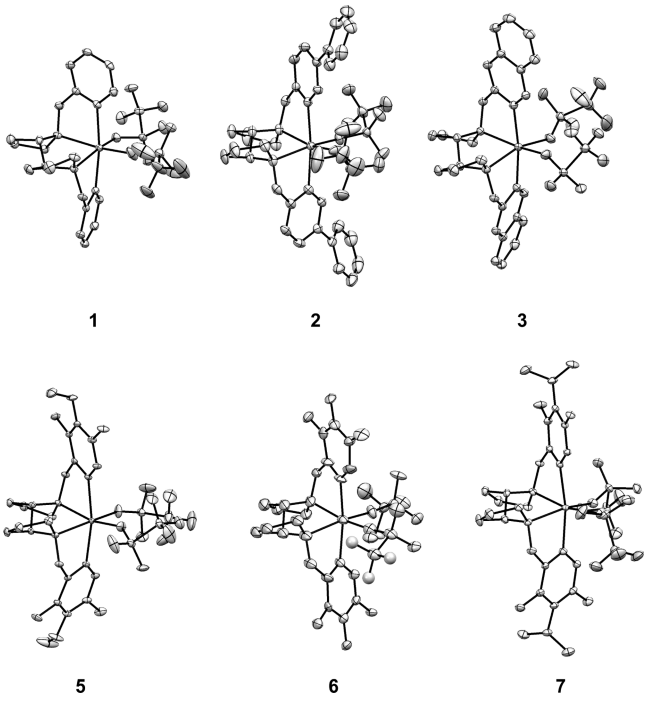


Figure 1. ORTEP plots of catalysts **1**,[67] **2**, **3**, and **5**−**7**. Ellipsoids are drawn at the 50% (**1**−**5** and **7**) or 25% (**7**) probability level, and hydrogen atoms have been omitted for the sake of clarity. See also Figure S1 of the Supporting Information.

Table 1. Asymmetric Epoxidations with H_2O_2 Catalyzed by Complexes 1−3[a]

entry	olefin	catalyst (mol %)	conversion (%)/yield (%)	ee (%) (configuration)
1[b]	bnh	**1** (0.1)	47/47	79[c]
2	bnh	**2** (0.1)	13/13	60[c]
3	bnh	**3** (0.1)	63/63	80[c]
4[b]	chalcone	**1** (0.1)	99/97	93 (2*R*,3*S*)
5[d]	chalcone	**2** (0.1)	43/41	87 (2*R*,3*S*)
6[d]	chalcone	**3** (0.1)	64/61	93 (2*R*,3*S*)
7[b]	dbpcn	**1** (0.1)	100/100	93 (3*R*,4*R*)
8	dbpcn	**2** (0.1)	17/17	90 (3*R*,4*R*)
9	dbpcn	**3** (0.1)	94/94	96 (3*R*,4*R*)

[a]At −30 °C. With 130 μmol of H_2O_2, 100 μmol of substrate, and 1400 μmol of EHA, H_2O_2 was added with a syringe pump over 2 h for catalysts **1** and **3** or over 1 h for catalyst **2**, and the mixtures were stirred for an additional 2 h. Conversions and yields calculated on the basis of the substrate. [b]From ref 67. [c]Not assigned. [d]H_2O_2 added over 30 min.

within 3−4 h at −30 °C. One could expect that the introduction of electron donors (cf. **1** and **4**−**7**) might affect the catalytic productivity, as well as the amount of carboxylic acid cocatalyst needed (cf. ref 70). The effect of the amount of added carboxylic acid was tested (Figure S2 of the Supporting Information). It appears that an optimum between substrate conversion and enantioselectivity can be found for each catalyst, more enantioselective catalysts requiring smaller amounts of the carboxylic acid (footnotes of Table 2).

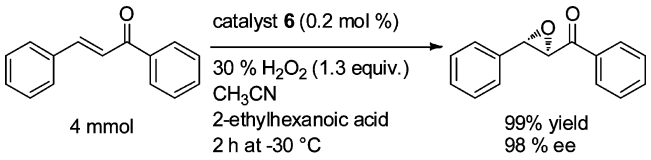
Some results of enantioselective epoxidations of olefins in the presence of complexes **1** and **5**−**7** are summarized in Table 2 (also Table S2 of the Supporting Information). The presence of electron donors in catalysts **5**−**7** notably improved their enantioselectivities with respect to parent complex **1** (Figure S3 of the Supporting Information). In effect, dbpcn and chalcone were epoxidized with 99% and 98% ee, respectively (entries 18 and 22, respectively).

Table 2. Asymmetric Epoxidations with H_2O_2 Catalyzed by Complexes 1 and 5−7[a]

entry	olefin	catalyst (mol %)	conversion (%)/yield (%)	ee (%) (configuration)
1[b]	bna	**1** (0.1)	37/37	74[c]
2	bna	**5** (0.05)	86/82	83[c]
3	bna	**6** (0.5)	89/87	96[c]
4	bna	**7** (0.1)	60/51	87[c]
5[b]	bnh	**1** (0.1)	47/47	79[c]
6	bnh	**5** (0.05)	79/76	85[c]
7	bnh	**6** (0.01)	91/88	96[c]
8	bnh	**7** (0.1)	80/63	92[c]
9[b]	mcm	**1** (0.1)	37/37	77 (2*R*,3*S*)
10	mcm	**5** (0.05)	71/71	82 (2*R*,3*S*)
11	mcm	**6** (0.5)	91/91	89 (2*R*,3*S*)
12	mcm	**7** (0.1)	62/62	85 (2*R*,3*S*)
13	*t*bcm	**5** (0.05)	76/76	90[c]
14	*t*bcm	**6** (0.5)	88/88	96[c]
15	*t*bcm	**7** (0.1)	58/58	93[c]
16[b]	dbpcn	**1** (0.1)	100/100	93 (3*R*,4*R*)
17	dbpcn	**5** (0.01)[d]	72.5/72.5	96 (3*R*,4*R*)
18	dbpcn	**6** (0.1)	100/100	99 (3*R*,4*R*)
19	dbpcn	**7** (0.02)	100/100	91 (3*R*,4*R*)
20[b]	chalcone	**1** (0.1)	99/97	93 (2*R*,3*S*)
21	chalcone	**5** (0.1)[d]	100/100	95 (2*R*,3*S*)
22	chalcone	**6** (0.2)	100/100	98 (2*R*,3*S*)
23	chalcone	**7** (0.05)	88/88	97 (2*R*,3*S*)
24	bdin	**6** (0.2)	90/90	93 (2*R*,3*S*)

[a]At −30 °C. With 130 μmol of H_2O_2 and 100 μmol of substrate, H_2O_2 was added with a syringe pump over 2 h for catalyst **1** or over 30 min for **6** and **7**, and the mixtures were stirred for an additional 2 h (4 h for **7**). With 200 μmol of H_2O_2 and 100 μmol of substrate, H_2O_2 was added with a syringe pump over 1 h for **5**. Conversions and yields calculated on the basis of the substrate. EHA: 1.4 mmol for **1**, 0.6 mmol for **5**, 0.1 mmol for **6**, and 0.5 mmol for **7**. [b]From ref 67. [c]Absolute configuration not assigned. [d]Mixed CH_3CN/CH_2Cl_2 [2/1 (v/v)] solvent.

Scheme 4. Gram-Scale Enantioselective Epoxidation of Chalcone



After recrystallization:
92 % yield
99.8 % *ee*

These values are the highest achieved in catalyst systems based on manganese complexes and H_2O_2 and are among the highest ever reported for the asymmetric epoxidations of dbpcn and chalcone.[47,51,74−77] All catalysts demonstrated high efficiencies; loads of 0.01−0.05 mol % were sufficient to achieve high levels of conversion (Table 2). Increasing the catalyst loads to 0.1 mol % in most cases led to very high levels of olefin conversion and epoxide yields (90−100%).

The epoxidation procedure can be scaled to gram quantities. For instance, chalcone epoxide was prepared in 99% yield at

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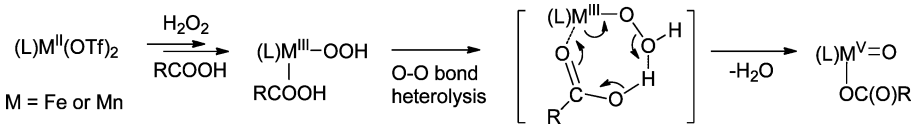
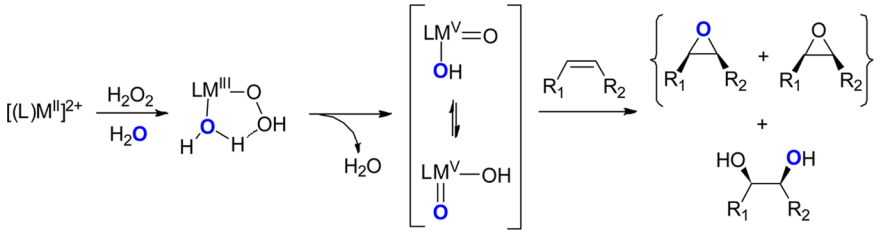
Scheme 5. Proposed Mechanism for Fe and Mn Aminopyridine Catalysts[67]



Scheme 6. Proposed Water-Assisted Oxidation Mechanism for Iron-Catalyzed Oxidations with H_2O_2[a]



[a] ^{18}O colored blue.[84,85]

Table 3. Catalytic Epoxidations over Catalyst 5 in the Presence of $H_2{}^{18}O$[a]

entry	olefin	epoxide (TON)	epoxide (% ^{18}O)	diol (TON)	diol (TON) (% $^{16}O^{16}O/^{16}O^{18}O$)
1	styrene	22	35	11	13/87
2	*p*-CF_3-styrene	15	44	16	14/86

[a] At 0 °C, with substrate (0.1 mmol), catalyst **5** (1.0 mol %), $H_2{}^{18}O$ (2.0 mmol, 97 atom % ^{18}O), and 88% H_2O_2 (0.1 mmol).

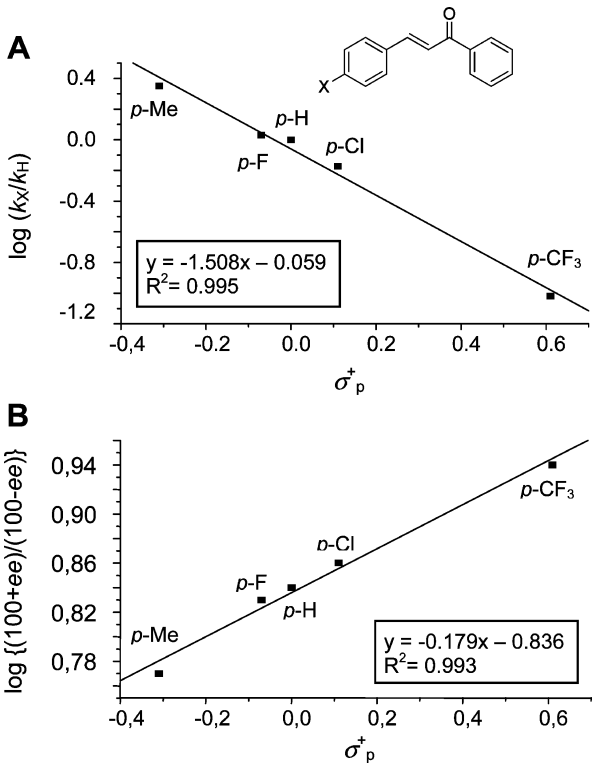


Figure 2. Hammett plots of $\log(k_X/k_H)$ (A) and $\log[(100 + ee)/(100 - ee)]$ (B) vs σ^+_p for the epoxidation of para-substututed chalcones by the **1**/AcOH/H_2O_2 system.

98% ee (Scheme 4). This is the best result ever reported for preparative enantioselective catalytic chalcone epoxidation. Subsequent recrystallization improved the epoxide optical purity to 99.8% ee.

Evidence of the Reaction Mechanism: Isotopic Study and Hammett Analysis. Recently, we contributed a comparative mechanistic study of Fe and Mn catalysts $[L_4M^{II}(OTf)_2]$ (M = Fe or Mn) in stereoselective oxidation of olefins with H_2O_2 in the presence of carboxylic acids.[67] A common mechanism (similar to the "carboxylic-acid assisted" mechanism previously discussed for Fe-catalyzed epoxidations in the presence of AcOH[78−80]) was proposed for both catalysts (Scheme 5), the reactions proceeding via common oxometal-(V) intermediates $[L_4M^V{=}O(OC(O)R)]^{2+}$ (M = Fe or Mn).[67] Herewith, further support for this mechanism is provided on the basis of an isotopic labeling study.

Isotopic (^{18}O) labeling has been extensively applied in mechanistic investigations of non-heme iron-based catalyst systems for hydrocarbon oxidations with H_2O_2.[80−90] The addition of a large excess of $H_2{}^{18}O$ to Fe complex/$H_2{}^{16}O_2$/olefin catalyst systems resulted in the formation of ^{18}O-labeled epoxide and 1,2-diol (in the latter, one oxygen stemmed from $H_2{}^{18}O$ and the other from $H_2{}^{16}O_2$), which was interpreted in terms of the "water-assisted" mechanism (Scheme 6).[84,85] The approaches developed for Fe-based catalysts, however, have not been extended to Mn catalysts; attempts to add $H_2{}^{18}O$ to the latter systems did not result in incorporation of ^{18}O into the reaction products.[91,93] This is not surprising because Mn aminopyridine catalysts reported so far were able to act as oxidation catalysts only in the presence of a (large) excess of a carboxylic acid additive, which hampered $^{16}O-{}^{18}O$ exchange via blocking the manganese coordination site with the abundant carboxylate.[94,95]

Fortunately, Mn complexes with electron-donating substituents turned out active catalysts even in the absence of carboxylic acid. For example, it was found that the active species originating from catalyst **5** does exchange with $H_2{}^{18}O$, yielding a 35% ^{18}O-enriched styrene epoxide (Table 3). The degree of ^{18}O incorporation is governed by competition between the epoxidation and the tautomeric oxo-hydroxo exchange (Scheme 6) and may be expected to increase with less reactive substrates. Indeed, *p*-CF_3-styrene showed a 44% ^{18}O enrichment (Table 3). For both substrates, the 1,2-diols were 86 or 87% singly ^{18}O-labeled (without $^{18}O^{18}O$-diol), thus indicating that one of the oxygens does stem from water rather than from H_2O_2.[84,85,92] C−H oxidations showed a 27% level of incorporation of ^{18}O into 1-adamantanol and an 18% level of incorporation of ^{18}O into *cis*-1,2-dimethylcyclohexanol (Table

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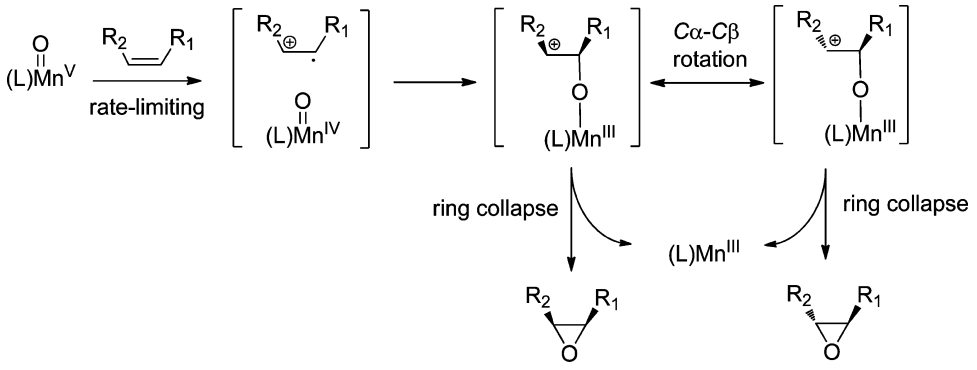
Scheme 7. Proposed Electron-Transfer Mechanism in Mn-Catalyzed Epoxidations with H_2O_2



S3 of the Supporting Information).[98] These data support the viability of the mechanism in Scheme 6 in the presence of water, invoking a *cis*-HO-Mn^V=O active species. In the presence of a large excess of carboxylic acid, the reaction should follow the carboxylic acid-assisted pathway shown in Scheme 5.[67]

To probe the nature of the oxygen-transferring species, competitive oxidations of para-substituted chalcones were conducted in the presence of complex **1**. The active species was found to be electrophilic (cf. ref 91); a good linear correlation between the $\log(k_X/k_H)$ and σ^+_p [with a negative ρ^+ of −1.51 indicating an electron-demanding transition state (Figure 2A)] was found, the more electron-rich substrates demonstrating higher oxidation rates. Furthermore, $\log[(100 + ee)/(100 - ee)]$[99] was also highly linear versus the σ^+_p of the substituents (Figure 2B), the epoxides of more easily oxidizing substrates displaying lower enantiomeric excesses.

We note that the negative ρ^+ of −1.51 falls within the range previously reported (−0.84 to −1.9) for olefin epoxidations with oxometal species proceeding via the electron-transfer mechanism of the rate-limiting stage, followed by the formation of carbocationic intermediates (Scheme 7).[100−105] The latter may undergo rotation around the C_α−C_β single bond, competitive with ring collapse, leading to the formation of two stereoisomeric epoxides. Indeed, our studies indicate a partial erosion of stereochemistry in the epoxidation of *cis*-stilbene with H_2O_2 in the presence of catalyst **1** and AcOH.[106]

Keeping these considerations in mind, we come to the following qualitative understanding of the observed correlation between the optical yields and the electronic nature of the substrates. In the case of less reactive (electron-deficient) olefins, the transition state should be more productlike, with stronger interactions between the substrate and the reactive oxometal complex (Figure S4 of the Supporting Information). This ensures better stereocontrol; the resulting highly unstable cationic intermediate undergoes a fast ring closure, to form the corresponding epoxide at high ee. In contrast, for more reactive olefins, the transition state is more reagentlike, with relatively poorer stereocontrol, which leads to weaker enantioselection.[107]

CONCLUSIONS

A family of chiral aminopyridine manganese catalysts demonstrating unprecedented high enantioselectivities (up to 99% ee) and epoxide selectivities (up to 100%) in asymmetric epoxidations of electron-deficient olefins with H_2O_2 has been developed; the epoxidation enantioselectivity increases with the improving electron-donating ability of the ligand substituents. ^{18}O isotopic studies provide evidence of active species of the type $[LMn^V{=}O(X)]^{2+}$ (X = OH or OCOR). Hammett analysis reveals an electrophilic oxidant; the overall epoxidation rate is limited by the transfer of an electron to the oxometal species, to form an acyclic (most likely carbocationic) intermediate. In effect, less reactive olefins are oxidized slower but with greater stereocontrol. The epoxide stereoconfiguration is also partially affected by the competition between the rotation around the C_α−C_β single bond in the cationic intermediate and epoxide ring collapse. This work provides a consistent mechanistic landscape of aminopyridine Mn-catalyzed bioinspired epoxidations with H_2O_2. Further studies are foreseen, aimed at direct experimental detection of the oxometal(V) intermediate.

ASSOCIATED CONTENT

Supporting Information

A list of abbreviations, materials and methods, synthetic procedures for the novel ligands and complexes, catalytic procedures, crystal data, and additional figures and tables. 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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(95) Very recently, a "13.3% ^{18}O incorporation" into acetophenone was reported (ref 96) in the course of ethylbenzene oxidation on a Mn complex, which, apparently, resulted from a postoxidative acetophenone exchange with $H_2{}^{18}O$ (ref 97). Our blank experiment (no Mn catalyst, 10 μmol of cyclohexanone with 100 equiv of $H_2{}^{18}O$ and 40 μL of AcOH in 0.5 mL of CH_3CN at 0 °C) evidenced a level of incorporation of ^{18}O into cyclohexanone of 91% within 1 h.
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(98) Zero ^{18}O incorporation into *trans*-1,2-dimethylcyclohexanol points to a different mechanism of its formation (cf. ref 83); one could expect that the oxygen atom in the *trans*-1,2-dimethylcyclohexanol is formed via capture of dissolved O_2 by the intermediate C-centered radical.
(99) The term $\log[(100 + ee)/(100 - ee)]$, equivalent to $\log(k_{major}/k_{minor})$, is proportional to $\Delta\Delta G^{\ddagger}$ (where $\Delta\Delta G^{\ddagger}$ is the difference in free energy between the two diastereomeric transition states leading to two enantiomeric products): $\log[(100 + ee)/(100 - ee)] = -\Delta\Delta G^{\ddagger}/(2.303RT)$.
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(106) At 0 °C, 96% *cis*-stilbene conversion, 87% *cis*-epoxide yield, and 4.5% *trans*-epoxide yield (from the Supporting Information of ref 67).
(107) Furthermore, in case of the electron-rich olefins, the resulting cationic intermediate (Scheme 7) is more efficiently stabilized by the electron-donating groups. In effect, it may have a relatively long lifetime and hence undergo rotation around the $C_\alpha-C_\beta$ single bond prior to ring collapse, further diminishing the reaction stereoselectivity (cf. ref 106).