Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 2730

www.rsc.org/obc

COMMUNICATION

Enantioselective oxidation of racemic secondary alcohols catalyzed by chiral Mn(III)-salen complexes with *N*-bromosuccinimide as a powerful oxidant†

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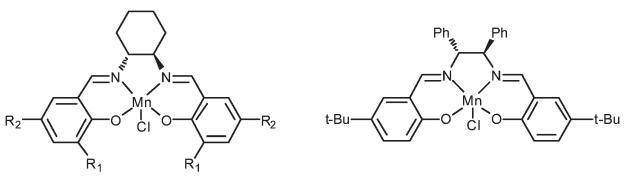
Received 13th December 2011, Accepted 21st February 2012
DOI: 10.1039/c2ob07087a

We demonstrate an efficient enantioselective oxidation of secondary alcohols catalyzed by Mn(III)-salen complex using *N*-bromosuccinimide (NBS) as the oxidant. The new protocol is very efficient for the oxidative kinetic resolution of a variety of secondary alcohols, including *ortho*-substituted benzylic alcohols.

Enantiomerically pure secondary alcohols are pivotal compounds in organic synthesis, and are represented in many important target molecules, intermediates, and reagents.[1] Generally, they have been prepared by many methods, including asymmetric hydrogenation of prochiral ketones catalyzed by metal complexes,[2] enzymatic kinetic resolution of racemic secondary alcohols through acylation–deacylation reactions,[3] and nonenzymatic kinetic resolution.[4] Among the many known processes, the oxidative kinetic resolution (OKR) of racemic alcohols to obtain enantioenriched alcohols is an attractive and practical method.[5,6] Recently, we have reported a convenient OKR of racemic secondary alcohols catalyzed by chiral Mn(salen) complexes together with the oxidant diace-toxyiodobenzene [$PhI(OAc)_2$] in water or biphasic system under mild conditions. The addition of substoichiometric amounts of a bromide salt is essential for high enantioselectivity.[7,8] Subsequently, the Corey group clarified the mechanism and origin of the enantioselectivity of the oxidation of racemic secondary alcohols catalyzed by chiral Mn(III)-salen complexes using $PhI(OAc)_2$–H_2O–KBr as a oxidant.[9] For most of the OKR systems, benzylic alcohols with functionalized aromatic rings serve particularly well as substrates for the OKR. Besides these substrates, our method based on Mn(III)-salen complexes are particularly effective for some racemic aliphatic sec-alcohols. However, benzylic alcohols with *ortho* substituted aromatic rings are rarely explored for most of the OKR systems, or such substrates generally result in poor OKR.[6a–e,7] Herein, we report successful examples that employ *N*-bromosuccinimide (NBS) as a powerful oxidant.

We were encouraged by Corey's reports on mechanism of the enantioselective oxidation of racemic secondary alcohols catalyzed by chiral Mn(III)-salen complexes. The key features of the proposed mechanism are as follows: (1) A positive bromine species HOBr is generated under the reaction conditions by oxidation of bromide ion with $PhI(OAc)_2$. (2) A Mn(V)-salen complex is then formed in the presence of the positive bromine species.[9] We envisioned that easily available NBS may be suitable as positive bromine regent. In the first, (±)-1-(2-bromophenyl)ethanol was chosen to test the possibility of OKR. Under our previous conditions, the OKR nearly did not occur, requiring prolonged reaction time in the presence of Mn(III)-salen complex **1a** (Jacobsen catalyst, Table 1, entry 1). Then NBS was used as oxidant precursor to test the possibility for the OKR of (±)-1-(2-bromophenyl)ethanol in a biphasic system. To our delight, OKR proceeded with a fairly good k_{rel} value (k_{rel} = 10) after 40 min in the presence of potassium acetate to neutralize the HBr generated during the oxidation (Table 1, entry 2).[10] NBS was totally consumed after 4 h, thereby providing 2′-bromoacetophenone in a 63% conversion and unreacted alcohol of 94% ee (k_{rel} = 12, Table 1, entry 3).

We further evaluated the catalyst by varying the C3- and C5-substituents in the *N*-salicylidene template of the Mn(III)-salen complexes (Fig. 1). The Mn(III)-salen complex **1b** bearing a 5-*tert*-butyl group exhibited the best performance on the OKR of (±)-1-(2-bromophenyl)ethanol with a 99% ee (Table 1, entry 4). Interestingly, an 85% ee was observed with the Mn(III)-salen complex **1c** as catalyst, without any substituent in the aromatic ring of ligand. Several analogues of NBS were tested, only *N*-bromophthalimine gave a comparable result (Table 1, entries 10–12). Further optimization of reaction with complex **1b** as



1a: R_1= t-Bu, R_2= t-Bu
1b: R_1= H, R_2= t-Bu
1c: R_1= H, R_2= H
1d: R_1= t-Bu, R_2= H

1e

Fig. 1 The structures of Mn(III)-salen complexes.

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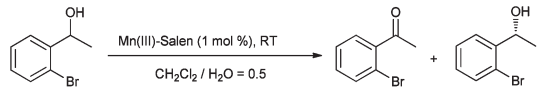
† Electronic supplementary information (ESI) available: Full experimental details for the catalytic reactions, and copies of GC or HPLC Spectra. See DOI: 10.1039/c2ob07087a

Table 1 Conditions screening[a]



Entry	Cat (1.0 mol%)	Oxidant	Conv (%)[b]	% ee[c]	k_{rel}[d]
1[e]	**1a**	$PhI(OAc)_2$	<3	0	—
2[f]	**1a**	NBS	40	48	10
3	**1a**	NBS	63	94	12
4	**1b**	NBS	64	99	17
5	**1c**	NBS	61	85	9
6	**1d**	NBS	64	93	10
7	**1e**	NBS	62	91	11
8	**1b** (0.5 mol%)	NBS	63	93	11
9	**1b** (2.0 mol%)	NBS	65	99	16
10	**1b**	NBP[g]	64	95	11
11	**1b**	NCS[h]	14	2	—
12	**1b**	NIS[i]	26	12	—

[a] Conditions: 1.0 mol% of Mn(III)-salen complex, 0.25 mmol of (±)-1-(2-bromophenyl)ethanol, 1 mL of H_2O, 0.5 mL of CH_2Cl_2, 0.163 mmol of oxidant (0.65 equiv.), 0.2 mmol of KOAc (0.80 equiv.), RT for 4 h. [b] Determined by GC. [c] Determined by GC with a chiral column. [d] k_{rel} = ln[(1 − conv)(1 − ee)]/ln[(1 − conv)(1 + ee). [e] 0.175 mmol of $PhI(OAc)_2$ (0.70 equiv.) and 0.02 mmol of KBr (8.0 mol%). [f] Reaction at RT for 40 min. [g] NBP = *N*-Bromophthalimine. [h] NCS = *N*-Chlorosuccinimide. [i] NIS = *N*-Iodosuccinimide.

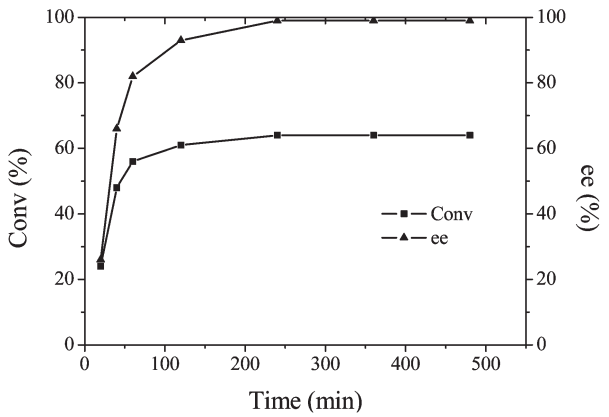
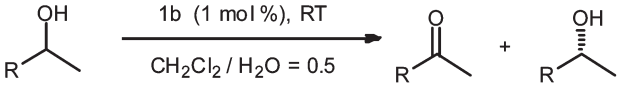


Fig. 2 Optimization of reaction time using complex **1b**.

catalyst, reaction at room temperature for 4 h gave the best results (Fig. 2).

Next, various benzylic alcohols with *ortho* substituted aromatic rings were explored with the new catalytic protocol using Mn(III)-salen complex **1b**. Most substrates bearing one *ortho* substituent are smoothly resolved with good selectivity (Table 2). Only (±)-1-(2-methoxyphenyl)ethanol gave moderate enantioselectivity (Table 2, entry 5). Notably, the OKR reaction proceeded uneventfully with excellent enantioelectivities for the (±)-1-(2,6-difluorophenyl)ethanol and (±)-1-(2,3-difluorophenyl) ethanol (Table 2, entries 6 and 7). Additionally, *meta*-substituted benzylic alcohols are well tolerated to afford high enantioelectivities with faster speed, compared to the *ortho*-substituted substrates (Table 2, entries 8 and 9). The newly developed system, Mn(III)-salen–NBS–H_2O, remains its excellent performance for the OKR of a variety of secondary alcohols, including benzylic

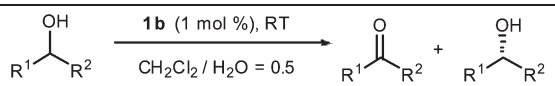
Table 2 OKR of *ortho*-substituted or *meta*-substituted benzylic alcohols[a]

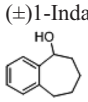


Entry	R	Conv (%)[b]	% ee[c]	k_{rel}[d]
1	*o*-Br–C_6H_4	64	99	17
2	*o*-Cl–C_6H_4	60	93	14
3	*o*-F–C_6H_4	59	94	16
4	*o*-Me–C_6H_4	58	94	18
5	*o*-MeO–C_6H_4	58	56	4
6	2,3-F_2–C_6H_3	62	99.4	22
7	2,6-F_2–C_6H_3	56	95	25
8[e]	3-Me–C_6H_4	63	99	18
9[e]	3-F–C_6H_4	62	99	20

[a] Reaction conditions: 1.0 mol% of Mn(III)-salen complex **1b**, 0.25 mmol of substrate, 1 mL of H_2O, 0.5 mL of CH_2Cl_2, 0.163 mmol of NBS (0.65 equiv.), 0.2 mmol of KOAc (0.80 equiv.), RT for 4 h. [b] Determined by GC. [c] Determined by GC with a chiral column. [d] k_{rel} = ln[(1 − conv)(1 − ee)]/ln[(1 − conv)(1 + ee). [e] RT for 20 min.

Table 3 OKR of various secondary alcohols[a]



Entry	Substrate, R^1, R^2	Conv (%)[b]	% ee[c]	k_{rel}[d]
1[e]	C_6H_5, Me	63	97	14
2[f]		61	77	6
3[e]	4-F–C_6H_4, Me	63	98	16
4[e]	4-Me–C_6H_4, Me	62	95	13
5[e]	4-CF_3–C_6H_4, Me	60	94	15
6[e]	4-Cl–C_6H_4, Me	61	94	13
7[f]		63	89	10
8[g]	(±)1-Indanol	61	99.9	31
9[g]		55	94	27
10[e]	(±)Menthol	64	99	16
11[g]		59	99.9	40
12[g]	2-Naphthyl, Me	58	99.8	30
13[g]	Bn, Me	64	98	16
14[e]		62	67	5
15[e]	*t*-Bu, Me	63	86	8

[a] Reaction conditions: 1.0 mol% of Mn(III)-salen complex **1b**, 0.25 mmol of substrate, 1 mL of H_2O, 0.5 mL of CH_2Cl_2, 0.163 mmol of NBS (0.65 equiv.), 0.2 mmol of KOAc (0.80 equiv.). [b] Determined by GC. [c] Determined by GC with a chiral column. [d] k_{rel} = ln[(1 − conv)(1 − ee)]/ln[(1 − conv)(1 + ee). [e] RT for 20 min. [f] 1.0 mol% of Mn(III)-salen complex **1b**, 0.25 mmol of substrate, 1 mL of H_2O, 0.5 mL of CH_2Cl_2, 8% mmol of KBr, 0.7 equiv. of $PhI(OAc)_2$, 5 min. [g] RT for 2 h.

alcohols, fused ring alcohols and aliphatic sec-alcohols that could be accessed in high ee with $PhI(OAc)_2$–H_2O–KBr as oxidant (Table 3). For example, the OKR of (±)-1-indanol, (±)-1,1-diphenyl-2-propanol and (±)-1-(2-naphthyl)ethanol were complete at about 60% conversion in 2 h, leading to recovery of

the (*S*)-enantiomers in > 99% ee, respectively (Table 3, entries 8, 11 and 12). The OKR of 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol proceeded well and the unreacted alcohol was recovered in good yields with high enantioselectivity under the same reaction conditions (Table 3, entry 9). Surprisingly, several aliphatic sec-alcohols, such as (±)-3,3-dimethyl-2-propanol or (±)-1-cyclopropylethanol, resulted in low ee using the NBS protocol.[7b]

The reported oxidations of alcohols with NBS are usually carried out using either anhydrous solvents or in acidic or basic media at varied temperatures.[11,12] In acidic media, NBS may react with water to form positive bromine species HOBr.[13] Based on NMR studies the behavior of NBS and D_2O, only a trace amount of succinimide was observed even in the presence of KOAc.[14] These findings indicate that the forming of HOBr from NBS and water in aqueous media is very slow. It seems that NBS directly acts as the oxidant in the OKR reaction instead of HOBr in the present system.[12] As a result, the Mn(III)-salen–NBS–H_2O system can be extended to the OKR of the *ortho*-substituted benzylic alcohols.

Conclusions

In conclusion, this communication has demonstrated the viability of enantioselective oxidative of racemic secondary alcohols catalyzed by chiral Mn(III)-salen complexes using NBS as stoichiometric oxidant. The mild reaction conditions and enantioselectivity of the catalyst system provide access to a range of secondary alcohols including the *ortho*-substituted benzylic alcohols in excellent enantioselectivity. Additionally, the utilization of cheap, easily available NBS as oxidant makes the protocol more practical toward the synthesis of enantiomerically pure secondary alcohols. Efforts are currently under way in our group to further expand the scope and synthetic utility of the asymmetric oxidation.

This work was funded by the Chinese Academy of Sciences and the National Natural Science Foundation of China (20873166, 21073210 and 21133011).

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