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The asymmetric induction and catalytic activity of new chiral Mn(III)-Schiff-base complexes with L-amino acids as steric groups

Xin-Wen Liu,[a,b] Ning Tang,[a,*] Yan-Hong Chang[b] and Min-Yu Tan[a]

[a]*College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China*
[b]*Department of Chemistry, Tianshui Normal University, Tianshui 741000, China*

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Abstract—L-Amino acids as inexpensive and readily available natural products showed significant chiral induction and stereo-directing abilities. The Mn(III)-Schiff-base complexes **3b** and **c** assembled with L-amino acid ethyl esters were found to be highly effective catalysts for the enantioselective epoxidation of conjugated olefins while the corresponding binuclear-Mn(III) complexes showed lower enantioselectivity.

1. Introduction

Catalytic reactions constitute an important tool in synthetic organic chemistry. The stereo- and chiral induction often plays the most important role in asymmetric catalysis.[1,2] While a variety of synthesized groups can serve to act as stereo-inducing groups,[3–6] developing or looking for simple and convenient chiral groups as inducing sources is more favourable due to practical and economical considerations. An ideal chiral source should be easily acquired and assembled and also possess characteristics of effectiveness and stability. Recently, a report showed that amino acid Schiff-base groups in Salen-V(IV) catalysts give a moderate directing effect for enantioselective oxidative coupling of 2-naphthols.[7] Natural L-amino acids would be ideal chiral sources, as they are inexpensive and readily available from natural materials. Surprisingly, their chiral and steric potential has not been thoroughly examined. The asymmetric epoxidation catalyzed by chiral Salen-Mn complexes is one of the most intensively studied with the results showing that the size and configuration of the C3 (3′) groups on the Salen structure play very important roles on directivity or chiral induction.[8,9] As a result, this is a suitable reaction for evaluating amino acid Schiff-base groups, which are incorporated at the C3 (3′) positions of a Salen-Mn catalyst. Previously, Katsuki et al. synthesized a series of Salen-Mn(III) complexes by introducing some complicated stereogenic groups [e.g., 1-(*p*-*tert*-butyl-phenyl)-propyl and binaphthyl groups etc.] at C3 (3′) to improve the enantioselectivity of epoxidation for olefins, particularly for *trans*-olefins.[9] This complex bearing chiral binaphthyl units has shown excellent enantioselectivity for a variety of conjugated *cis*-olefins[10] with inexpensive hydrogen peroxide being used successfully as a co-oxidant.[11] Some of these catalysts, however, are involved in more difficult syntheses, therefore, their utilization is limited.

Herein, we report a facile synthesis along with catalytic results of new Mn(III)-Schiff-base complexes bearing natural amino acid groups for the epoxidation of alkenes (Scheme 1, **3a**—**MnL^{g}Cl**, **3b**—**MnL^{a}Cl** and **3c**—**MnL^{p}Cl**). Glycine, L-alanine and L-phenylalanine were selected as representatives to be examined, because the ligand can be used to synthesize binuclear complexes with two metal ions in close proximity. One corresponding binuclear Mn(III) complex **$Mn_2L^aCl_4$ 4b** was also prepared and studied.

2. Results and discussion

As shown in Scheme 1, the synthetic route for complexes **3a**–**c** and **4b** involves two main steps: the initial preparation of chiral half-cyclic matrix **2** was carried out by condensing 2,6-diformal-4-methylphenol with (*R*,*R*)-1,2-diphenylethylene-diamine in a 2:1 molar ratio. The

* Corresponding author. Tel.: +86-931-8626264; fax: +86-931-8912582; e-mail: liuxw9391@163.com

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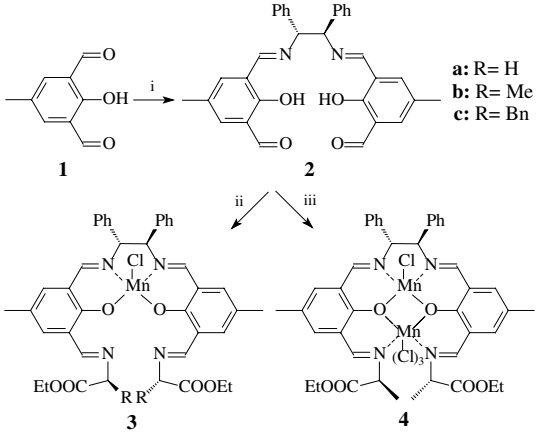


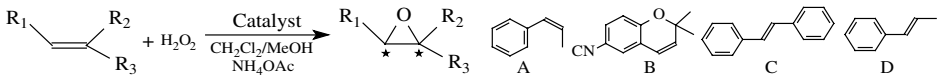
Scheme 1. Synthesis route for complexes. Reagents and conditions: (i) (*R*,*R*)-1,2-diphenylethylenediamine, CH_2Cl_2/EtOH, <10 °C. (ii), (iii) Manganese acetate, amino acid ethyl ester hydrochloride/NaOH, lithium chloride, CH_2Cl_2/EtOH, reflux.

second step was an in situ facile-step reaction of **2** with an amino acid (glycine, L-alanine or L-phenylalanine) ethyl ester hydrochloride and a metal salt in a 1:2:1 ratio to afford the chiral complexes **MnLCl** (or 1:2:2 ratio to **Mn_2LCl_4**). These complexes were characterized by microanalysis, conductance and IR spectroscopies.

We first examined the epoxidation of conjugated *cis*-alkenes using **3a**–**c** as the catalyst with inexpensive H_2O_2 as the oxidant in the presence of an ammonium acetate co-catalyst[12] at 2 °C in a 1:1 CH_2Cl_2–CH_3OH. Some representative results are shown in Table 1 (entries 1–6). The catalytic reactions proceeded smoothly to afford the corresponding epoxides with high enantiometric excesses of >80% and yields of >77%. The best result of 95% ee was observed in the epoxidation of the electron deficient cyano-chromene with **3c** as the catalyst (entry 6). Compounds **3b** and **3c**, which contained bulkier chiral L-amino acid groups did not alter much the ee's and yields (entries 2–3 and 5–6), which were slightly higher than those of **3a**. It is worth noting that the reaction products of *cis*-β-methyl-styrene were a mixture of the corresponding *cis*- and *trans*-epoxides with the *cis*/*trans* ratios being increased from 8.2 to 21.6 following the catalyst order from **3a**, **3b** to **3c**. This showed that the type and size of amino acid side arms at the C3 (3′) positions of the catalyst obviously influenced the form and *cis*/*trans* ratio of the epoxides of *cis*-β-methyl-styrene.

In the epoxidation of *trans*-olefins, the catalytic effects of the three complexes were obviously different (Table 1, entries 7–12). Surprisingly, complexes **3b** and **3c** showed much higher enantioselectivities than complex **3a** bearing achiral glycine esters (entries 7 and 10). The results of 63–66% ee's and 69–72% yields of the epoxide of the *trans*-diphenylethene were higher than the best value of 62% ee and 65% yield by using Katsuki's catalysts reported.[9] Interestingly, **3b** showed higher enantioselectivity than **3c** in the epoxidation of *trans*-diphenylethene. The latter, in contrast, gave a slightly better ee for *trans*-phenylpropene than the former though there were similar levels of yields (entries 8–9 and 11–12).

Table 1. [a]Epoxidation of nonfunctionalized alkenes using complexes **3a**–**c** as catalysts



Entry	Alkene[b]	Complex	Time (h)	Yield[c] (%)	Ee[d] (%)	Configuration[e]
1	A	**3a (MnL^{g}Cl)**	2	78 (8.2:1)[f]	80[g]	1*R*,2*S*
2	A	**3b (MnL^{a}Cl)**	2	77 (17.5:1)[f]	82[g]	1*R*,2*S*
3	A	**3c (MnL^{p}Cl)**	2	80 (21.6:1)[f]	83[g]	1*R*,2*S*
4	B	**3a (MnL^{g}Cl)**	1.5	86	88	3*R*,4*R*
5	B	**3b (MnL^{a}Cl)**	1.5	92	93	3*R*,4*R*
6	B	**3c (MnL^{p}Cl)**	1.5	91	95	3*R*,4*R*
7	C	**3a (MnL^{g}Cl)**	3	61	43	*R*,*R*
8	C	**3b (MnL^{a}Cl)**	3	72	66	*R*,*R*
9	C	**3c (MnL^{p}Cl)**	3	69	63	*R*,*R*
10	D	**3a (MnL^{g}Cl)**	4	47	36	1*R*,2*R*
11	D	**3b (MnL^{a}Cl)**	4	52	53	1*R*,2*R*
12	D	**3c (MnL^{p}Cl)**	4	54	56	1*R*,2*R*
13	B	**3c′ (MnL′^{p}Cl)**	1.5	87	90	3*S*,4*S*
14	C	**3a′ (MnL′^{g}Cl)**	3	47	38	*S*,*S*
15	C	**3b′ (MnL′^{a}Cl)**	3	56	52	*S*,*S*
16	C	**3c′ (MnL′^{p}Cl)**	3	57	55	*S*,*S*

[a] Reactions were carried out in CH_2Cl_2/MeOH (1:1) at 2 °C using 30% H_2O_2 as oxidant and NH_4OAc as the co-catalyst with a molar ratio of substrate:catalyst:NH_4OAc:H_2O_2=1:0.05:0.8:3.

[b] A=*cis*-β-methyl-styrene; B=6-cyano-2,2-dimethyl chromene; C=*trans*-diphenylethene; D=*trans*-β-methyl-styrene.

[c] Determined on GC.

[d] Determined by HPLC with a chiral OD-H pipe.

[e] Determined by comparison with the literature data.

[f] Values in parentheses were the ratios of the corresponding *cis*- and *trans*-epoxides.

[g] Ee (%) for *cis*-epoxide.

Table 2. Epoxidation of nonfunctionalized alkenes using dinuclear-Mn(III) complex **4b** as catalyst[a]

Entry	Alkene	Complex	Time (h)	Yield[b] (%)	Ee[c] (%)	Configuration[d]
1	A	**4b** ($\mathbf{Mn_2L^aCl_4}$)	2	65 (5.0:1)[e]	51[f]	1*R*,2*S*
2	B	**4b** ($\mathbf{Mn_2L^aCl_4}$)	1.5	82	69	3*R*,4*R*
3	B	**4b** ($\mathbf{Mn_2L^aCl_4}$)	3	84	67	3*R*,4*R*
4[g]	B	**4b** ($\mathbf{Mn_2L^aCl_4}$)	3	83	65	3*R*,4*R*
5	C	**4b** ($\mathbf{Mn_2L^aCl_4}$)	3	46	31	*R*,*R*
6[h]	C	**4b** ($\mathbf{Mn_2L^aCl_4}$)	3	50	27	*R*,*R*
7	D	**4b** ($\mathbf{Mn_2L^aCl_4}$)	5	38	18	1*R*,2*R*

[a] Reactions were carried out in CH_2Cl_2/MeOH (1:1) at 2 °C using 30% H_2O_2 as oxidant and NH_4OAc as co-catalyst with a molar ratio of substrate:catalyst:NH_4OAc:H_2O_2 = 1:0.05:0.8:3.
[b] Determined on GC.
[c] Determined by HPLC with a chiral OD-H column.
[d] Determined by comparison with the literature data.
[e] Value in parentheses was the ratio of the corresponding *cis*- and *trans*-epoxides.
[f] The number was the ee (%) for *cis*-epoxide.
[g] Reaction was carried out with NMO as co-catalyst in CH_3CN.
[h] Reaction was carried out at 25 °C.

Obviously, the chiral amino acid groups (L-alanine and L-phenylalanine), when compared with the achiral glycine, showed better stereo-effects as well as chiral inducing functions. This effect of two kinds of amino acid side arms was also observed when the (*S*,*S*)-diphenylethylene-diamine was used instead of the (*R*,*R*)-in catalysts **3a**–**c** to form diastereomeric catalysts **3a**′–**c**′ (Table 1, entries 13–16).

The above results fully indicate that the directivity of L-amino acid esters armed at the C3 (3′) of Mn(III)-complex **3** is very similar to the *tert*-butyl groups used in chiral Jacobsen's catalysts.[2,13] Their chiral induction ability in the epoxidation for *trans*-olefins is a little higher (e.g., L-phenylalanine ethyl ester) than that of the more complicated groups bonded at the C3 (3′) positions in Salen catalysts.[9] Previous studies of Schiff-base complexes have shown lower ee's in the asymmetric epoxidation of *trans*-olefins; however this study resulted in complexes **3b** and **c** showing higher levels of asymmetric induction. One possible reason is that the two closer and bulkier amino-acid-Schiff-base groups on these complexes may be forced to produce torsion due to stereo-repulsion. This torsion could then enhance the stereo-selectivity of the whole ligand, increasing the steric effect between the C3 (3′) groups and the substrate. This would result in improved enantioselectivity of the epoxides.

Under similar reaction conditions, the catalytic activity of the binuclear Mn(III)-catalyst **4b** was then investigated (Table 2). Using **4b** as the catalyst unfortunately meant that the enantioselectivity of the corresponding epoxides were dramatically decreased; for *trans*-olefins the ee's were especially poor (Table 2, entries 5–7). The yields were also lower than using mono-nuclear catalyst **3b** whether *cis*- or *trans*-olefins. We attempted to improve the catalytic activity of the binuclear catalyst by changing the reaction conditions but to no effect. The results indicate that the binuclear Mn(III) complexes are less efficient epoxidation catalysts than the mono-nuclear ones.[14] One possible explanation is that the stereo-electronic effect of two active-Mn species too close together limits the formation of Mn(V)=O intermediate. It should also be noted that a second manganese ion could induce a conformational change around the original Salen skeleton in the binuclear Schiff-base complex so that the reactivity of Mn(V)=O species and enantioselectivity would be affected. It has been demonstrated that the Salen ligand is readily flexible[15] and its non-planar conformation significantly contributes to high asymmetric induction by Mn(III)-Salen epoxidation catalysts.[10] The more rigid structure of the binuclear catalysts may influence the effective stereo-chemical communication with oncoming substrates,[13] that is, the conformational inflexibility of the amino acid groups on the binuclear complex may impede their inducing function. Conversely, this brings to light the important role played by L-amino acid groups on asymmetric inductivity in mono-nuclear complexes **3b** and **c**.

3. Conclusion

In conclusion, a new type of chiral Mn-Schiff-base complexes bearing amino acid ethyl ester has been developed by a facile stepwise procedure. These complexes have been successfully used for the first time in the asymmetric epoxidation of unfunctionalized alkenes **3b** and **c** showing highly chiral inductivity and catalytic activity. Through epoxidation studies, the significant stereo- and chiral-inducing roles played by the natural L-amino acid groups have been revealed. The studies may offer the opportunity for developing new stereo- and chiral groups. The inherent advantages also include readily available and selectable chiral/inductive groups, as well as facile preparation. We believe that the natural L-amino acids may also be effective as chiral groups with directing effects in other asymmetric reactions by choosing and assembling rationally.

4. Experimental

^{1}H NMR spectra were obtained at 200 MHz on a Bruker DRX-200 spectrometer. IR spectra were recorded

on a Nicolet NEXUS 670 FT-IR spectrometer. FAB-MS was acquired on a MASPEC II System mass spectrometer. Elemental analyses were performed on an Elementary VarioEL instrument in the Center of Analysis and Test. TLC was conducted on glass plates coated with silica gel $60F_{254}$. The chiral 1,2-diphenylethylenediamine and amino acid ethyl ester hydrochlorides were purchased from the Likai Chiral Technique Company Ltd. 2,6-Diformal-4-methylphenol was prepared with reference to literature.[16] Other solvents and chemicals were obtained from commercial sources.

4.1. Synthesis of previous ligand 2[17]

A solution of (*R*,*R*)-**1**,2-diphenylethylenediamine (0.01 mol) in EtOH was slowly added to 5-methyl-1,3-diformylalicylaldehyde (0.022 mol) in CH_2Cl_2 with stirring at <10 °C. The reaction was kept for an additional 5 h. The resulting solution, upon concentration, precipitated out the crude solid. The yellow solid was washed with alcohol and ether and purified by silica gel column chromatography to afford **2**. Yield 68%. ^1H NMR ($CDCl_3$): δ ppm 2.21 (s, 6H), 4.58 (s, 2H), 7.21 (b s, 10H), 7.41 (d, 2H), 7.64 (d, 2H), 8.44 (s, 2H), 9.96 (s, 2H), 13.86 (b s, 2H exchangeable with D_2O). FAB-MS: M+1 505.74 (FM 504). Anal. Calcd for $C_{32}H_{28}N_2O_4$: C, 76.17; H, 5.59; N, 5.55%. Found: C, 76.43; H, 5.67; N, 5.32%.

4.2. Synthesis of complexes 3a–c and 4b

Synthesis of amino acid Schiff base complexes were carried out with reference to literature.[14,18] Manganese acetate (0.001 mol in EtOH) was added to a solution of Schiff base **2** (0.001 mol) in CH_2Cl_2 under an inert atmosphere, refluxing for 2 h. A solution of amino acid ethyl ester hydrochloride (0.0021 mol) and NaOH (0.0021 mol) in EtOH was then added with stirring, and continuously refluxed for an additional 3–4 h. Lithium chloride (0.006 mol) was added and the mixture stirred for a further 2 h while being exposed to air. The solvent was removed and the residue extracted with dichloromethane. The extract was washed with water, brine and dried over sodium sulfate. On partial removal of the solvent and the addition of petroleum ether (30–60 °C), the desired chiral complexes precipitated from solution. The mixture was filtered and the filter cake dried to afford a dark brown powder.

Compound **3a** was prepared from glycine ethyl ester (yield 83%). Anal. Calcd for $C_{40}H_{40}ClMnN_4O_6\cdot H_2O$: C, 60.50; H, 5.42; N, 7.17; Mn, 7.03%. Found: C, 60.65; H, 5.52; N, 6.98; Mn, 7.27%. IR (KBr): 3428, 3042, 3008, 2957, 2905, 2867, 1735, 1619, 1593, 1538, 1438, 1382, 1306, 1266, 1047, 829, 767, 705 cm^{-1}. Λ_M (CH_3CN): 13 mho cm^{-1} mol^{-1}.

Compound **3b** was prepared from L-alanine ethyl ester (yield 78%). Anal. Calcd for $C_{42}H_{44}ClMnN_4O_6\cdot H_2O$: C, 62.34; H, 5.73; N, 6.92; Mn, 6.79%. Found: C, 62.57; H, 5.59; N, 6.80, Mn, 6.61%. IR (KBr): 3430, 3040, 3008, 2951, 2906, 2867, 1737, 1621, 1596, 1538, 1435, 1381, 1310, 1267, 1050, 833, 746, 698 cm^{-1}. Λ_M (CH_3CN): 15 mho cm^{-1} mol^{-1}.

Compound **3c** was prepared from L-phenylalanine ethyl ester (yield 75%). Anal. Calcd for $C_{54}H_{52}ClMnN_4O_6\cdot H_2O$: C, 67.46; H, 5.66; N, 5.83; Mn, 5.71%. Found: C, 67.81; H, 5.48; N, 5.93, Mn, 5.54%. IR (KBr): 3430, 3060, 3038, 3007, 2947, 2906, 2866, 1737, 1620, 1602, 1521, 1472, 1435, 1381, 1267, 1048, 830, 757, 701 cm^{-1}. Λ_M (CH_3CN): 8 mho cm^{-1} mol^{-1}.

Compound **4b** was synthesized similar to **3b** except additional 0.001 mol manganese acetate in EtOH was added under reflux before lithium chloride was added. Yield 82%. Anal. Calcd for $C_{42}H_{44}Cl_4Mn_2N_4O_6$: C, 52.96; H, 4.66; N, 5.88; Mn, 11.54%. Found: C, 52.75; H, 4.62; N, 5.81; Mn, 11.77%. IR (KBr): 3012, 2947, 2866, 1735, 1618, 1593, 1540, 1433, 1381, 1323, 1266, 1047, 838, 767, 710 cm^{-1}. Λ_M (CH_3CN): 2 mho cm^{-1} mol^{-1}.

4.3. General procedure for epoxidation reaction

Enantioselective epoxidation reaction was carried out according to the reported procedure.[12] To a cooled (2 °C) solution of catalyst **3** (5.0 mol %), substrate (0.5 mmol) and NH_4OAc (0.4 mmol) in dichloromethane/methanol was added a pre-cooled solution of 30% H_2O_2 (1.5 mmol) in four portions during reaction. The mixture was stirred at 2 °C and the reaction monitored by TLC. After completion of the reaction, the mixture was diluted with dichloromethane and water. The organic phase was separated, washed with saturated NaCl solution, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (eluent hexane/*iso*-C_3H_7OH) to give the corresponding epoxide. The ee of the epoxide was determined by HPLC with a chiral OD-H pipe.

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