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Efficient Oxidation of Secondary Alcohols to Ketones by NaOCl Catalyzed by Salen-Mn(III)/NBS[1]

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Abstract—An efficient catalytic system salen–Mn(III)/NBS for oxidation of secondary alcohols to ketones by inexpensive and readily available oxidizing agent NaOCl has been developed. The process resulted in good to excellent yields under the action of 2 mol % of salen–Mn(III) and 13 mol % of NBS at room temperature. However, such system was not efficient in oxidation of secondary benzyl alcohols with a strong electronic-donating substituent attached to the benzene ring due to bromination of the alcohols.

Keywords: salen–Mn(III), NaOCl, NBS, oxidation, secondary alcohols

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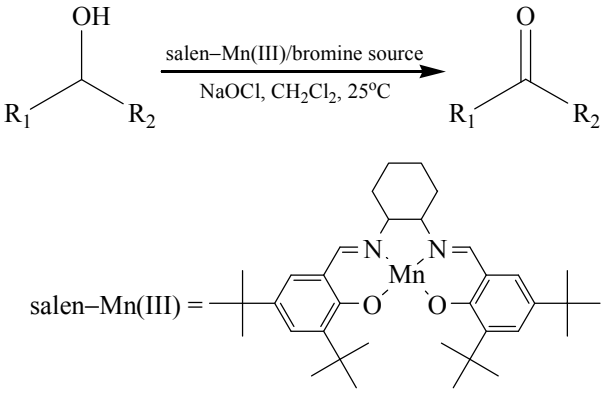
Selective oxidation of alcohols into the corresponding carbonyl compounds is an important transformation in organic synthesis. Traditionally such processes had been performed with stoichiometric amounts of organic or inorganic oxidizing agents including dimethyl sulfoxide, lead acetate, chromates and manganese oxides [1]. The reaction had been accompanied by formation of significant quantities of toxic side products. Therefore, efficient catalysis of the process became an objective of intensive research. A number of TEMPO-based (2,2,6,6-tetramethylpiperidyl-1-oxy) catalytic systems were efficient in oxidation of alcohols to aldehydes and ketones by oxygen [2].

Anelli and coworkers [3] had developed another TEMPO-based protocol for oxidation of alcohols to the carbonyl compounds that involved NaOCl as the stoichiometric oxidant. The reaction had been carried out at 0°C in a biphasic CH_2Cl_2–water mixture with an excess of NaOCl, $NaHCO_3$, KBr, and catalytic amount of 4-MeO-TEMPO giving aldehydes in high yields in the course of minutes. Oxidation of secondary alcohols required for clear reasons longer reaction time. Sodium hypochlorite acted as an oxidizing agents of alcohols with high efficiency in accordance with other protocols [4, 5] that involved also somewhat problematic TEMPO-based systems [2, 6, 7]. In this respect salen–Mn(III) complexes had been versatile catalysts in organic reactions. Xia et al. [8] utilized chiral salen–Mn(III) complexes as catalysts in combination with (diacetoxyiodo)benzene [$PhI(OAc)_2$] as terminal oxidant in the oxidative kinetic resolution (OKR) of secondary alcohols. Key points of the mechanism of the process proposed by Corey and co-workers [9] included formation of Mn(V)–salen dibromide, its subsequent reaction with an alcohol to give alkoxy Mn(V) species and carbonyl-forming elimination to give the corresponding ketone via a highly organized transition state with intramolecular transfer of hydrogen from carbon to oxygen of the salen ligand. Based on this mechanism there was developed a new protocol with *N*-bromosuccinimide (NBS) oxidant instead of $PhI(OAc)_2$ which proved to be highly efficient in oxidative kinetic resolution of a variety of secondary alcohols catalyzed by chiral salen–Mn(III) complexes [10]. Recently we determined that the OKR of secondary alcohols catalyzed by chiral salen–Mn(III) complexes could be achieved with a catalytic amount of Br_2 as a cycling agent and stoichiometric oxidant NaOCl [11]. This method was inexpensive and simple at the step of products purification due to formation of NaCl from NaOCl.

In the course of the method development we replaced chiral salen–Mn(III) complex with its achiral counterpart as a catalyst of oxidation of secondary alcohols by stoichiometric amount of NaOCl and catalytic amount of NBS. Herein, we report the efficient oxidation of secondary alcohols of such system.

[1] The text was submitted by the authors in English.



Oxidation of secondary alcohols to ketones by NaOCl catalized by salen–Mn(III).

Corey's mechanism led to a conclusion that substances that can be oxidized to Br_2 in situ act as the sources of bromine in salen–Mn(III) complex catalyzed oxidation of alcohols. Therefore, several bromides and bromines were tested in oxidation of 1-phenylethanol (see figure) as a reference reaction.

Results of the reaction carried out under various conditions (Table 1) can be associated with formation of HOBr and its direct oxidizing of alcohols to aldehydes or ketones [13]. Therefore, NBS was chosen as bromine cycling agent in the novel catalytic system.

Activity of each component of the catalytic system was studied (Table 2). According to the presented data without Salen Mn(III) and NBS (Table 2, entry 1) almost no reaction took place. Upon slow addition of NaOCl (2.3 mmol), salen–Mn(III) (2 mol %), and NBS (13 mol %) oxidation of 1-phenylethanol to acetophenone completed smoothly in 10 min (Table 2, entry 5). Without salen–Mn(III) 1-phenylethanol was converted to acetophenone in 1 h (Table 2, entry 2). Probably it proceeded via the initial NBS reaction with water leading to HOBr species with positively charged bromine that acted as an oxidant of 1-phenylethanol giving acetophenone along with HBr as by-product [14]. HBr was oxidized by NaOCl to Br_2, which formed HOBr in presence of water. Replacement of salen–Mn(III) by manganese acetate resulted in very low rate of oxidation indicating that salen–Mn(III) itself could catalyze oxidation of 1-phenylethanol by NaOCl to acetophenone without bromine but rate of the reaction was lower than in the process supported by NBS or Br_2. Such effect was consistent with the chiral salen–Mn(III) catalyzed oxidative kinetic resolution of secondary alcohols [9]. Without NaOCl or with molecular oxygen the process resulted in low conversion of 1-phenylethanol (Table 2, entries 3, 6). Overall, the data presented in Table 2 indicated that each component was essential for the efficient oxidation reaction.

The effect of salen–Mn(III) amount on the reaction was studied at room temperature with NBS (13 mol %) and NaOCl (2.3 mmol). Generally under same conditions conversion rate of 1-phenylethanol became

Table 1. Effect of various bromine sources on oxidation reaction of 1-phenylethanol.[a] Reation condition: 1-phenylethanol (1 mmol), salen–Mn(III) (2 mol %), bromine source (13 mol %), dichloromethane (2 mL), room temperature, NaOCl (2.3 mmol)

Entry	Bromine source	Reaction time, h	Conversion, %	Selectivity, %
1	NBS	0.17	>99	>99
2	Br_2	0.67	>99	>99
3[b]	Br_2	3.0	68	>99
4	KBr	2.0	53	>99
5	NaBr	5.0	60	>99

[a] NaOCl addition time 10 min. The products were tested by GC.
[b] Br_2 (6 mol %).

Table 2. Oxidation of 1-phenylethanol to acetophenone catalyzed by salen–Mn(III).[a] Reation condition: 1-phenylethanol (1 mmol), dichloromethane (2 mL), room temperature, NaOCl addition time 10 min

Entry	Mn(III), mol %	NBS, mol %	NaOCl, mmol	Reaction time, h	Conversion, %
1	0	0	2.3	1.0	–
2	0	13	2.3	1.0	52
3	2	0	2.3	6.0	53
4	2	13	0	1.0	3.5
5	2	13	2.3	0.17	>99
6[b]	2	13	2.3	5.0	22
7[c]	2	13	0	2.0	3.0

[a] mol % vs. the substrate as indicated by GC; selectivity > 99%.
[b] The reaction was carried out with 2 mol % manganese acetate without Salen Mn(III).
[c] The reaction was carried out under O_2 without NaOCl.

Table 3. Effect of each component rate on oxidation of 1-phenylethanol[a]. Reation condition: 1-phenylethanol (1 mmol), dichloromethane (2 mL), room temperature

Entry	Salen Mn(III), mol %	NBS, mol %	NaOCl, mmol	Reaction time, h	Conversion, %
1	0	13	2.3	1.0	52
2	1.5	13	2.3	0.17	95
3	2	13	2.3	0.17	>99
4	2	13	2.0	0.83	85
5	2	13	2.3	0.17	>99
6	2	13	2.5	0.17	>99
7	2	5	2.3	8.0	70
8	2	8	2.3	4.5	88
9	2	10	2.3	2.0	94
10	2	16	2.3	0.17	>99

[a] mol % vs. the substrate; tested by GC; selectivity > 99%.

higher with the increase of salen–Mn(III) content (Table 3, entries 1–3). Similar relationship was observed for NaOCl with the optimum rate of it being 2.3 mmol. The data accumulated were higher than that in Anelli's protocol [3] and comparable with the process carried out in acetic acid [5].

Influence of NBS amount on the reaction was studied within the margins 5 to 16 mol % with constant amounts of salen–Mn(III) (2 mol %) and NaOCl (2.3 mmol) at room temperature. Conversion of 1-phenylethanol increased from 70% in 7 h to higher than 99% in 10 min upon increased NBS rate. Higher content of NBS did not influence upon the reaction rate. We applied 13 mol % as the most efficient amount of NBS in the subsequent experiments.

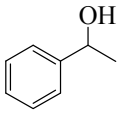
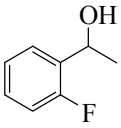
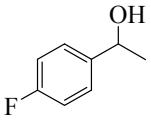
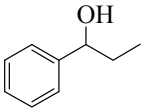
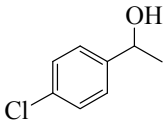
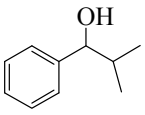
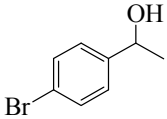
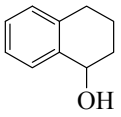
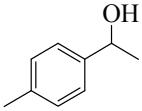
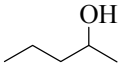
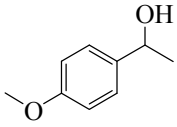
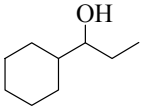
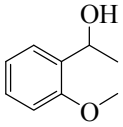
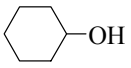
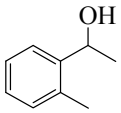
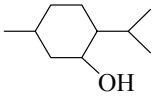
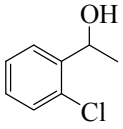
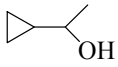
Based on the above data we correlated influence of the novel catalytic system with the structure of secondary alcohols (Table 4). 1-Phenylethanol and its *para*-substituted derivatives including those bearing electron-withdrawing or weak electron-donating groups (F, Cl, Br, and CH_3) were selectively converted to corresponding ketones under the optimized conditions (Table 4, entries 1–5). However, in the presence of the OMe substituent this catalytic system had low activity in oxidation of 1-(4-methyloxyphenyl)ethanol. Higher content of NaOCl did not improve the yield (Table 4, entry 6). The reaction was accompanied by formation of bromine-substituted by-products due to the electron-donating nature of the substituent which promoted the electrophilic substitution in the benzene ring. Bromination reaction consumed the source of bromine which retarded the process of oxidation.

Due to steric effects *ortho*-substituted secondary alcohols had lower activity than their *para*-substituted analogues (Table 4). The low reaction rate of *ortho*-substituted secondary alcohols can be ascribed to steric hindrance between a substituent and Salen ligand in the alkoxy complex $[salen–Mn(V)–Br–OR]^+$ which was the key reaction intermediate and precursor of the ketones formed [9]. The size of aliphatic chain of 1-phenyl alcohols also had some influence upon the process (Table 4).

This system was efficient in oxidation of secondary alcohols in fused rings and secondary aliphatic alcohols. 1,2,3,4-Tetrahydro-1-naphthol was converted into 1,2,3,4-tetrahydro-1-naphthalenone in 1.5 h. Secondary aliphatic alcohols were converted to the corresponding ketones with high yield. Higher content of NaOCl and longer reaction time were required (Table 4, entries 14–7). Even cyclohexanol and its derivative menthol were oxidized to ketones with yields higher than 90% (Table 4).

In conclusion, an active catalytic system salen–Mn(III)/NBS for oxidation of secondary alcohols by inexpensive and readily available NaOCl has been

Table 4. Selective oxidation of secondary alcohols by salen–Mn(III)/NBS/NaOCl. Reation conditions: substrate (1 mmol), salen–Mn(III) (2 mol %), NBS (13 mol %), CH_2Cl_2 (2 mL), room temp., NaOCl addition time 10 min

Entry	Substrate	NaOCl, mmol	Reaction time, h	Conversion[a], %	Selectivity, %	Entry	Substrate	NaOCl, mmol	Reaction time, h	Conversion[a], %	Selectivity, %
1		2.3	0.17	>99	>99	10		2.5	0.17	93.0	98
2		2.7	0.17	98.4	>99	11		2.3 3.0	0.17 0.17	84.0 98.4	>99 >99
3		2.3	0.17	>99	>99	12		3.0 3.2	0.17 0.17	80.0 84.0	>99 >99
4		2.3	0.17	>99	>99	13		2.3	1.5	>99	>99
5		2.3	0.17	>99	>99	14		2.7	0.17	>99	>99
6		2.5 3.0	5.0 5.0	65 65	85 86	15		3.0	1.0	95.0	>99
7		2.5 3.0	4.5 4.5	28 30	96 97	16		3.0	0.17	>99	>99
8		2.5	0.17	86	>99	17		3.0	0.17	90.0	>99
9		2.5	0.17	34	79	18		2.5	0.17	55	>99

[a] The products were tested by GC and confirmed by ^{1}H NMR.

developed. This system had high efficiency in oxidation of various secondary alcohols to the corresponding ketones in good to excellent yields with salen–Mn(III) (2 mol %) and NBS (13 mol %) in CH_2Cl_2 at room temperature. However, it is not efficient in oxidation of secondary benzyl alcohols containing strong electronic-donating substituents in the benzene ring.

EXPERIMENTAL

Materials and instruments. Aqueous solutions of sodium hypochlorite (active chlorine ≤10%), *N*-bromosuccinimide (NBS), bromine (Br_2) and other reagents were produced by Tianjin Fuchen Chemical Reagent Factory, China. No additional purification was required. The secondary alcohols were purchased from Alfa Aesar China (Tianjin) Co., Ltd. The salen–Mn(III) complex *N,N*'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclo-hexanediaminomanganese(III) chloride was produced in accordance with the method that had been published earlier [12]. Oxidation reaction products were tested by Gas Chromatograph SP-6800A equipped with a FID and a polar column (1533-04, 0 m × 0.25 mm × 0.50 μm). The ^{1}H NMR spectra were recorded by a Bruker AC-P400 spectrometer in $CDCl_3$ or DMSO media with TMS internal standard.

Catalytic oxidation. In a typical experiment an alcohol (1 mmol), salen–Mn(III) complex (0.02 mmol), NBS (0.13 mmol), and CH_2Cl_2 (2 mL) was loaded into a 5 mL flask at room temperature. NaOCl (2.3 mmol) was added dropwise within 10 min and progress of the reaction was monitored by GC. Upon completion of the process the reaction mixture was treated twice with 10 mL of 10% $NaHSO_3$ solution and the organic phase was dried over anhydrous sodium sulfate and filtered off. The solvent was removed by distillation. The residue was distilled under low pressure.

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