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Highly Stereoselective Epoxidation with H_2O_2 Catalyzed by Electron-Rich Aminopyridine Manganese Catalysts

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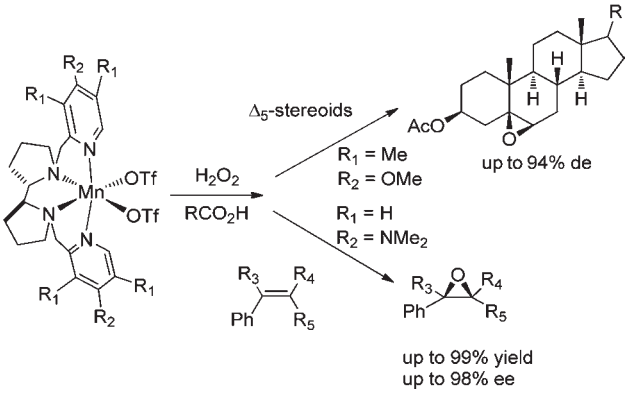
ABSTRACT



Fast, efficient, and highly stereoselective epoxidation with H_2O_2 is reached by manganese coordination complexes with e-rich aminopyridine tetradentate ligands. It is shown that the electronic properties of these catalysts vary systematically with the stereoselectivity of the O-atom transfer event and exert fine control over the activation of hydrogen peroxide, reducing the amount of carboxylic acid co-catalyst necessary for efficient operation.

Asymmetric epoxidation is an important reaction in organic synthesis because of the versatility of epoxides as useful intermediates in the preparation of a diverse array of functional molecules.[1,2] Current challenges for this reaction lay in finding environmentally more sustainable methods; for example, oxidations with catalysts based on first-row, non-toxic earth-abundant metals and oxidants exhibiting good atom economy that generate minimum waste are highly desirable. In this regard, selected manganese coordination complexes with aminopyridine-based ligands have emerged as efficient oxidation catalysts. Seminal studies by Stack and co-workers described [$Mn(CF_3SO_3)_2$-(*R,R*)-MCP)], MCP = *N,N′*-bis(2-pyridylmethyl)-*N,N′*-dimethyl-*trans*-1,2-diaminocyclohexane as a very active epoxidation catalyst employing peracetic acid (AcOOH) as oxidant.[3] Further elaboration of the manganese complex by Sun et al. led to the development of a catalyst that showed good enantioselectivity in the epoxidation of chalcones.[4] Hydrogen peroxide constitutes a particularly interesting oxidant, but its use in manganese-catalyzed reactions is challenging because of competing hydrogen peroxide disproportionation reactions. Garcia-Bosch et al. showed that hydrogen peroxide could be used as terminal

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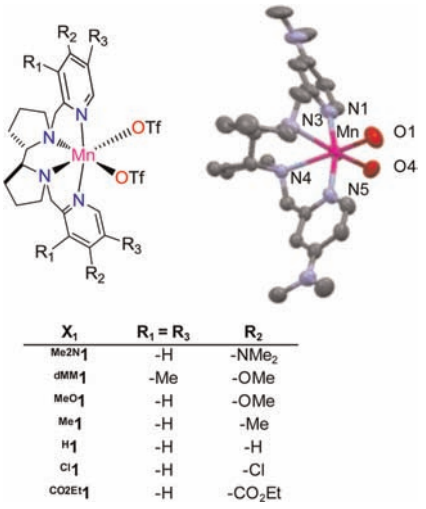
oxidant with this type of catalysts in the presence of acetic acid (14 equiv).[5] Subsequently, several manganese catalysts containing aminopyridine tetradentate ligands have been described to efficiently operate under these experimental conditions.[6] Good to excellent enantioselectivities have been obtained in the epoxidation of chalcones, but rational strategies for further improvement of these catalysts allowing for extending their rather narrow substrate scope, and hopefully without requiring extensive trial and error testing, need to be developed.



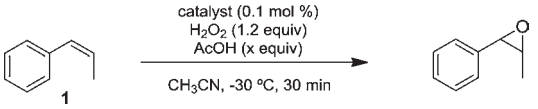
X_1	$R_1 = R_3$	R_2
^{Me2N}1	-H	-NMe_2
^{dMM}1	-Me	-OMe
^{MeO}1	-H	-OMe
^{Me}1	-H	-Me
^{H}1	-H	-H
^{Cl}1	-H	-Cl
^{CO2Et}1	-H	-CO_2Et

Figure 1. Manganese complexes studied and an ORTEP diagram of the X-ray-determined structure of (*R,R*)-^{Me2N}**1**. For clarity, H atoms and triflate groups, except for O atoms bound to the metal, are omitted.

To this end, in this paper we show that the electronic properties of the manganese catalysts in the series of complexes [Mn(CF_3SO_3)$_2$(^{x}PDP)] (^{H}PDP = 2-[[2-(1-(pyridin-2-ylmethyl)pyrrolidin-2-yl)pyrrolidin-1-yl]methyl]pyridine, Figure 1) exert a profound and systematic impact in the activation of H_2O_2 to efficiently generate epoxidizing species and also in the stereoselectivity exhibited by these species in epoxidation reactions. This analysis has led us to the discovery of a very active Mn catalyst that requires substoichiometric amounts of a carboxylic acid for efficient H_2O_2 (1.2−2 equiv) activation, providing epoxides in short reaction times (30−60 min) with improved stereoselectivities and substrate scope in comparison with any aminopyridine−manganese system described so far.

The series of manganese complexes [Mn(CF_3SO_3)$_2$((*S,S*)-^{x}PDP)] (***S,S*)-^{X}1** (Figure 1) (X = Me_2N, MeO, Me, Cl and CO_2Et) was prepared, characterized (see the Supporting Information for details), and studied as epoxidation catalysts employing H_2O_2 as oxidant. Catalysts [Mn(CF_3SO_3)$_2$-((*S,S*)-^{H}PDP)], (***S,S*)-^{H}1**, previously prepared and studied by Talsi and co-workers, serves as a comparative benchmark.[6c,g] Crystallographic characterization of (*R,R*)-^{Me2N}**1** serves as an illustrative example of the series, showing a C_2-symmetric octahedral complex where the ligand adopts a *cis*-α topological coordination geometry.[7] Structural and metrical parameters are very similar to those described for the Mn(mcp) catalyst,[3] and ^{H}**1**[6g] and will not be described further (see the Supporting Information). Hydrogen peroxide (1.2 equiv) diluted in acetonitrile (1:1 v:v) was used as oxidant and delivered by syringe pump over 30 min to an acetonitrile solution of the catalyst (0.1 mol %), a substrate (*cis*-β-methylstyrene, **1**), and AcOH (14 equiv) at −30 °C. After a further 30 min of stirring, reactions were analyzed by chiral GC. Poor epoxide yield and enantioselectivity were obtained with ^{H}**1** (Table 1, entry 1). Yield and enantioselectivity turned out to respond in a sensitive manner to the electronic properties of the pyridine rings of the ligand. When electron-withdrawing groups were introduced at the *para*-position of the pyridine (Table 1, entries 2 and 3), yields remained moderate and enantioselectivities were lower. However, we observed a very substantial improvement in both parameters in the presence of electron-donating substituents (Table 1, entries 4−7). Up to 82% ee was attained with ^{Me2N}**1**, the most e-rich catalyst of the series. The reaction was stereospecific, providing only epoxides where stereoconfiguration was retained. Good performance was also obtained with catalyst ^{dMM}**1**. Therefore, we concluded that chemo- and stereoselectivity were

Table 1. Epoxidation of *cis*-β-Methylstyrene (**1**) Using Various Manganese Complexes[a]



entry	catalyst	AcOH (*x* equiv)	conv (yield, %)	ee (%)
1	^{H}**1**	14	61 (38)	43
2	^{Cl}**1**	14	57 (33)	40
3	^{CO2Et}**1**	14	44 (22)	43
4	^{Me2N}**1**	14	100 (75)	82
5	^{dMM}**1**	14	100 (86)	76
6	^{MeO}**1**	14	80 (59)	69
7	^{Me}**1**	14	100 (67)	63
8	^{Me2N}**1**	0.35	100 (79)	73
9	^{dMM}**1**	0.35	23 (2)	55
10[b]	^{Me2N}**1**	14	100 (89)	90
11[b]	^{Me2N}**1**	**0.35**	**100 (86)**	**92**

[a] Unless stated, reaction conditions are (*S,S*)-catalyst (0.1 mol %), H_2O_2 (1.2 equiv) and AcOH (*x* equiv) in CH_3CN at −30 °C. [b] 2-ethylhexanoic acid (2-eha) was used instead of AcOH.

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systematic and substantially improved as the ligand was more e-rich. For this reason, catalysts ^{Me2N}**1** and ^{dMM}**1** were chosen for further investigations.

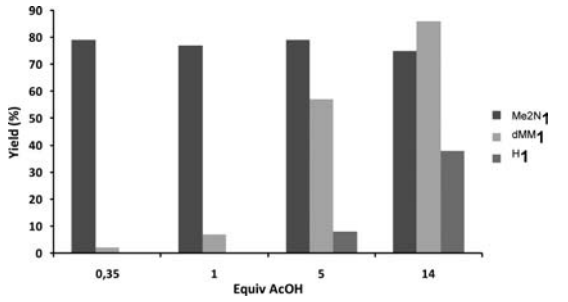
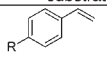
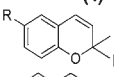


Figure 2. Epoxidation of **1** as a function of AcOH loading for catalysts (*S,S*)-^{Me2N}**1**, (*S,S*)-^{dMM}**1**, and (*S,S*)-^{H}**1**. Reaction conditions: catalyst (0.1 mol %), H_2O_2 (1.2 equiv), and AcOH (0.35−14 equiv) in CH_3CN at −30 °C.

Carboxylic acids have been previously recognized as a key additive in manganese catalyzed oxidations in order to divert H_2O_2 consumption from nonproductive peroxide disproportionation reactions toward substrate oxidation.[8] Very interestingly, the amount of acetic acid necessary for efficient operation in the ^{X}**1** series appeared to be systematically dependent in the nature of the manganese catalyst, and more specifically in the e-releasing character of the ligand. Catalyst ^{Me2N}**1** retained full epoxidation activity with only 0.35 equiv of AcOH, although enantioselectivity was somewhat eroded (Table 1, entry 8). A further decrease to 0.1 equiv of AcOH provided moderate epoxide yield (51%). In contrast, for ^{dMM}**1** the epoxide yield was reduced substantially as the acetic acid loading was reduced from 14 to 0.35 equiv, and a more drastic effect was observed for ^{H}**1** (see Figure 2, and entry 9 in Table 1). Therefore, the data from Table 1 and Figure 2 show that activation of H_2O_2 to form epoxidizing species is uniquely facilitated by ^{Me2N}**1**. Lyakin and co-workers have recently reported that alkyl carboxylic acids can be used instead of acetic acid, and in some specific cases this change results in improvement of the enantioselectivity.[6g] Therefore, a range of carboxylic acids were tested in the epoxidation of **1** (see the Supporting Inforamtion, Table 1). When ^{Me2N}**1** was used with low loadings of racemic 2-ethyl hexanoic acid (2-eha), the enantioselectivity was improved up to 90% ee, and this value was slightly improved at low carboxylic acid loading (0.35 equiv) (entries 10 and 11, respectively).

A substrate scope study is presented in Table 2. Reaction conditions involved low catalyst loadings (0.1−0.5 mol %), H_2O_2 in slight to moderate excess (1.2−2 equiv), and relatively low amounts of the carboxylic acid 2-eha (0.35 to 1 equiv). With this set of conditions in hand, the present system provides good yields and enantioselectivity in the epoxidation of various families of olefinic substrates. In general, more e-deficient olefins such as enones required higher catalyst, H_2O_2, and carboxylic acid loadings.

Table 2. Substrate Scope on the Asymmetric Epoxidation[*]

entry	substrate	isolated yield (%)	Ee (%)
1[a]	 R = H(**2**)	85(63)[b]	69
2[a]	R = Cl(**3**)	84(64)[b]	68
3[c]	 (**4**)	100(88)[b]	26
4[c]	 R= CN (**5**)	95	97
5	 R = CO_2Et (**6**)	77	98
6	R = C(O)N(OMe)(Me)(**7**)	99	96
7	R = C(O)Ph(**8**)	65	90
8	 R = Ph(**9**)	95	96
9	R = OEt(**10**)	93	92
10	R = Me(**11**)	81	96
11	R = N(OMe)(Me)(**12**)	99	97
12	 (**13**)	95	57
13[d]	 (**14**)	67	84

[*] Unless stated, reaction conditions are (***S,S***)-^{Me2N}**1** (0.5 mol %), H_2O_2 (2 equiv) and 2-eha (1 equiv) in CH_3CN at −30 °C. [a] 0.2 mol % of catalyst, H_2O_2 (2 equiv), 2-eha (0.5 equiv). [b] GC conversion and (yield). [c] 0.1 mol % of catalyst, H_2O_2 (1.5 equiv), and 2-eha (0.35 equiv). [d] Temp −10 °C. ee's and configuration determined by chiral GC and HPLC (see the Supporting Information for details).

Styrenes are recognized as particularly difficult substrates for asymmetric epoxidation and are epoxidized with a remarkable 68−69% ee (entries 1 and 2). However, introdution of a methyl group in the α-olefin site results in poor stereoselection (entry 3). Excellent enantioselectivity was achieved for a substituted chromene (97% ee, entry 4) and also for *cis*-cinnamic derivatives (90−98% ee, entries 5−7). Epoxidation of aromatic enones proceeded with good to excellent yields, including not only the commonly studied *trans*-chalcone (**9**) (96% ee, entry 8) but also more challenging substrates such as *cis*-chalcone (**8**) (90% ee, entry 7), *trans*-ethyl cinnamate (**10**) (92% ee, entry 9), an alkyl styryl ketone (**11**) (96% ee, entry 10), and also an amide derivative (**12**) (97% ee, entry 11). However, as noticed for styrenes, the epoxidation of the α-methyl-substituted chalcone (**13**) proceeded with moderate enantioselectivity (57% ee, entry 12), albeit with high epoxide yield and stereospecificity. Finally, the trisubstituted tetralone-derived (**14**) epoxide was achieved with moderate yield and good enantioselectivity (84% ee, entry 13). Overall, with the single exception of the epoxidation of substrate **4**, catalyst ^{Me2N}**1** provides improved enantioselectivities with regard to any of the Mn-based catalyst with N-based polydentate ligands described up to date[6] and broader or complementary[6f] substrate scope.

An important and interesting set of olefinic substrates is Δ^5-unsaturated steroids. It is well established that some

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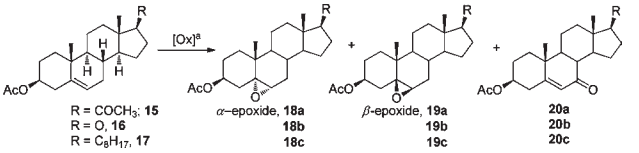
β-epoxide stereoids, such as withanolides, exhibit antitumoral activities,[9] and for this reason, their β-selective epoxidation is an interesting target. These natural products contain methyl groups in their β face that exert steric protection, and their epoxidation with peracids usually produces the α-epoxide as the major product.[10] Reagents for selective β-epoxidation include the Parish reagent,[10,11] structurally elaborated dioxiranes,[12] and catalytic oxidations with porphyrin ruthenium catalysts that use 2,6-Cl_2pyNO as oxidant.[13] An attractive alternative is to employ Mn-based catalysts, making use of H_2O_2 as oxidant, but to the best of our knowledge, this approach has been described with modest selectivity.[14] Considering the highly selective nature of electron-rich catalysts ^{Me2N}**1** and ^{dMM}**1**, their application to the oxidation of Δ^5-unsaturated steroids was studied. Preliminary optimization experiments disclosed that pivalic acid was a more convenient coligand than 2-eha and that 15 equiv was necessary since the use of 0.35 equiv resulted in no epoxide formation (Table 3, entry 1). Using 15 equiv of pivalic acid **(*S,S*)-^{Me2N}1** provided excellent β-diastereoselectivites in the epoxidation of **15** but with poor yield and formation of 23% of allylic oxidation side product **20a** (Table 3, entry 2). Enantiomeric **(*R,R*)-^{Me2N}1** isomer retained the low product yield and modest selectivity toward the β isomer (entry 3). Fortunately, **(*S,S*)-^{dMM}1** proved to be a more convenient catalyst providing improved yields, chemoselectivity, and excellent diastereoselectivity (Table 3, entry 4). On the other hand, as also observed for **(*R,R*)-^{Me2N}1** (entry 3), the enantiomer **(*R,R*)-^{dMM}1** offered a more modest diastereoselectivity (Table 3, entry 5). Under optimized conditions Δ^5-unsaturated stereoids **16** and **17** were also epoxidized with moderate to good yields and excellent β-diastereoselectivities (table 3, entries 6 and 7) in short reaction times (1 h). Interestingly, oxidation of the same steroidal substrates with the analogous iron complexes[15] **(*S,S*)-^{dMM}1Fe** and **(*S,S*)-^{Me2N}1Fe** afforded an equimolar ratio of β/α epoxides and modest selectivity toward the β epoxide, respectively.

In conclusion, the present work describes highly efficient and stereoselective manganese catalysts for the epoxidation of olefins with H_2O_2 under mild conditions and short reaction times. The work demonstrates that electronic effects can be used to improve the activation of H_2O_2 in a productive manner, as well as the steroselectivity in the oxygen atom transfer event, providing a useful guiding principle for rational design of a future generation of catalysts. Catalysts described herein complement or compare favorably in terms of enantioselectivities and substrate scope against structurally related examples described so far. When compared with the analogous iron complexes, obvious similarities arise in the electronic effects,[15] but in addition the manganese catalysts require lower catalyst loadings, are more tolerant to aromatic substrates, and show enhanced β-selectivities in the epoxidation of Δ^5-unsaturated steroids.

Table 3. Epoxidation of Δ^5-Unsaturated Steroids[a]



entry	substrate	catalyst	yield (%) (**18** + **19**) (**20**)[b]	ratio **19**/**18**
1[c]	**15a**	(*S,S*)-^{Me2N}**1**	– (–)	–
2	**15a**	(*S,S*)-^{Me2N}**1**	36 (23)	93:7
3	**15a**	(*R,R*)-^{Me2N}**1**	39[d] (20)	67:33
4	**15a**	(*S,S*)-^{dMM}**1**	**50 (5)**	**96:4**
5	**15a**	(*R,R*)-^{dMM}**1**	66 (4)	69:32
6	**15b**	(*S,S*)-^{dMM}**1**	**56 (8)**	**94:6**
7	**15c**	(*S,S*)-^{dMM}**1**	**66**[e] **(5)**[f]	**97:3**
8[g]	**15b**	(*S,S*)-^{Me2N}**1Fe**	46 (4)	66/34
9[h]	**15b**	(*S,S*)-^{dMM}**1Fe**	60 (2)	48/52

[a] Unless stated, reaction conditions are catalyst (0.25 mol %), H_2O_2 (2 equiv), and pivalic acid (15 equiv) in ACOEt/CH_3CN (4:1) at room temperature. [b] Isolated yields. [c] Pivalic acid (0.35 equiv). [d] GC yield. [e] H NMR yield. Ratio β/α determined by GC, except for entry 7 which was determined by ^{1}H NMR. [f] Allylic 7-β-OH alcohol. [g] Reaction catalyzed by [Fe(CF_3SO_3)$_2$((*S,S*)-^{Me2N}PDP)]. [h] Reaction catalyzed by [Fe(CF_3SO_3)$_2$-((*S,S*)-^{dMM}PDP)],

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Supporting Information Available. Experimental details for preparation of catalysts, epoxidation reactions, and product characterization. X-ray data for (*R,R*′)-^{Me2N}**1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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