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Short Communication

Enantioselective oxidation of racemic secondary alcohols catalyzed by chiral Mn(III)-salen complex with sodium hypochlorite as oxidant

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ABSTRACT

Chiral Mn(III)-salen complex catalyzed oxidative kinetic resolution (OKR) of secondary alcohols has been achieved with cheap and easily available sodium hypochlorite (NaClO) as oxidant. The novel protocol is very efficient for the OKR of a variety of secondary alcohols at room temperature.

1. Introduction

Enantiomerically pure secondary alcohols are useful chiral auxiliaries and intermediates in the pharmaceutical, agrochemical, and fine chemical industries [1–3]. Generally, they have been prepared by many methods, including asymmetric hydrogenation of prochiral ketones catalyzed by metal complexes [4,5], enzymatic kinetic resolution of racemic secondary alcohols through acylation–deacylation reactions [6], and nonenzymatic kinetic resolution [7]. Among the known processes, the oxidative kinetic resolution (OKR) of racemic alcohols to obtain enantioenriched alcohols is an attractive and efficient method [8–17]. Many catalysts or catalytic systems with excellent or good resolution results, including (−)-sparteine-Pd(II), sparteine analogues-Pd(II), N-heterocyclic carbine(NHC)-Pd(II), chiral difunctional-Ir complexes, chiral(ON)-Ru(salen) complexes and chiral Mn(III)-salen complexes, have been developed [18]. The OKR of alcohols with chiral Mn(III)-salen complexes as catalysts and (diacetoxyiodo) benzene ($PhI(OAc)_2$) as terminal oxidant in the presence of potassium bromide was first established by Xia et al. in 2003 [19–22]. The system for the OKR of alcohols has the advantages of easy availability and handling of the chiral Mn(III)-salen complexes. However, it also has the disadvantage of using stoichiometric $PhI(OAc)_2$ as oxidant which is poor in atom economy, very expensive and unfriendly to the environment. Recently, N-bromosuccinimide (NBS) was used as oxidant to replace $PhI(OAc)_2$ in the chiral Mn(III)-salen complex catalyzed OKR of alcohols and proved very efficient for the oxidative kinetic resolution of a variety of secondary alcohols, including ortho-substituted benzylic alcohols [23,24].

Corey and his co-workers [25] made detailed investigations on the mechanism of Xia's system for the OKR of alcohols. Some of the salient features of the proposed mechanism are as follows: (1) A positive bromine species Br_2 or HOBr is generated under the reaction conditions by oxidation of bromide ion with $PhI(OAc)_2$. (2) It is the positive bromine species that oxidizes the Mn(III)-salen complex to a dibromo-Mn(V) species. (3) The dibromo-Mn(V) species enantioselectively converts one enantiomer of the racemic alcohols to a ketone and left another alcohol. These conclusions are supported by the facts that $PhI(OAc)_2$ and KBr can be replaced by Br_2 or HOBr as the stoichiometric oxidant in the enantioselective oxidation. Although highly enantioselective oxidations can be carried out with Br_2 or HOBr as stoichiometric oxidant instead of $PhI(OAc)_2$, using stoichiometric Br_2 or HOBr as the oxidant will suffer from the inherent disadvantages of low atom efficiency (less than 50%) of bromine and environmental pollution due to one equivalent of HBr as by-product being produced, and inconvenience in use from the perspective of synthesis. In light of the oxybromination reaction developed recently [26–29] and Corey's mechanism about Xia's system for the OKR of alcohols, we envisioned a new system with catalytic amount of Br_2 as cycling agent and stoichiometric NaClO as oxidant for the OKR of alcohols catalyzed by the Jacobsen's chiral Mn(III)-salen complex [30] (Fig. 1) in the biphasic CH_2Cl_2/H_2O medium in the presence of KOAc. Herein, we report the successful resolution examples by employing the cheap and convenient system.

2. Experimental

2.1. Materials and apparatus

Hydrogen peroxide and sodium hypochlorite were obtained from Tianjin Fuchen Chemical Reagent Factory, China. All the chemicals

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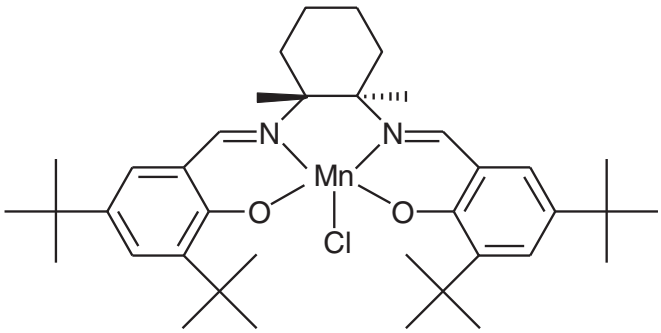


Fig. 1. Structure of Jacobsen's chiral Mn(III)-salen complex.

were used as received. The secondary alcohols were obtained from Alfa Aesar China (Tianjin) Co., Ltd. Samples were analyzed on a Shandong Lunan Ruihong Gas Chromatograph (SP-6800A) equipped with a hydrogen flame detector and a chiral column (Cyclodex-β, 30 m × 0.25 mm (i.d.), 0.25 μm). HPLC experiments were performed on Agilent-1260 plus (Daicel Chemical Industries, Tokyo Japan) equipped with a 1260-DAD detector and a normal Daicel Chiralcel OD-H column, ø4.6 × 250 mm.

2.2. Catalytic procedure

In a typical process, a mixture of (±)-1-phenylethanol (0.122 g, 1 mmol), chiral Mn(III)-salen complex (0.0127 g, 2 mol%), Br_2 (4.1 μL, 8 mol%), KOAC (0.1962 g, 2 mmol), CH_2Cl_2 (2.0 mL), and water (4.0 mL) was magnetically stirred in a 10-mL two-necked flask at 20 °C. The oxidant NaClO (0.289 g, 0.80 mmol) was then added slowly within 40 min, and the reaction was monitored by GC/HPLC equipped with a suitable chiral column.

2.3. Analysis of the reaction mixture

After the addition of (±)-1-phenylethanol, chiral Mn(III)-salen complex, CH_2Cl_2, H_2O and Br_2, 10 μL of the organic phase was removed and put into a 10 mL of volumetric flask, the mixture 1 was dissolved with mobile phase to constant volume. After the addition of NaClO, another 10 μL of the organic phase was removed and put into a 10 mL of volumetric flask, the mixture 2 was dissolved with mobile phase to constant volume. The conversion of (±)-1-phenylethanol was determined by HPLC with single-point external standard method. HPLC conditions: Hexane/i-ProH = 95: 5 (v/v), 1.0 mL/min, 210 nm, 20 °C.

$$\text{Conversion}(\%) = \frac{\text{the peak area of mixture 1} - \text{the peak area of mixture 2}}{\text{the peak area of mixture 1}} \times 100\% \quad (1)$$

$$ee(\%) = \frac{R\text{-}S}{R+S} \times 100\% \quad (2)$$

$$k_{rel} = \frac{\ln(1-Conv)(1-ee)}{\ln(1-Conv)(1+ee)}. \quad (3)$$

Besides, the conversion of (±)-1-phenylethanol was also determined by GC with area normalization method. GC conditions: column temperature: 100 °C, injector 220 °C, detector: 220 °C, pressure: 0.05 MPa.

3. Results and discussion

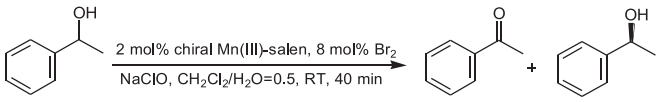
In principle any oxidants able to oxidize HBr to Br_2 are candidates for the chiral Mn(III)-salen complex catalyzed OKR of alcohols. From a "green" chemistry perspective [31,32], the best choice would be either molecular oxygen or hydrogen peroxide since water would be the only by-product in oxidation. Besides, molecular oxygen, as the most abundant and cheapest oxidant, was successfully used to replace $PhI(OAc)_2$ in the oxidation of alcohols with Br_2 as active oxidant [33]. Additionally, the cheap and easily available hydrogen peroxide was also applied to the oxidation of HBr in literature [34,35]. Therefore, we first tested molecular oxygen and hydrogen peroxide respectively as oxidants in the OKR of α-phenylethanol. It is disappointing that no enantioselective oxidation occurred in both cases (Table 1, entries 1, 2). Then another oxidant *tert*-butyl hydroperoxide (TBHP) was tried again, a failure was received too (Table 1, entry 3). Finally, we used sodium hypochlorite as oxidant to carry out the reaction, a delightful result was obtained (Table 1, entry 4). In the initial experiment the enantioselectivity reached about 100% when the conversion of α-phenylethanol was kept 62.8%. Though sodium hypochlorite is not good compared to molecular oxygen and hydrogen peroxide as oxidant from an environmental point of view, it is still a good choice due to its cheapness and easy availability. Besides, the main by-product in the reaction is sodium chloride, which can be recycled in large scale chemical process. Only NaClO as oxidant is efficient in the reaction can be explained as NaClO can oxidize Br^- to Br_2 in the catalytic cycle in basic medium, however, acidic medium is necessary for the same transformation with the other tested oxidants.

The initial experimental results indicated that NaClO was feasible to replace $PhI(OAc)_2$ in the OKR of α-phenylethanol, therefore, we investigated it in detail. Corey [25] pointed that slow addition of oxidant to prevent the detrimental build up of HBr was very important in the chiral Mn(III)-salen complex catalyzed OKR of alcohols. Thus, we inspected the effect of the addition time of NaClO on the OKR of α-phenylethanol. The results are shown in Fig. 2. It can be seen that both the conversion and the enantiomeric excess increased with extending the addition time of NaClO as expected, when the addition time of NaClO was 40 min, both of them reached their maximums, and did not increase with prolonging the addition time of NaClO. Thus, we chose 40 min as the suitable addition time of NaClO in the subsequent experiments.

The OKR of various secondary alcohols was explored with the novel catalytic system. The results are summarized in Table 2.

It can be observed from Table 2 that most of the tested substrates were smoothly resolved with good to excellent enantioselectivity comparable to those obtained from Xia's catalytic system in literature [19–22]. Similar to the results in literature [19–22], the OKR of α-phenylethanol and its derivatives including 1-(4-fluorophenyl) ethanol, 1-(4-chlorophenyl)ethanol, 1-(4-bromophenyl)ethanol, 1-(4-methylphenyl) ethanol, proceeded readily with excellent

Table 1
Choice of oxidant with α-phenylethanol as substrate.[a]



Entry	Oxidant	Dosage (mmol)	Conv (%)[b]	ee (%)[c]	k_{rel}[d]
1	O_2–$NaNO_2$–Br_2	Oxygen ball	3.37	13.48	−1.94
2	H_2O_2	0.70	5.57	7.34	−9.88
3	TBHP	0.80	26.37	12.06	2.26
4	NaClO	0.80	62.85	~100	–

[a] Reaction conditions: α-phenylethanol 1 mmol, Mn(III)-salen 0.02 mmol, Br_2 0.08 mmol, KOAc 2 mmol, CH_2Cl_2 2 mL, H_2O 4 mL, reaction temperature 20 °C, reaction time 40 min (the oxidants were added within 40 min).
[b] The conversion was determined by GC with area normalization method.
[c] Determined by GC with a chiral column.
[d] $k_{rel} = \ln[(1 - Conv)(1 - ee)]/\ln[(1 - Conv)(1 + ee)]$.

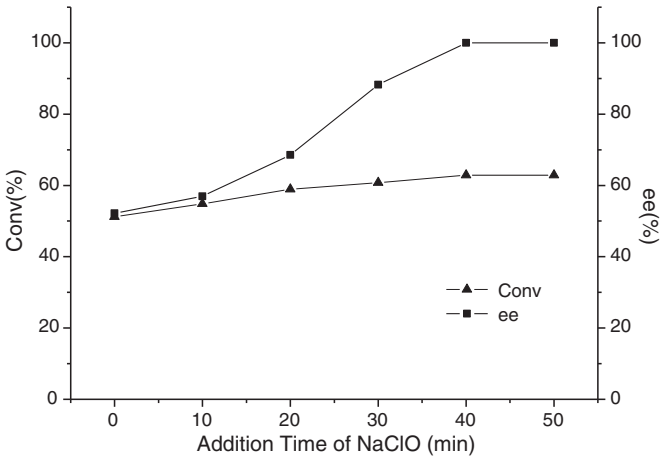


Fig. 2. Optimization of the addition time of NaClO.

enantioelectivity (Table 2 entries 3–6). For example, a conversion of 64.5% and ee of 95.4% were received in case of 1-(4-methylphenyl) ethanol as substrate. However, this system was not efficient in the OKR of substrate having a strong electron donating substituent at the para position. Only a conversion of 29.8% and ee of 19.7% were obtained in case of 1-(4-methoxyphenyl)-1-ethanol as substrate (Table 2, entry 7). The results indicated that the electrostatic properties of the substituents have influence on the reaction.

This system also showed good performances on the OKR of substrate with a substituent ortho to the -hydroxyethyl. For instance, the ee and k_{rel} for the OKR of 1-(2-chlorophenyl)-1-ethanol were 82.1% and 51.9 (Table 2, entry 8). These results are compared to the ones received with NBS as oxidant [23], and much higher than the ones (3.0% and 1.6) with $PhI(OAc)_2$ as oxidant [19]. It is difficult to tell what causes this improvement. Same as the cases with $PhI(OAc)_2$ as oxidant the alcohols with a long aliphatic carbon chain were oxidized with poor selectivity. The longer the carbon chain is, the lower enantioselectivity is received (Table 2, entries 1, 10, 11). Besides, this system is also effective in the OKR of the secondary alcohols with fused-rings (Table 2 entries 12–14). In case of 1-(2-naphthyl)ethanol as substrate, the enantioselectivity was 85.2% when the conversion was kept 52.4%. Hence, the newly developed OKR system, Mn(III)-salen/Br_2/NaClO, remains the excellent performances of Mn(III)-salen/$PhI(OAc)_2$ developed by Xia et al. [19–22]. To demonstrate practicality of this methodology, a multigram scale reaction was carried out with α-phenylethanol as substrate. Similar results were received when the loading amount of α-phenylethanol was increased to 50 mmol (Table 2, entry 2).

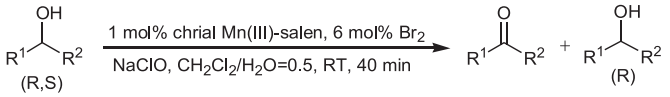
Based on our experimental results and the knowledge in literature [25,33], we propose a mechanism for the novel catalytic system catalyzed OKR of alcohols (Scheme 1).

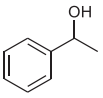
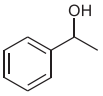
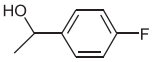
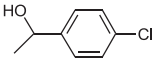
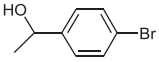
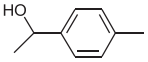
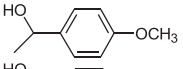
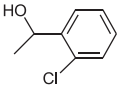
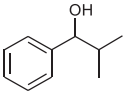
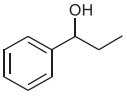
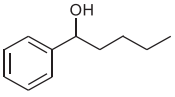
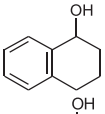
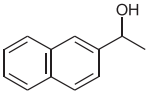
In the OKR process, the Br^- from Br_2 previously added in catalytic amount replaces Cl^- of complex **1** to give complex **2**. Complex **2** reacts with Br_2 to generate dibromo-Mn(V) species **3** and HBr. The generated HBr is oxidized by NaClO to regenerate Br_2, meanwhile, the species **3** enantioselectively converts one enantiomer of the racemic alcohols to a ketone remaining another enantiomer to complete the OKR as described by Corey [25].

4. Conclusions

In conclusion, we replaced $PhI(OAc)_2$ with cheap and easily available NaClO as oxidant to construct a novel chiral Mn(III)-salen catalyzed system for the OKR of secondary alcohols. The novel system exhibited similar performances with that with stoichiometric $PhI(OAc)_2$ as oxidant.

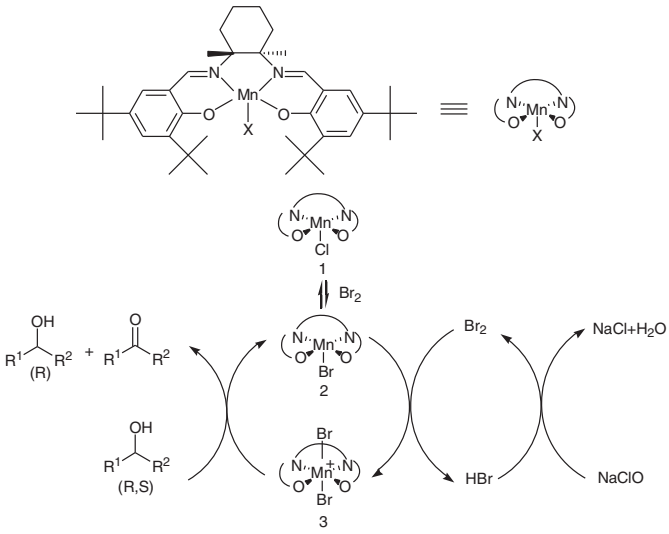
Table 2
OKR of various secondary alcohols.[a]



Entry	Substrates	Conv (%)[b]	ee (%)[c]	k_{rel}[d]
1[e]		46.9	84.3	120.2
2[f]		55.5	85.9	14.6
3[g]		61.8	93.4	12.1
4[g]		60.1	96.9	18.1
5[g]		56.0	95.2	25.2
6[g]		64.5	95.4	11.2
7[g]		29.8	19.7	3.3
8[h]		47.5	82.1	51.9
9[i]		48.8	66.9	11.3
10[i]		50.4	20.2	1.8
11[i]		52.6	11.8	1.4
12[i]		53.4	67.6	7.6
13[i]		54.0	75.4	10.1
14[i]		52.4	85.2	21.1

[a] Reaction conditions: substrate 1 mmol, KOAc 2 mmol, CH_2Cl_2 2 mL, H_2O 4 mL, reaction temperature 20 °C, reaction time 40 min.
[b] The conversion was determined by HPLC with single-point external standard method.
[c] Determined by HPLC with Daicel Chiralcel OD-H column.
[d] $k_{rel} = \ln[(1 - Conv)(1 - ee)]/\ln[(1 - Conv)(1 + ee)]$.
[e] 1 mol% of Mn(III)-salen complex, 6 mol% Br_2, 0.80 equiv of NaClO.
[f] α-Phenylethanol 50 mmol, 1 mol% of Mn(III)-salen complex, 6 mol% Br_2, 0.90 equiv of NaClO, CH_2Cl_2 100 mL, H_2O 200 mL.
[g] 1 mol% of Mn(III)-salen complex, 6 mol% Br_2, 1.00 equiv of NaClO.
[h] 2 mol% of Mn(III)-salen complex, 8 mol% Br_2, 1.00 equiv of NaClO, reaction time 100 min.
[i] 2 mol% of Mn(III)-salen complex, 8 mol% Br_2, 0.80 equiv of NaClO.

This system was very effective for the OKR of α-phenylethanol and its derivatives as well as secondary alcohols with fused-rings under mild reaction conditions.



Scheme 1. Plausible catalytic cycle for the OKR of alcohols with the novel system.

Acknowledgments

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