ORGANIC LETTERS

2009
Vol. 11, No. 16
3622−3625

Asymmetric Epoxidation of Olefins with Chiral Bioinspired Manganese Complexes

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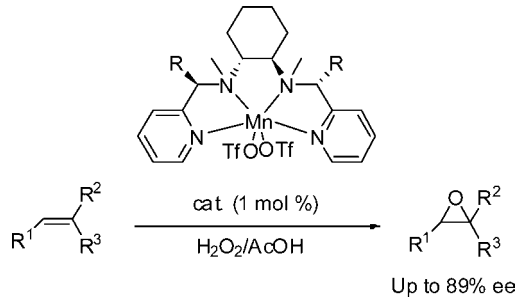
Received June 20, 2009

ABSTRACT



A novel series of chiral tetradentate N_4 ligands together with their manganese complexes have been designed and synthesized. With 1 mol % manganese catalyst loading, the enantioselective epoxidation of olefins proceeds with nearly full conversion and enantiomeric excess values of up to 89 % for the first time.

The asymmetric epoxidation of olefins is a very important organic transformation since the resulting enantiomerically pure epoxides are highly useful intermediates and building blocks.[1] Many efforts have been dedicated to the development of chiral catalysts that can perform an asymmetric epoxidation reaction effectively. The most successful examples are the chiral metal−salen complexes and their derivatives.[1,2,3] In recent years, biologically inspired tetradentate nitrogen (N_4) based ligands and their metal complexes, Fe and Mn complexes derived from *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl) ethane-1,2-diamine (mep) and (*R*,*R*)-*N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)cyclohexane-1,2-diamine (*R*,*R*-mcp), have been synthesized and utilized in the oxidation reaction.[4,5] A major breakthrough

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10.1021/ol901400m CCC: $40.75
Published on Web 07/24/2009

in the field has been done by Que and co-workers who reported highly enantioselective *cis*-dihydroxylation of alkenes with synthetic Fe complexes of N_4 ligands.[4d] Stack and co-workers recently described manganese complexes of N_4 ligands that in combination with peracetic acid (AcOOH) act as very fast and efficient epoxidation agents. Unfortunately, asymmetric version with this highly active manganese catalyst has proven to be a challenging task.[5,6] Subsequently, Costas and co-workers have demonstrated that manganese complexes with chiral tetradentate N_4 ligands derived from (*R,R*-mcp) by fusing pinene rings can promote the epoxidation reaction with modest yet remarkable enantiomeric excess.[7] Pfaltz and co-workers have prepared a series of chiral N_4 ligands containing two oxazoline rings instead of pyridine rings, and their manganese complexes only exhibit low enantioselectivities in the epoxidation reaction.[8]

Obviously, more endeavors need to be made to these biomimetic systems. As a part of continuous interest in the asymmetric oxidation,[9] we describe herein the development of a novel family of chiral Mn(II) complexes of N_4 ligands for asymmetric epoxidation of unfunctionalized olefins and enones[1d,e,10] with H_2O_2, in the presence of acetic acid. With 1 mol % catalyst loading, the enantioselective epoxidation of olefins proceeds with nearly full conversion and enantiomeric excess values of up to 89% for the first time.

Pioneering studies by Stack and co-workers have demonstrated that a 10% ee for epoxidation of vinyl cyclohexane was observed and catalyzed by [Mn^{II}(*R,R*-mcp)$(CF_3SO_3)_2$] (OTf = trifluoromethane sulfonate) with AcOOH as oxidant.[6a] On the basis of the previous research work, aromatic groups were introduced into both of the 2-pyridylmethyl positions (C7 and C7′, as shown in Figure 1, *R,R*-

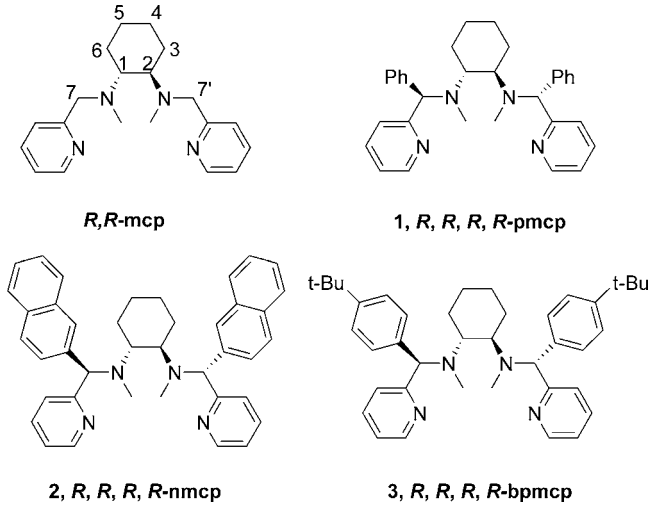


Figure 1. Chiral ligands used in this study.

mcp) of the ligand of *R,R*-mcp. To this end, several novel N_4 ligands were prepared, and corresponding manganese(II) complexes were obtained by the reactions of equimolar amounts of ligand and $Mn^{II}(OTf)_2$ in MeCN under an argon atmosphere at room temperature for 2 h.[11] The off-white crystals suitable for X-ray crystallographic analysis were afforded from MeCN/ether, formulated as [Mn^{II}(pmcp)-$(CF_3SO_3)_2$] (**4**) and [Mn^{II}(nmcp) $(CF_3SO_3)_2$] (**5**). In both structures, the ligands coordinate the manganese center in a *cis*-α topology (Figure 2).[12]

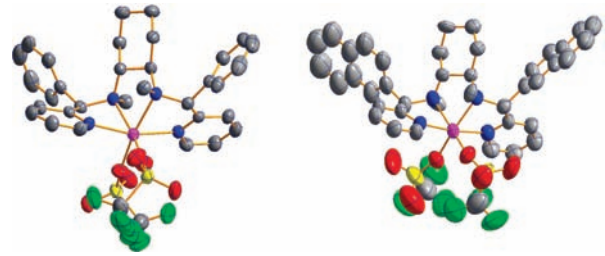
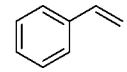
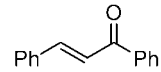


Figure 2. X-ray structures of Mn^{II} complex **4** and **5** with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms are omitted for clarity (C, gray; N, blue; O, red; F, green; S, yellow; Mn, pink).

Jacobsen et al. have found Fe^{II}(mep) with SbF_6^- counterions to be an efficient epoxidation catalyst with H_2O_2 in the presence of acetic acid (AcOH).[4a] Que et al. have determined that iron complexes of N_4 ligands catalyze in situ formation of AcOOH from H_2O_2 and AcOH.[13a] Very recently, Costas described a method for the epoxidation of olefins using H_2O_2/AcOH oxidant.[13b] In preliminary studies, we evaluated the catalytic property of these new catalysts in the asymmetric epoxidation of styrene with H_2O_2 as oxidant, in the presence of acetic acid (Table 1). All of the

Table 1. Screening of the Catalysts and Reaction Conditions[a]

entry	substrate	time	complex	yield[b]	ee[c]
1[d]		90min	**6**	46	44
2		90min	**6**	85	43
3		90min	**4**	89	46
4		90min	**5**	78	46
5		90min	**Mn^{II}(mcp)**	30	26
6		60min	**4**	90	77
7		60min	**5**	87	71
8		60min	**6**	91	78

[a] Reactions were carried out in 1.5 mL of MeCN at room temperature with 0.25 mmol of styrene or chalcone, 1 mol % catalyst, 6 equiv of H_2O_2, and 5 equiv of AcOH. [b] For styrene, GC yield; for chalcone, isolated yield. [c] For details, see Supporting Information. [d] 3 equiv of H_2O_2, 5 equiv of AcOH.

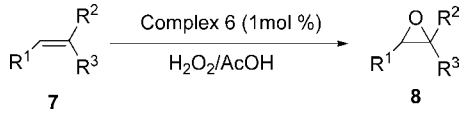
examined catalysts demonstrated excellent catalytic activity under the optimal conditions. The influence of the aromatic substituents on the enantioselectivity of the catalysis was dramatic. The complex **6** bearing 4-*t*-Bu-phenyl groups on the C7 and C7′ positions exhibited 43% ee (Table 1, entry 2). Mn^{II} complex **4** [Mn^{II}(pmcp)$(CF_3SO_3)_2$] was employed

in the asymmetric epoxidation, affording the epoxide product in an 89% yield and 46% ee (Table 1, entry 3). However, Mn^{II}(*R*,*R*-mcp) only gave rise to 26% ee in the asymmetric epoxidation of styrene (Table 1, entry 5) under the same conditions. Chalcone was also selected as a model substrate; 78% ee was observed using complex **6** as catalyst (Table 1, entry 8). This is a great improvement in enantioselectivity compared to those displayed by the system with previously reported chiral bioinspired manganese catalysts.[6−8]

Encouraged by these preliminary results, the catalysis of the enantioselective epoxidation of a variety of unfunctionalized olefins was then investigated by using complex **6** with H_2O_2/AcOH oxidant (Table 2). For most tested substrates, good epoxidation yields were achieved, and unfunctionalized olefins such as 6-cyano-2,2-dimethylchromene are generally epoxidized with higher enantioselectivities (Table 2, entry 6, up to 63% ee) than previously reported, although ee values still fall short of synthetically useful levels.[6a,7,8]

To further demonstrate the substrate scope and the potential for the asymmetric bioinspired epoxidation, the enantioselective epoxidation of a variety of α,β-unsaturated ketones was also evaluated by using complex **6** under the same conditions. As summarized in Table 3, the reactions proceeded efficiently and rapidly to give the corresponding epoxides in >80% yields with moderate to excellent enantioselectivities for most cases (70−89% ee). Clearly, the substituted groups of different electronic characters on the phenyl ring of the carbonyl side influenced the reaction activities and enantioselectivities (Table 3, entries 1−6). Substitution by the *p*-NO_2 group led to a considerable improvement, and 86% ee was obtained (Table 3, entry 3). However, the more hindered 2-naphthyl derivative could be converted to the corresponding epoxy ketone in both low yield and ee. The substituted groups on the phenyl ring of the olefin side were also investigated under the identical conditions. The highest ee values were obtained in the epoxidation of *o*-Br-substituted chalcone (Table 3, entry 9, 89% ee).

Table 2. Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by Complexes **6**[a]



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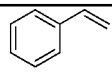
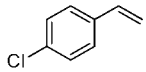
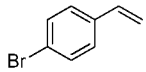
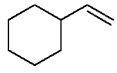
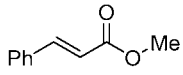
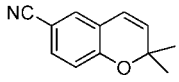
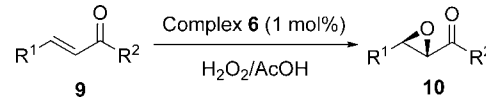
entry	substrate	yield [b]	ee [c]
1		85 (**8a**)	43
2		89 (**8b**)	43
3		85 (**8c**)	42
4		90 (**8d**)	18
5		75 (**8e**)	34
6[d]		62 (**8f**)	63

[a] Reactions were carried out in 1.5 mL of MeCN for 90 min at room temperature with 0.25 mmol of substrate, 1 mol % complex **6**, 6 equiv of H_2O_2, and 5 equiv of AcOH. [b] Epoxide yields determined by GC with an internal standard. [c] Determined by GC with a CP-Chirasil-Dex-CB column. [d] Isolated yield and ee value are determined by HPLC with a Daicel OD column.

Table 3. Asymmetric Epoxidation of α,β-Enones Catalyzed by Complexes **6**[a]



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entry	R^1	R^2	yield[b]	ee[c]
1	Ph	Ph	91 (**10a**)	78 (2*R*,3*S*)
2	Ph	*p*-MeO-C_6H_4	63 (**10b**)	76 (2*R*,3*S*)
3	Ph	*p*-NO_2-C_6H_4	82 (**10c**)	86 (2*R*,3*S*)
4	Ph	*p*-Cl-C_6H_4	89 (**10d**)	72 (2*R*,3*S*)
5	Ph	*p*-Me-C_6H_4	72 (**10e**)	80 (2*R*,3*S*)
6	Ph	2-naphthyl	52 (**10f**)	70 (2*R*,3*S*)
7	*p*-Cl-C_6H_4	Ph	89 (**10g**)	85 (2*R*,3*S*)
8	*o*-Cl-C_6H_4	Ph	87 (**10h**)	86 (2*R*,3*S*)
9	*o*-Br-C_6H_4	Ph	87 (**10i**)	89 (2*R*,3*S*)
10	*p*-Me-C_6H_4	Ph	72 (**10j**)	85 (2*R*,3*S*)
11	*p*-F-C_6H_4	Ph	94 (**10k**)	81 (2*R*,3*S*)
12	Ph	*p*-F-C_6H_4	90 (**10l**)	82
13	*p*-F-C_6H_4	*p*-Me-C_6H_4	94 (**10m**)	79

[a] Reactions were carried out in 1.5 mL of MeCN for 60 min at room temperature with 0.25 mmol of substrates, 1 mol % complex **6**, 6 equiv of H_2O_2, and 5 equiv of AcOH. [b] Isolated yield. [c] Determined by HPLC with a Daicel chiral column (for details see Supporting Information).

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All these facts clearly indicate that these novel Mn^{II} complexes of chiral N_4 ligands are capable of achieving high enantiomeric excess in the catalytic asymmetric epoxidation. By comparison of [Mn^{II}(*R*,*R*-mcp)(CF_3SO_3)$_2$] and complexes **4**−**6**, it is clear that the size of the C7 and C7′ substituents is crucial to gain high asymmetric induction. To introduce proper groups on these positions will tune the steric bulk and electronic property of the ligands and result in significant improvement in enantioselectivity.

In summary, we have successfully devised and synthesized a novel family of chiral Mn(II) complexes of N_4 ligands that exhibit rapid, highly enantioselective epoxidation of various α,β-enones under mild conditions. Furthermore, the present study indicates a conceptual strategy to improve the stereoselectivity of biologically inspired oxidation catalysis. Further studies focus on expanding the scope of this catalytic asymmetric epoxidation of olefins as well as the development of even more efficient bioinspired catalysts and on understanding the detailed reaction mechanism.

Acknowledgment. We are grateful for financial support from the Chinese Academy of Sciences and the National Natural Science Foundation of China (20873166, 20625308).

Supporting Information Available: Experimental procedures for catalyst synthesis and asymmetric epoxidation reactions, spectroscopic data for catalysts and products, and crystallographic data (cif) of complexes **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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