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The Mn(Salen)-catalyzed oxidative kinetic resolution of secondary alcohols: reaction development and scope

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ABSTRACT

A series of chiral Mn(Salen) complexes have been synthesized and submitted to the kinetic resolution of secondary alcohols bearing a large hindrance in the biphasic system, which is composed of water and CH_2Cl_2. After evaluating the appropriate complex, additive, and other conditions, chiral secondary alcohols were obtained with enantiomeric excesses of up to 98.6% in 6 min.

1. Introduction

Enantiomerically pure secondary alcohols are pivotal compounds in organic synthesis, and are represented in many important target molecules, intermediates, and reagents.[1] They have been prepared by many methods, including asymmetric hydrogenation of prochiral ketones catalyzed by metal complexes;[2] however, the oxidative kinetic resolution (OKR) of racemic alcohols to obtain optically active alcohols is also an attractive and practical method.[3,4]

Recently, we have reported a convenient OKR of racemic secondary alcohols catalyzed by chiral Mn(salen) catalysts together with the cooxidant diacetoxyiodobenzene ($PhI(OAc)_2$) in water or biphasic system.[5,6] Although we have successfully built a system for the oxidative kinetic resolution, and the values of enantiomeric excess for a great deal of secondary alcohols can reach >99.9%, the substrate scope remains to be extended. We found that when the small substituents in secondary alcohols were made to change from methyl to ethyl or other large groups (Fig. 1), the enantiomeric excesses value decreased sharply.[5a] As a result, we envisioned that the substituents on the Mn(salen) catalysts may play a crucial role in this change. Therefore, we synthesized a series of chiral Mn(salen) complexes with diverse substituents and different diamine backbones, and evaluated their abilities in the OKR of racemic secondary alcohols.

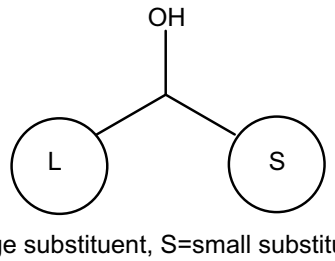

Figure 1. Structure of the secondary alcohol.

2. Results and discussion

2.1. Synthesis of the chiral Mn(Salen) complexes

As shown in Figure 2, a variety of chiral Mn(salen) complexes with different substitutes on the aromatic rings and diamine backbones were prepared by the procedure reported in the literature.[5a,7]

2.2. OKR reaction of secondary alcohols

These chiral Mn(salen) complexes, based on different chiral diamine backbones and bearing various groups on the aromatic rings, were then evaluated for the OKR with racemic 1-phenyl-1-propanol as a representative substrate. In a typical experiment, as we reported previously,[5] the reactions were carried out in a 1 equiv of 1-phenyl-1propanol and 0.7 equiv of $PhI(OAc)_2$ with 2 mol % of chiral Mn(salen) complexes and 8 mol % of $N(C_4H_9)_4Br$ at room temperature for 0.5 h (Table 1). Among all the tested Mn(salen) complexes, complex **1c** showed the highest enantioselectivity, and only 24.2% ee was observed (Table 1, entry 3).[8] From the results summarized in Table 1, we can conclude that the *tert*-butyl groups on the 5,5′-positions of salicylaldehyde parts are very important for OKR. At the same time, the chiral diamine backbone also plays a critical role in the OKR of the secondary alcohol. When

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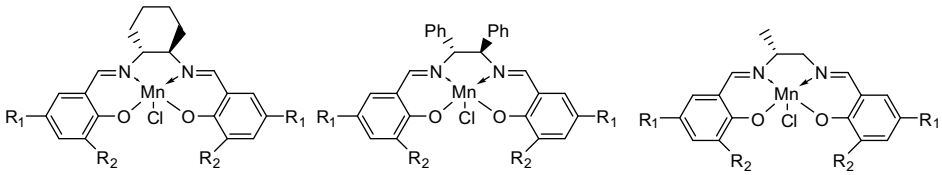
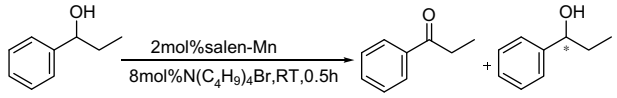


1a R_1=R_2=*t*-Bu; **2a** R_1=R_2=*t*-Bu; **3a** R_1=R_2=*t*-Bu;
1b R_1=*t*-Bu, R_2=CH_3 **2b** R_1=*t*-Bu, R_2=CH_3 **3b** R_1=*t*-Bu, R_2=H
1c R_1=*t*-Bu, R_2=H **2c** R_1=*t*-Bu, R_2=H
1d R_1=H, R_2=*t*-Bu **2d** R_1=H, R_2=*t*-Bu
1e R_1=CH_3,R_2=Adamantyl

Figure 2. The various chiral Mn(Salen) complexes.

Table 1
Screening of Mn(salen) complex for the OKR of racemic 1-phenyl-1-propanol[a]



Entry	Catalyst	Conversion[b] (%)	ee[c] (%)	k_{rel}[d]
1	**1a**	61.1	12.2	1.30
2	**1b**	54.1	11.2	1.33
3	**1c**	59.0	24.2	1.73
4	**1d**	54.3	3.4	<1.1
5	**1e**	51.6	0	
6	**2a**	46.9	11.5	1.44
7	**2b**	48.6	0	
8	**2c**	63.2	1.7	<1.1
9	**2d**	44.0	2.9	<1.1
10	**3a**	53.3	3.5	<1.1
11	**3b**	62.3	12.9	1.30

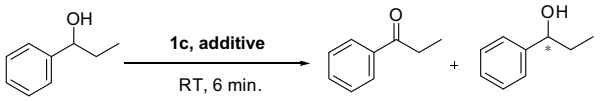
[a] Reaction was carried out at room temperature for 0.5 h with catalyst (2 mol %), $N(C_4H_9)_4Br$ (8 mol %), 1-phenyl-1propanol (0.25 mmol), $PhI(OAc)_2$(0.175 mmol), and H_2O(1 ml), CH_2Cl_2 (0.5 ml).
[b] Determined by GC using an internal standard.
[c] Determined by GC on a CP-Chirasil-Dex CB Capillary column.
[d] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$.

(1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine was used as the diamine backbone, although *tert*-butyl groups were at the 5,5′-positions of the salicylaldehyde regions, only 1.7% ee was observed (Table 1, entry 8).

Based on these results, we decided to choose complex **1c** as the catalyst for OKR of racemic 1-phenyl-1-propanol to evaluate other reaction conditions (Table 2). Initially, we evaluated the influence of the additive (Fig. 3). Replacing $N(C_4H_9)_4Br$ **4** by KBr **5** as an additive, the reaction time was reduced from 30 min to <10 min to attain about 50% conversion. It was observed that the molar ratio of KBr **5** and that of the catalyst were promoted from 4 to 8, the enantiomeric excess value rose from 11.3% to 56.8% (Table 2, entries 3–5). No increase in the enantiomeric excesses value was detected, when we continued to enhance the loading of KBr **5** (Table 2, entries 6 and 7). The same result did not occur when using 8 mol % of additive **4** and 1 mol % of **1c** (Table 2, entry 2). We next attempted different quaternary ammoniums with a bromonium ion. We found that most of the quaternary ammoniums tested could enhance the enantiomeric excess values, and the largest increase occurred with additive **8** with up to 68.0% ee (Table 2, entry 10). This phenomenon illustrates that the positive ion of the additive influences the reaction results.

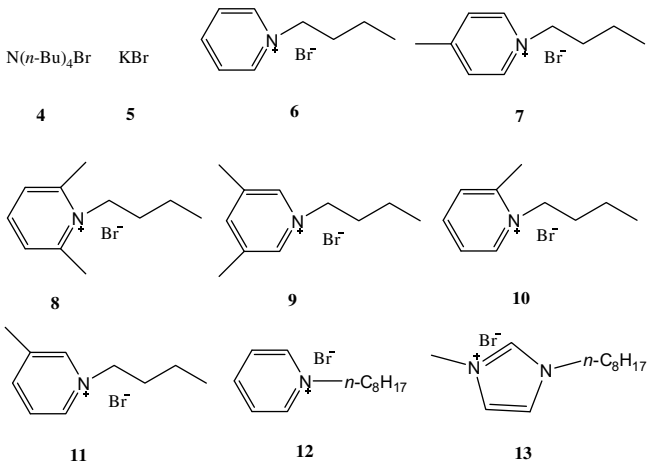
As can be seen in Table 2 (entry 16), an increase in the amount of the $PhI(OAc)_2$ from 0.35 mmol to 0.4 mmol improved the enantiomeric excess from 68.0% to 74.0%, and also improved the conversion. An increase in the concentration of the substrate and catalyst resulted in an improvement of the enantiomeric excess from 74.0% to 85.4% (Table 2, entry 17). Based on these results,

Table 2
Evaluation of the kinetic resolution of 1-phenyl-1-propanol under different reaction conditions[a]



Entry	Additive	Additive loading (mol %)	CH_2Cl_2 (ml)	H_2O (ml)	Conv.[b] (%)	ee[c] (%)	k_{rel}[g]
1	**4**[d,e]	8	1	2	59.0	24.2	1.73
2	**4**[e]	8	1	2	60.5	8.4	1.20
3	**5**	4	1	2	44.4	11.3	1.47
4	**5**	6	1	2	60.7	46.5	2.83
5	**5**	8	1	2	63.8	56.8	3.28
6	**5**	10	1	2	63.8	56.6	3.28
7	**5**	12	1	2	66.0	56.4	3.02
8	**6**	8	1	2	68.6	63.6	3.26
9	**7**	8	1	2	68.2	64.4	3.36
10	**8**	8	1	2	68.0	68.0	3.67
11	**9**	8	1	2	64.6	61.6	3.58
12	**10**	8	1	2	67.6	61.7	3.24
13	**11**	8	1	2	68.3	67.3	3.58
14	**12**	8	1	2	65.0	32.3	1.87
15	**13**	8	1	2	64.4	35.1	2.00
16	**8**[f]	8	1	2	73.7	74.0	3.43
17	**8**[f]	8	0.5	1	77.7	85.4	3.88

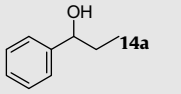
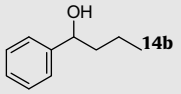
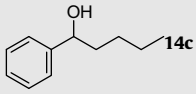
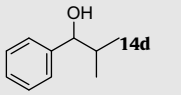
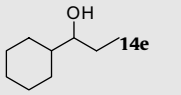
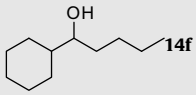
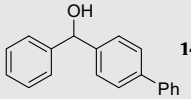
[a] Reaction conditions: 0.5 mmol of substrate, 0.35 mmol of $PhI(OAc)_2$, 1 mol % of **1c** as catalyst, CH_2Cl_2 and H_2O as solvent, room temperature for 6 min.
[b] Determined by GC using an internal standard.
[c] Determined by GC on a CP-Chirasil-Dex CB Capillary column.
[d] 2 mol % of **1c** as catalyst was used.
[e] The reaction time was 30 min, when $N(n\text{-}Bu)_4Br$ was selected as an additive.
[f] 0.4 mmol of $PhI(OAc)_2$ was used.
[g] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$.



4 5 6 7 8 9 10 11 12 13

Figure 3. The additives used in the reaction.

Table 3
OKR of secondary alcohols[a]

Entry	Substrate	Conversion[b] (%)	ee[c] (%)	k_{rel}[g]
1	 **14a**	77.7	85.4	3.88
2	 **14b**	77.1	84.8	3.90
3	 **14c**	76.3	82.6	3.80
4	 **14d**	72.1	72.5	3.51
5	 **14e**	77.8	98.6	7.05
6[d]		69.5	92.4	7.05
7[e]		59.3	72.7	6.23
8	 **14f**	77.8	98.4	7.05
9[d]		69.6	95.3	8.15
10[e]		57.7	70.9	6.46
11	 **14g**	55.0[f]	11.0	1.32

[a] Reaction conditions: 1 mol % catalyst **1c**, 8 mol % **8**, 0.5 mmol substrate, 0.4 mmol $PhI(OAc)_2$, 0.5 ml CH_2Cl_2, 1 ml H_2O, room temperature for 6 min.
[b] Conversion determined by GC using an internal standard.
[c] Determined by GC on a CP-Chirasil-Dex CB Capillary column or by HPLC on a Daicel Chiral OD column.
[d] 0.35 mmol $PhI(OAc)_2$ was used.
[e] Reaction condition: 1 mol % Jacobsen's catalyst **1a**, 8 mol % **5**, 0.5 mmol substrate, 0.35 mmol $PhI(OAc)_2$, 1 ml CH_2Cl_2, 2 ml H_2O, room temperature for 6 min.
[f] Isolated conversion.
[g] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$.

the optimal conditions for OKR of 1-phenyl-1-propanol were as follows: 0.5 mmol substrate was dissolved in 0.5 ml CH_2Cl_2 and 1 ml H_2O in the presence of 1 mol % catalyst **1c** and 8 mol % of additive **8** with 0.4 mmol $PhI(OAc)_2$ as cooxidant.

After the optimal conditions for OKR of 1-phenyl-1-propanol were established, this methodology was employed to other secondary alcohols. The OKR results are shown in Table 3. The OKR of **14a**, **14b**, and **14c** was mediated by complex **1c** to afford the corresponding chiral secondary alcohols with 85.4%, 84.8%, and 82.6% enantiomeric excesses, respectively (Table 3, entries 1–3). Although the ee values of **14e** and **14f** exceeded 70%, when Jacobsen's catalyst **1a** was employed as the catalyst, it could attain >90% ee when **1c** was selected as the catalyst with 0.35 mmol $PhI(OAc)_2$ as the cooxidant. When the amount of the $PhI(OAc)_2$ was 0.4 mmol, the ee values of the residues reached up to >98%. Unfortunately, the system for OKR of secondary alcohols was still not suitable for substrates such as **14g**, with only 11.0% ee being detected.

3. Conclusion

OKR with chiral Mn(salen) complexes is a powerful tool for the preparation of enantioenriched secondary alcohols. We have established an improved edition of the OKR of secondary alcohols catalyzed by chiral Mn(salen) complexes, which is more effective for many secondary alcohols bearing large groups. Under the optimal conditions, the OKR of 1-phenyl-1-propanol and 1-cyclohexyl-1-propanol can attain 85.4% ee and 98.6% ee, respectively. Efforts to further enhance reactivity and selectivity in these oxidations are currently ongoing.

4. Experimental

4.1. General

Solvents were of analytical grade and used as received. $PhI(OAc)_2$, tetrabutylammonium bromide, KBr, racemic *trans*-1,2-diaminocyclohexane, (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine, and (*R*)-(−)-propylenediamine dihyrochloride were purchased from commercial sources and were used as received. Quaternary ammoniums were synthesized from the corresponding pyridine or *N*-methyl-imidazole and bromoalkanes. Secondary alcohols which were used in the present study were prepared by the reduction of the corresponding ketones with $NaBH_4$. (1*R*,2*R*)-Jacobsen's catalyst was purchased from ACROS, and other chiral Mn(salen) complexes were prepared as the procedures reported in the literature.[5a,7] GC analyses were performed on a HP6890 instrument with a CP-Chirasil-Dex CB Capillary column to determine the enantiomeric excesses. NMR spectra were recorded on a Bruker Avance III (400 MHz) operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR).

4.2. General procedure for the kinetic resolution of racemic secondary alcohols

A mixture of the substrate (0.5 mmol), catalyst (0.005 mmol), KBr (0.04 mmol), water (1 ml), and CH_2Cl_2 (0.5 ml) was stirred in a 5 ml tube for a few minutes at room temperature. The cooxidant $PhI(OAc)_2$ (0.4 mmol) was then added, and the reaction mixture was stirred for a further 6 min. The products were extracted with diethyl ether, when the reaction was complete. The conversion and enantiomeric excesses were determined by GC. ESI-MS spectra were recorded on a Waters ZQ4000 mass spectrometer. The HPLC chiral column used was a Chiralcel OD-H for determination of the enantiomeric excesses.

4.3. GC and HPLC analysis for determination of the enantiomeric excesses

The enantiomeric excess of **14a** shown in Table 3 was analyzed by GC/FID in a chiral capillary column (CP-Chirasil-Dex CB Capillary column). GC conditions: Injector 250 °C; detector: 250 °C; pressure: 6.9 MPa. Column temperature: 80 °C, 10 °C/min up to 170 °C.

Retention times for **14a**: [t_{14a1} = 19.075 min, t_{14a2} = 19.314 min].

GC conditions of **14b**, **14c**, and **14d**: Injector 250 °C; detector: 250 °C; pressure: 6.9 MPa. Column temperature: 120 °C.

Retention times for **14b**: [t_{14b1} = 25.978 min, t_{14b2} = 26.476 min].

Retention times for **14c**: [t_{14c1} = 42.036 min, t_{14c2} = 43.887 min].

Retention times for **14d**: [t_{14d1} = 25.182 min, t_{14d2} = 25.708 min].

GC conditions for **14e** and **14f**: Injector 250 °C; detector: 250 °C; pressure: 6.9 MPa. Column temperature: 60 °C, 2 °C/min up to 120 °C, final time: 10 min. Then 10 °C/min up to 150 °C, final time: 2 min.

Retention times for **14e**: [t_{14e1} = 34.485, t_{14e2} = 34.811].

Retention times for **14f**: [t_{14f1} = 45.995, t_{14f2} = 46.252].

The ee value of **14g** was determined by HPLC on a Daicel Chiral OD column. Hexane/*i*-PrOH = 95:5, 0.8 ml/min, 254 nm, 2 °C.

Acknowledgments

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8. Ligand **1c**, (*R*,*R*)-*N*,*N*′-bis(5-*tert*-butyl-salicylidene)-1,2-cyclohexanediamine: $[\alpha]_D^{20} = -206$ (*c* 0.0142, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 13.10 (s, 2H), 8.19 (s, 2H), 7.21–7.17 (m, 2H), 7.05 (s, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 3.24–3.20 (m, 2H), 1.84–1.78 (m, 4H), 1.64–1.62 (m, 2H), 1.41–1.36 (m, 2H) 1.16 (s, 18H); ^{13}C NMR: 163.9, 157.5, 140.2, 128.4, 126.9, 117.2, 115.2, 71.8, 33.0, 32.2, 30.5, 23.2; Complex **1c:** ESI-MS: *m*/*z* 487.6 $[M-Cl]^+$.