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Macrocyclic Mn(III) salen complexes as recyclable catalyst for oxidative kinetic resolution of secondary alcohols

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ABSTRACT

New macrocyclic chiral Mn(III) salen complexes (**C1**–**C4**) were synthesized and were used as catalysts for oxidative kinetic resolution (OKR) of secondary alcohols with diacetoxyiodobenzene ($PhI(OAc)_2$) and *N*-bromosuccinimide (NBS), in biphasic dichloromethane: water solvent mixture. Good to excellent enantioselectivities were achieved with catalyst **C2** for several secondary alcohols having different steric environment. In general with catalyst **C2**, NBS as a co-oxidant showed better enantioselectivity than $PhI(OAc)_2$ in OKR. The catalyst **C2** was easily retrieved from the reaction mixture by the addition of hexane and recycled seven times both with NBS and $PhI(OAc)_2$ as co-oxidants without losing its performance. Based on the experimental results a mechanism for OKR of racemic 1-phenylethanol has been proposed where (*R*,*R*)-Mn-salen preferably binds with (*S*)-1-phenylethanol to give (*R*)-1-phenylethanol in excess at the end of the reaction.

1. Introduction

Oxidative kinetic resolution (OKR) of racemic secondary alcohols is one of the significant methods to get optically pure secondary alcohols having several applications viz., chiral auxiliary and synthetic intermediates in pharmaceutical, agrochemical and fine chemical industries [1]. Several chiral ligands with Pd [2], Ru [3], Ir [4], Co [5] and Fe [6] metal ions have been used as catalyst for OKR in the past. But, chiral Mn(III) complexes [7], particularly Mn(III) salen type complexes [7a–7h] are of particular interest due to their easy synthesis, mild reaction condition and very short reaction time. Till date commercially available Jacobson's Mn(III) salen complex has shown highest activity and enantioselectivity in the OKR of racemic secondary alcohols by using oxidative mixtures such as KBr + PhIO and KBr + $PhI(OAc)_2$. However, the recovery of the catalyst from the reaction mixture for further use was hampered by its high solubility in all the commonly used solvents. Moreover, a fair amount of black particles was observed in the post catalysis work-up process, possibly due to the oxidative degradation of the catalyst. This resulted in poor recovery of the catalyst even by silica gel chromatographic separation. In the oxidative environment the situation is further complicated as Mn(III) salen complex, if not properly designed, tend to form catalytically inactive (and/or non-selective) dimeric and polymeric μ-oxo Mn(IV) species. Undoubtedly, catalyst recycle is an important issue, more so to offset the high cost of the catalyst for practical application. In this context, it is prudent to design a ligand/complex that has built-in capability of (a) preventing di(poly)merisation of the catalyst by site isolation, (b) minimizing auto oxidation and (c) altering its solubility so that it is easily retrieved in post-catalytic work-up step. Some of these issues particularly catalyst recyclability in OKR of racemic alcohol was addressed earlier by incorporating sulfonato-Mn(III) salen complex on an organic resin [7i], but the catalyst showed only moderate enantioselectivity although recycled up to 4th cycle. Later on our group [7d,e] and Xia et al. [7g] introduced dimeric and polymeric Mn(III) salen complexes as recyclable catalysts which were recycled up to 5th and 4th cycles respectively. Towards the goal of catalyst recyclability, the immobilization of the chiral Mn(III) salen complexes into ionic liquid modified mesoporous silica [7j,k], could retain its activity and enantioselectivity only up to 4th cycle. Very recently Tan et al. [7f] have synthesized imidazolium based ionic liquid bridged Mn(III) salen complexes which were recycled successfully up to 5th cycle for OKR of secondary alcohols with very good enantiomeric excess for selected sterically similar substrates. We visualized the synthesis of Mn(III) salen system embedded in a macrocycle to address above mentioned issues. For this we have taken clue from the "Nature" for which T. J. Collins very aptly stated – 'reaction sites and transition states are crafted (in Nature) not only to accelerate desired reaction but also to exclude undesired process such as

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attack at the ligand system and protein' [8]. Our own experience with the use of macrocyclic salen ligands with V [9], Mn [10] and Cu [11] for the enantioselective cyanoformylation, epoxidation and nitroaldol reactions respectively also vouched to attempt this class of ligands with Mn for the OKR of racemic alcohols as well. Herein, we have synthesized a new series of reusable macrocyclic Mn(III) salen complexes (**C1**–**C6**) to catalyze OKR of secondary alcohols with $PhI(OAc)_2$ and NBS as co-oxidant in water-dichloromethane solvent mixture. In the present system the separation of the catalyst is easy and the recovered catalyst was reused seven times without any loss in its activity and enantioselectivity. The stability of the catalyst was demonstrated by UV–vis spectrophotometric studies that showed recovery of the original spectral characteristics on culmination of the catalytic run.

2. Experimental

2.1. General methods and materials

Nuclear magnetic resonance (NMR) of ligands, substrates and products were obtained from Bruker-Avance-DPX-200 (200 MHz) spectrometer using TMS as internal standard. Electronic spectra were recorded in chloroform on a Varian Cary 500 Scan UV–vis–NIR spectrophotometer. Microanalysis of the intermediates was done by CHN analyser. High resolution mass spectra were obtained with a LC–MS (QTOFF)LC (Waters), MS (Micromass) instruments. The enantiomeric excess of unreacted alcohols were determined by chiral Shimadzu-HPLC with SPD-M10A-VP and SPD-M20A UV detector and PDR-advanced Laser Polarimeter (PDR-ALP), using Daicel Chiralcel OD, OD-H and AD-H chiral columns with 2-propanol/hexane mixture as eluent of the reaction mixture after separating the catalyst. Absolute configurations of chiral 1-phenylethanol were determined by comparing the sign of optical rotation (obtained from PDR-ALP) with the standard. Tetrabutylammonium bromide, tetraethylammonium bromide, $PhI(OAc)_2$, NBS chiral auxiliaries, racemic alcohols; 1-indanol, 1-phenyl-2-propanol, 4-phenyl-2-butanol and 2-butanol were purchased from Sigma–Aldrich (USA) but the other racemic alcohols were prepared by the reduction of their corresponding ketones purchased from Sigma–Aldrich (USA), with sodium borohydride. The chloromethyl salicylaldehyde (**1**) [12], 3-butyl-1-methyl-1H-imidazolium bromide (**O**) [13], ligand for the synthesis of complex **C5** [14] and **C6** [12] were synthesized according to the previously reported procedures in the literature. Thin layer chromatography (TLC) was carried out on silica plates (Merck).

2.2. General procedure for the synthesis of bis-aldehyde *2a*, *2b* and *3*

To a dry two necked round bottom flask (RBF) containing Teflon coated magnetic bead, NaH (8 mmol) was added and washed three times with freshly dried tetrahydrofuran (THF) (5 mL × 3) under N_2 atmosphere. Subsequently 50 mL of freshly dried THF was added to the RBF. To the suspension of NaH in THF, ethylene glycol/trigol/1,1′-bi-2-naphthol (BINOL) (2 mmol) was added slowly and stirred for 30 min. Then to the reaction mixture the aldehyde **1** (4 mmol) was added and stirred for another 8–10 h (monitor on TLC), followed by complete removal of solvent. The crude product was extracted with CH_2Cl_2 and the organic layer was washed sequentially with dilute HCl (5 mL × 3), water and brine. The organic layer was dried on anhydrous Na_2SO_4 and evaporated and subjected to flash chromatography with hexane and ethyl acetate as eluent to give the desired product in high purity.

2.3. General procedure for the synthesis of macrocyclic ligands *L1*–*L4*

To an ice cold solution of bis-aldehyde **2a**/**2b**/**3** (1 mmol) in dry methanol (50 mL) methanolic solution (5 mL) of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane/(1*R*,2*R*)-(+)-1,2-diphenylethelenediamine (1 mmol) was added drop-wise and the resulting solution was stirred for 5–6 h at room temperature (RT). After the completion of the reaction (checked on TLC), solvent was evaporated under reduce pressure to have the macrocyclic ligands **L1**–**L4**.

2.4. Characterization data for *L1*–*L3*

L1: Yellow solid; yield 96%, m.p. 80–83 °C; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.49 (br, 2H), 8.27 (s, 2H), 7.41 (s, 2H), 7.08 (s, 2H), 4.54–4.69 (m, 4H), 3.68–3.79 (m, 4H), 3.28 (br, 2H), 1.55–1.86 (m, 8H), 1.24 (s, 18H).^{13}C NMR (50 MHz, $CDCl_3$) 164.797, 156.477, 140.536, 129.038, 127.069, 124.818, 117.300, 72.340, 69.551, 67.549, 33.653, 33.260, 32.969, 31.102, 24.601, 24.358, 23.898. Anal. Calcd. for $C_{32}H_{44}N_2O_4$ C, 73.81; H, 8.52; N, 5.38; Found C, 73.76; H, 8.50; N, 5.31. LC–MS: *m/z* Calcd. for [$C_{32}H_{44}N_2O_4$] 520.33, Found 521.85 [M + H].

L2: Yellow solid; yield 92%, m.p. 98–101 °C; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): 8.26 (s, 2H), 7.39 (d, 2H, *J* = 2 Hz), 7.07 (d, 2H, *J* = 2 Hz), 4.53–4.69 (m, 4H), 3.68 (s, 12H), 3.27–3.30 (m, 2H), 1.58–1.92 (m, 8H), 1.59–1.62 (m, 4H), 1.23 (s, 18H).^{13}C NMR (50 MHz, $CDCl_3$)165.056, 156.740, 140.797, 129.357, 129.282, 127.387, 125.000, 117.587, 72.658, 70.614, 69.750, 35.362, 33.945, 33.256, 31.404, 24.148, 23.560. Anal. Calcd. for $C_{36}H_{52}N_2O_6$ C, 71.02; H, 8.61; N, 4.60; Found C, 71.10; H, 8.58; N, 4.54. LC–MS: *m/z* Calcd. for [$C_{36}H_{52}N_2O_6$] 608.38, Found 609.84 [M + H].

L3: Yellow solid; yield 95%, m.p. 104–107 °C; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 13.31 (br, 2H), 8.37 (s, 2H), 7.07–7.25 (br, 12H), 4.63–4.71 (m, 4H), 3.69 (s, 12H), 1.22 (s, 18H).^{13}C NMR (50 MHz, $CDCl_3$) 140.777, 139.202, 129.234, 128.028, 127.946, 127.653, 127.393, 127.230, 70.369, 69.525, 67.359, 33.665, 31.106. Anal. Calcd. for $C_{44}H_{54}N_2O_6$ C, 74.76; H, 7.70; N, 3.96; Found C, 74.69; H, 7.66; N, 3.90. LC–MS: *m/z* Calcd. for [$C_{44}H_{54}N_2O_6$] 706.40, Found 707.55 [M + H].

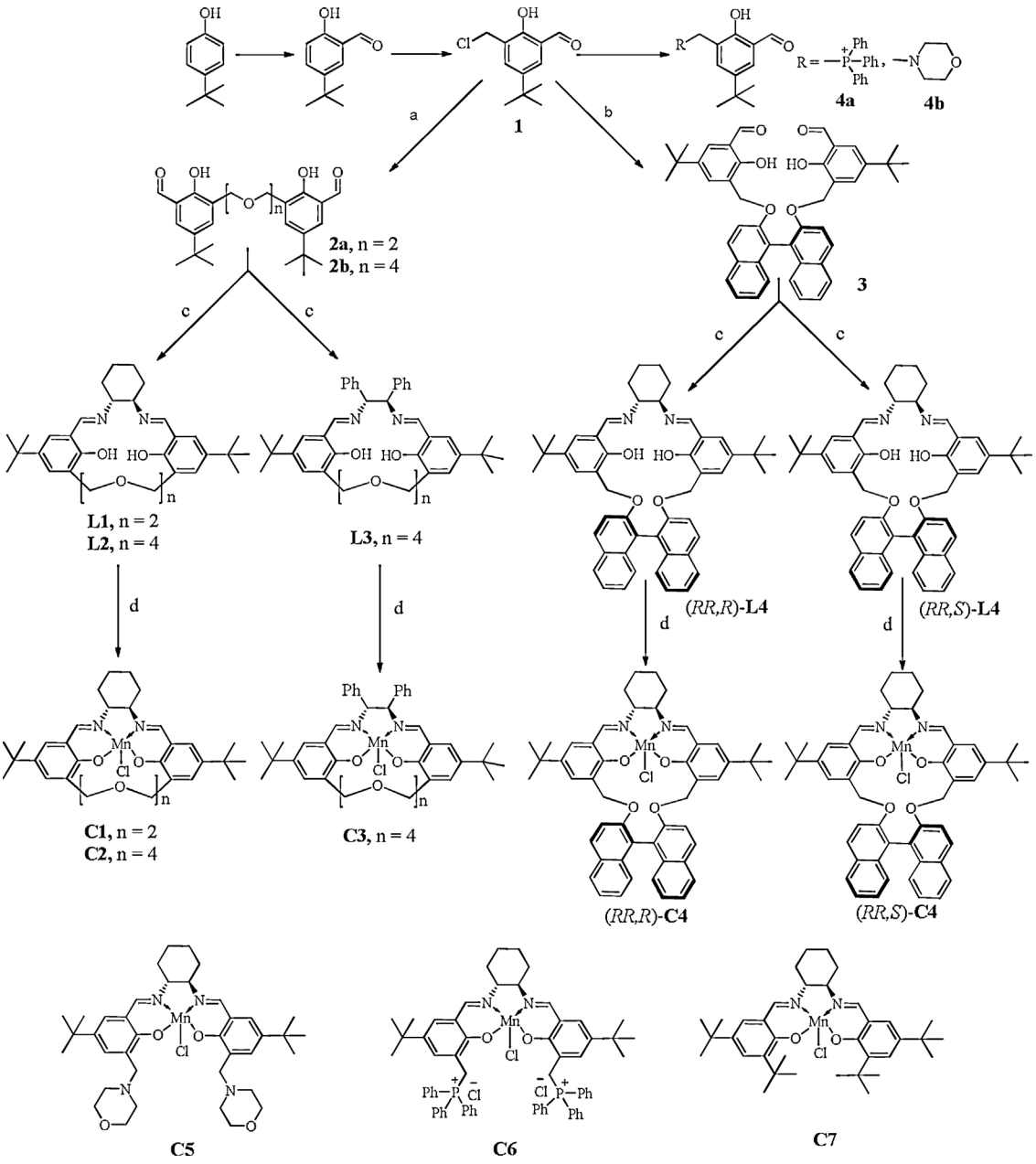
2.5. General procedure for the synthesis of macrocyclic Mn(III) salen complexes *C1–C4*

To a solution of above synthesized macrocyclic ligands (**L1**–**L4**, 1 mmol) in 20 mL dry methanol, solid $Mn(OAc)_2{\cdot}4H_2O$ (2 mmol) was added under N_2 atm. and the resulting solution was refluxed for about 6–8 h. Then the reaction mixture was cooled to RT, followed by the addition of LiCl (4 mmol) and the stirring was continued for another 5 h under air for the aerial oxidation of Mn(II) to Mn(III). Subsequently, the solvent was evaporated and the residue was extracted with CH_2Cl_2. The organic layer was washed three times with water, two times with brine and dried over anhydrous Na_2SO_4. Finally the solvent was evaporated under reduce pressure to get the macrocyclic Mn(III) salen complexes.

2.6. Characterization data for *C1*–*C3*

C1: Brown solid; yield 90%, m.p. 172–175 °C; Anal. Calcd. for $C_{32}H_{42}MnN_2O_4Cl$: C, 63.10; H, 6.95; N, 4.60; Found C, 63.14; H, 6.90; N, 4.55. LC–MS: *m/z* Calcd. for [$C_{32}H_{42}MnN_2O_4Cl$] 608.22, Found 573.34 [M–Cl].

C2: Brown solid; yield 93%, m.p. 168–171 °C; Anal. Calcd. for $C_{36}H_{50}MnN_2O_6Cl$: C, 62.02; H, 7.23; N, 4.02; Found C, 61.70; H, 7.19; N, 4.08. LC–MS: *m/z* Calcd. for [$C_{36}H_{50}MnN_2O_6Cl$] 794.29, Found 759.32 [M–Cl].



Scheme 1. Synthesis of chiral macrocyclic ligands and their corresponding catalysis. (i) NaH, ethelene glycol/trigol, dry THF, N_2 atm, RT, 8–10 h, (b) NaH, (*R*)-1,1′-bi-2-naphthol (BINOL), dry THF, N_2 atm, RT, 8–10 h; (c) chiral diamine, dry methanol, RT, 6 h (d) (i) $Mn(OAc)_2{\cdot}4H_2O$, dry methanol, N_2 atm, reflux. (ii) LiCl, air, RT, 6 h.

C3: Brown solid; yield 91%, m.p. 177–180 °C; Anal. Calcd. for $C_{44}H_{52}MnN_2O_6Cl$: C, 66.45; H, 6.59; N, 3.52; Found C, 66.41; H, 6.51; N, 3.57. LC–MS: *m/z* Calcd. for [$C_{44}H_{52}MnN_2O_6Cl$] 696.27, Found 661.83 [M–Cl].

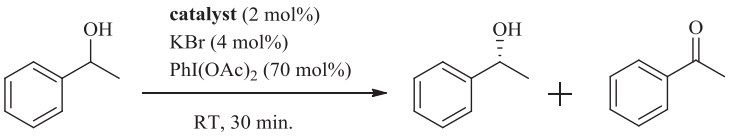
2.7. Typical procedure for the OKR of racemic secondary alcohols with **C2**–PhI(OAc)$_2$ system

To a 5 mL glass reactor substrate (0.25 mmol), catalyst **C2** (0.005 mmol, 2 mol%), CH_2Cl_2 (0.3 mL) and H_2O (0.6 mL) were added and the resulting mass was magnetically stirred for 5 min. To the above stirring mass, KBr (4 mol%) was added at room temperature. The reaction mixture was then cooled to 15 °C and $PhI(OAc)_2$ (0.7 equiv.) was added slowly in small fractions over 15 min and stirring was continued to the specified time. After the completion of the reaction, catalyst was precipitated out by the addition of hexane to the reaction mixture. The recovered catalyst was dried and stored for future use. An aliquot of organic layer was subjected to HPLC analysis to determine enantiomeric excess (ee) of the product. The resulting ketone and enantio-enriched secondary alcohol were separated by silica gel flash chromatography.

2.8. Typical procedure for the OKR of racemic secondary alcohols with **C2**–NBS system

To a 5 mL glass reactor substrate (0.25 mmol), catalyst **C2** (0.0037 mmol, 1.5 mol%), KOAc (0.8 equiv.), CH_2Cl_2 (0.5 mL) and H_2O (1 mL) were added and the resulting mass was magnetically stirred for 5 min. To the stirring mass NBS (0.7 equiv.) was added slowly in small fractions over 20 min and stirring was continued for the specified time. After the completion of the reaction, catalyst was precipitated out by the addition of hexane to the reaction mixture. The recovered catalyst was dried and stored for further use. An aliquot of organic layer was subjected to HPLC analysis to

Table 1
Selection of catalyst for the oxidative kinetic resolution of racemic secondary alcohols using 1-phenylethanol as representative substrate.[a]



Racemic

Entry	Catalyst	Conversion (%)[b]	ee (%)[c]	k_{rel}[d]
1	**C1**	64	43	2.4
2	**C2**	62	65	3.3
3	**C3**	60	5	1.9
4	(*RR*,*R*)-**C4**	63	38	2.2
5	(*RR*,*S*)-**C4**	67	36	1.9
6	**C5**	69	16	1.3
7	**C6**	65	23	1.6
8[e]	**C1**	60	50	2.5
9[e]	**C2**	58	42	2.3
10	**C7**	60	97	18
11	–	22	–	–

[a] Reaction condition: substrate; 1-phenylethanol (0.25 mmol), catalyst (2 mol%), additive (KBr) (4 mol%), $PhI(OAc)_2$ (70 mol%) in 0.5 mL CH_2Cl_2 and 1 mL H_2O solvent mixture.
[b] Determined by ^1H NMR measurement of alcohol and corresponding ketone relative concentration.
[c] Determined by HPLC with a Daicel Chiralcel OD column, flow rate = 0.5 mL/min hexane/*i*-PrOH = 9/1 (v/v).
[d] Selectivity factor k_{rel} was calculated using the equation, $k_{rel} = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$ (where the *C* is the conversion of secondary alcohol and ee is the enantiomeric excess of secondary alcohol).
[e] Reaction was carried out using 8 mol% $(C_2H_5)_4NBr$ as an additive, in 1.5 mL H_2O at RT for 2 h.

determine enantiomeric excess (ee) of the product. The resulting ketone and enantio-enriched secondary alcohol were separated by silica gel flash chromatography.

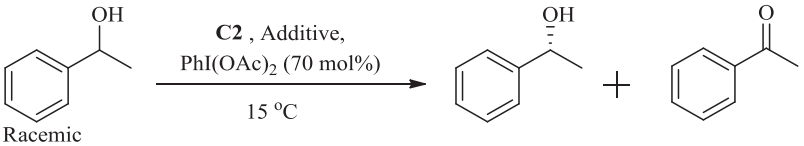
3. Result and discussion

In the OKR of secondary alcohols with Mn(III) salen complexes as catalyst, Xia et al. [7c] noticed that *tert*-butyl group at 5th position of the salicylaldehyde moiety in the catalyst is crucial for higher product enantioselectivity. Taking clue from this study, for synthesizing macrocyclic salen ligands, we visualized a linker at 3,3′ positions of salicylaldehyde by retaining *tert*-butyl group at the 5th position. Accordingly we have synthesized bis-salicylaldehydes **2a** and **2b** with variable ether linker length (Scheme 1).

The condensation of these bis-salicylaldehydes with chiral diamines under controlled condition gave macrocyclic chiral salen ligands **L1–L3**, which on metallation with manganese gave complexes **C1–C3** (Scheme 1). We also synthesized macrocyclic salen ligands (*RR*,*R*)-**L4** and (*RR*,*S*)-**L4** and their respective complexes (*RR*,*R*)-**C4** and (*RR*,*R*)-**C4** with chiral BINOL as linker in order to know the effect of additional element of chirality/flexibility in the ligand on the catalytic performance. For the sake of comparison open salen complexes **C5** and **C6** with N and P heteroatoms respectively and well-known complex **C7** were also synthesized and used as catalysts (2 mol%) in the OKR of 1-phenylethanol (0.25 mmol) using KBr (4 mol% as an additive) and $PhI(OAc)_2$ (70 mol%) as an oxidant in dichloromethane/water biphasic solvent mixture at 25 °C (RT).

Preliminary screening of the catalyst **C1–C6** was carried out by using racemic 1-phenyl ethanol as a representative substrate under standard OKR reaction condition (Table 1). In terms of enantioselectivity, the results with catalysts **C1–C3** clearly show the suitability

Table 2
Optimization of catalyst loading, additive and additive amount.[a]

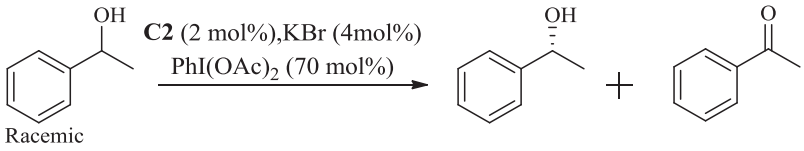


Racemic

Entry	Catalyst loading (mol%)	Additive	Amount of additive (mol%)	Conversion (%)[b]	ee (%)[c]
1	1	KBr	4	60	32
2	2	KBr	4	62	65
3	4	KBr	4	65	47
4	2	NaBr	4	64	52
5	2	LiBr	4	59	38
6	2	**M**	4	62	35
7	2	**N**	4	64	29
8	2	**O**	4	63	59
9	2	KBr	2	54	25
10	2	KBr	6	65	46
11	2	KBr	8	67	43

[a] Reaction condition: Substrate (1-phenylethanol 0.25 mmol), catalyst, additive, $PhI(OAc)_2$ (0.7 equiv.) in 0.5 mL CH_2Cl_2 and 1 mL H_2O solvent mixture.
[b] Determined by ^1H NMR measurement of alcohol and corresponding ketone relative concentration.
[c] Determined by HPLC with a Daicel Chiralcel OD column, flow rate = 0.5 mL/min. Hexane/*i*-PrOH = 9/1 (v/v). **M**, Tetrabutylammonium bromide. **N**, Tetraethylammonium bromide. **O**, 3-butyl-1-methyl-1H-imidazolium bromide.

Table 3
Optimization of reaction temperature and organic solvent.[a]



Racemic

Entry	Temp (°C)	Solvent	Time (min)	Conversion (%)[b]	ee (%)[c]
1	25	CH_2Cl_2	30	62	65
2	15	CH_2Cl_2	30	61	72
3	10	CH_2Cl_2	30	60	65
4	5	CH_2Cl_2	60	62	48
5	0	CH_2Cl_2	60	58	31
6	15	$CHCl_3$	30	62	60
7	15	dichloroethane	30	64	68
8	15	acetone	30	61	32
9	15	ethyl acetate	30	59	24
10	15	chlorobenzene	30	59	21
11[d]	15	CH_2Cl_2	30	63	78
12[e]	15	CH_2Cl_2	30	63	83

[a] Reaction condition: *rac*-1-phenylethanol (0.25 mmol), catalyst **C2** (2 mol%), KBr (4 mol%), $PhI(OAc)_2$ (0.7 equiv.) in organic solvent (0.5 mL) and H_2O (1 mL) mixture.
[b] Determined by ^1H NMR measurement of alcohol and corresponding ketone relative concentration.
[c] Determined by HPLC with a Daicel Chiralcel OD column, flow rate = 0.5 mL/min. Hexane/*i*-PrOH = 9/1 (v/v).
[d] The oxidant was added slowly over 15 min.
[e] The reaction was carried out in 0.3 mL CH_2Cl_2 and 0.6 mL H_2O with slow addition of oxidant.

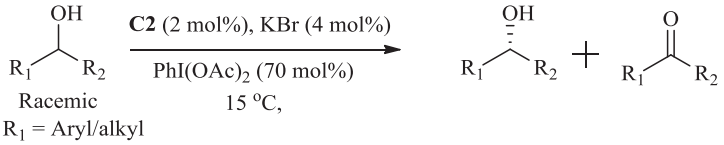
of 1,2-diaminocyclohexane as salen collar (entries 1 and 2) over 1,2-diphenyldiamine (entry 3), as evident from the relative rate of the reactions of one enantiomer over the other viz., k_{rel} for **C1** and **C2** is 2.4 and 3.3 respectively which are higher than catalyst **C3** (k_{rel} = 1.9). Further, catalyst **C2** with more flexible 12-atom linker (ee, 65%, k_{rel} = 3.3) whose core environment is expected to be close to highly enantioselctive catalyst **C7** except for steric features (entry 10 ee, 97%, k_{rel} = 18), was found to be better enantioselective than relatively less flexible catalyst **C1** with 6-atoms linker (ee, 43%, k_{rel} = 2.4). The complexes (*RR*,*R*)-**C4** and (*RR*,*S*)-**C4** with relatively rigid BINOL linker were found to be less enantioselective (ee, 38 and 35% for entries 4 and 5 respectively) than catalysts **C1** and **C2** possibly due to distortion in the geometry of these complexes as against open salen complex **C7**. Interestingly, the absolute configuration of linker BINOL had no effect on product ee and absolute configuration, thus it can be concluded that linker has no direct influence on catalytic enantioselective path required for OKR. Apart from these macrocyclic complexes, two more Mn(III) salen complexes **C5** (entry 6; ee 16%) and **C6** (entry 7; ee 23%) with bulkier groups at 3,3′ positions were found to be less enantioselectivity after similar level of conversion of the racemic alcohols.

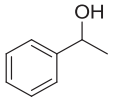
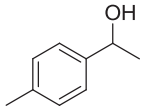
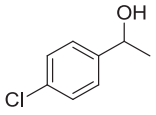
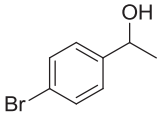
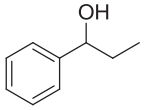
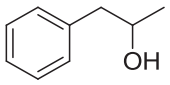
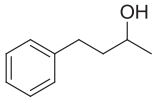
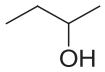
Motivated by the work of Xia et al. we have tested the catalytic efficiency of our two catalysts **C1** and **C2** exclusively in water as reaction medium by using tetrabutylammonium bromide as a phase transfer catalyst. Under this reaction condition, with the catalyst **C2**, the ee of the alcohol decreased sharply to 42% (entry 9), but in the case of the catalyst **C1** the enantioselectivity increased to 50% (entry 8) from earlier 43% (entry 1). However, several attempts by altering other reaction parameters failed to improve ee beyond 50%. Therefore, we restricted our study with biphasic solvent system as reaction medium and took the complex **C2** as preferred catalyst for further optimization of the reaction conditions and substrate variation in the OKR of secondary alcohols.

Catalyst loading was our first target for the optimization of OKR reaction parameters with catalyst **C2** and 1-phenylethanol in water: CH_2Cl_2 biphasic solvent system at RT (Table 2, entry 1–3). Evidently 2 mol% catalyst loading was found to be optimum (entry 1) as its increase (4 mol%, 38% ee; entry 2) or decrease (1 mol%, 32% ee; entry 3) resulted in lower enantiomeric excess at nearly similar conversion. Next, we screened various inorganic (entries 4 and 5) and organic co-catalysts/bromide ion source (entries 6–8) with optimized catalyst loading of **C2** (2 mol%) under the above used reaction conditions. The inorganic salt NaBr as a bromide ion source provided almost comparable enantiomeric excess (Table 2, entry 4), however it was lower with LiBr (Table 2, entry 5). This can be explained on the basis of the higher covalent character of LiBr due to smaller size of the Li-ion and hence the active concentration of the bromide ion is less in the reaction mixture, which is essential to generate the actual oxidizing agent HOBr by *in situ* oxidation of bromide ion with $PhI(OAc)_2$ [7k]. As we were dealing with biphasic reaction, we used three organic bromide salts (Table 2, entries 6–8) considering that it may play dual role, both as additive and phase transfer catalyst by increasing the interaction between the reagents from two phases. However, except for 3-butyl-1-methyl-1H-imidazolium bromide **O** (entry 8; ee = 59%), the other two additives viz., tetrabutylammonium/tetraethylammonium bromides **M** and **N** could not match the results obtained with KBr. So KBr was finalized as an additive with the catalyst **C2** for our further studies. As stated earlier, bromide ion in the presence of $PhI(OAc)_2$ generates an active oxidizing agent HOBr *in situ*, therefore, the concentration of Br^- in the OKR reaction medium should play important role. Therefore, we decreased (2 mol%; entry 9) and increased (6 mol%; entry 9) KBr loading from our standard 4 mol% (entry 2) but either way a marked decrease in the ee was observed. It is to be noted that the KBr with $PhI(OAc)_2$ is able to oxidized secondary alcohols even in the absence of Mn(III) salen catalyst in water-organic biphasic solvent mixture (Table 1, entry 11) [7k]. This explains the reason for the decrease in ee of secondary alcohol on increasing KBr amount that increases non-enantioselctive back-ground oxidation.

Thereafter, we have optimized the temperature and solvent by retaining the above optimized parameter (Table 3). During the temperature variation we observed an increase in the ee (65–72%) of the product on decreasing the reaction temperature from RT to 15 °C (entry 2). But on further decreasing the temperature to 10–0 °C, there was a decrease in the ee values (entries, 3–5). Hence, for the solvent variation experiments we took 15 °C as optimum reaction temperature. Due to solubility issues of the complex **C2**, nonpolar solvents were not considered in the present study. Also, alcoholic solvents were avoided as they are prone to oxidation under the reaction condition used. Therefore, a limited number of solvents (Table 3, entries 6–10) were checked, but in terms of reactivity and

Table 4
OKR of racemic secondary alcohols with **C2** using $PhI(OAc)_2$ as oxidant.[a]



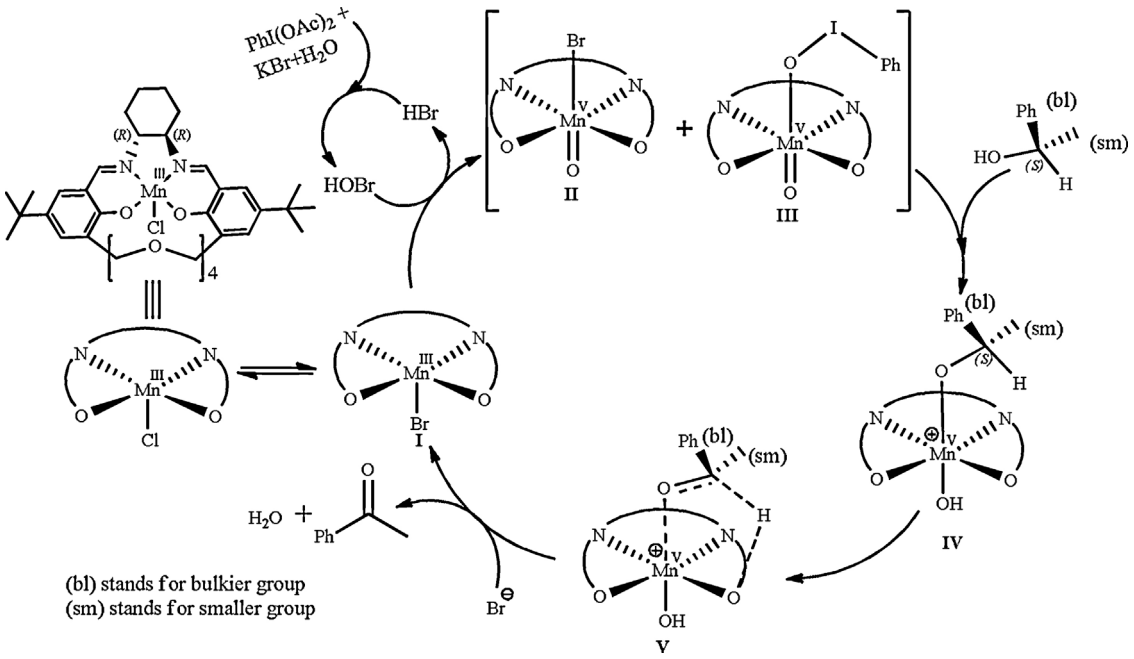
Entry	Racemic alcohol	Catalyst loading (mol%)	Additive amount (mol%)	Conversion (%)[b]	ee (%)[c]	k_{rel}[d]
1		2	4	63	83	7.09
2		2	4	64	84	6.93
3		2	4	62	70	4.97
4		2	4	61	40	2.38
5		2	4	53	7	1.20
6		2	4	63	98	15.77
7		2	4	60	93	13.82
8[e]		2	4	58	99	30.52

[a] Reaction condition: Substrate 0.25 mmol, catalyst 2 mol%, additive 4 mol%, $PhI(OAc)_2$ 0.7 equiv. for 30 min at 15 °C in 0.3 mL CH_2Cl_2 and 0.6 mL H_2O solvent mixture.
[b] Determined by ^1H NMR measurement of alcohol and corresponding ketone relative concentration.
[c] Determined by HPLC with a chiral Daicel Chiralcel columns (see supporting information for details), using hexane/*i*-PrOH as eluent.
[d] Selectivity factor k_{rel} was calculated using the equation, $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$ (where the C is the conversion of secondary alcohol and ee is the enantiomeric excess of secondary alcohol).
[e] Determined by GC with BTA column.

enantioselectivity, none of these solvents could match the performance of dichloromethane.

Further, during the optimization of reaction parameter we found that the slow addition of $PhI(OAc)_2$ helps in achieving higher enantioselectivity (entry 11). Here it is important to mention that total amount of solvent i.e., CH_2Cl_2:H_2O should be 0.3:0.6 mL for the present scale of substrate (0.25 mmol) for optimum catalyst performance (entry 12), implying thereby that the OKR reaction is concentration dependent. Finally, it is concluded that for the present OKR protocol, 2 mol% catalyst loading, 4 mol% KBr at 15 °C (as per the entry 12) is optimum, therefore the same parameters were used to carry out OKR of several aromatic and aliphatic secondary alcohols.

Table 4 represents the performance of the catalyst **C2** for OKR of different racemic secondary alcohols. In general substitution at *para* position of racemic 1-phenylethanol are the preferred substrate for OKR with **C2** which is in line with the earlier reports on OKR with other Mn(III) salen catalysts [7b,d,e,g]. However, in the present system we found that electron donating group on the phenyl ring of the substrate as in 1-(4-methylphenyl) ethanol (Table 4, entry 2) higher ee (84%) of the alcohol was achieved with k_{rel} value of 7.09. But, for moderately electron withdrawing chloro (Table 4, entry 3) and bromo group (Table 4, entry 4) the ee values decreased to 65%, (k_{rel} = 4.97) and 40% (k_{rel} = 2.38) respectively. Substrates with different steric demands such as 1-phenyl-1-propanol also resulted in poor ee (7%, entry 5). This is possibly due to the



Scheme 2. Probable catalytic cycle is represented with 1-phenyl ethanol with (*R*,*R*)-**C2**. For other substrates Ph is replace with bulkier group (bl) and with smaller groups (sm).

presence of more than two bulkier groups in the secondary alcohol, which hampers enantioselective binding with the catalyst at transition stages (**III** and **IV**) during the catalytic cycle as proposed in Scheme 2. Possibly due to this reason a substrate like racemic 1-phenyl-2-propanol after OKR with the catalyst (*R*,*R*)-**C2** gave the (*R*)-1-phenyl-2-propanol in excellent ee (98% with high k_{rel} = 15.77). Similarly, substrates 4-phenyl-2-butanol and aliphatic alcohol-2-butanol (entries 7 and 8) were resolved with this protocol successfully with 93% and 99% ee respectively.

To further improve the performance of the catalyst **C2** for variable substrate we used the OKR protocol developed by Sun et al. [7h] where NBS was used as an oxidant in place of PhI(OAc)$_2$. In fact, with the very first catalyst loading (0.5 mol%) we tested (Table 5, entry 1) for the OKR of racemic 1-phenylethanol at RT, we got the enantio-enriched alcohol in high ee (77%), which was further improved to 99.3% ee (entry 3) by increasing the catalyst loading to 1.5 mol% (entries 2–4). The replacement of dichloromethane with 1,2-dichloroethane (DCE) which is the second best solvent with **C2**/PhI(OAc)$_2$ system gave almost similar enantiomeric excess. So after the minor changes in the Sun et al.'s procedure with our catalyst, we have taken 1.5 mol% of catalyst loading, 70% of NBS and 80% of KOAc in 0.5 mL dichloromethane and 1 mL water at RT as optimized reaction condition for OKR of various racemic secondary alcohols (Table 5).

As we mentioned earlier that substitution at *para* of racemic 1-phenylethanol are the preferred substrates for OKR with previously reported Mn(III) salen based catalytic system. We ended up with moderate to good enantioselectivity for this type of substrates with **C2**/PhI(OAc)$_2$ based catalytic system, but when the oxidant PhI(OAc)$_2$ was replaced by NBS, we observed a great improvement in the enantioselectivity with the same catalyst. For the weakly electron donating methyl group, and withdrawing group such as chloro, bromo and fluoro at the *para* position of the phenyl ring, the catalyst gave 96%, 98%, 97%, and 96%, enantiomeric excess of the unreacted alcohols respectively (Table 5, entries 6–9). But in the case of strongly electron donating methoxy group containing substrate, the enantioselectivity decreased to 88% (Table 5, entry 10). According to the previous reports, when the methyl group is replaced by the bulkier ethyl group, the ee decreased drastically. However, with **C2**/NBS system, the enantioselectivity e.g., with racemic 1-phenyl-1-propanol remained excellent (99.5% ee, entry 11) as was in the case of 1-phenyl-1-ethanol (99.3%, entry 2). Finally when non benzylic racemic alcohols such as 1-phenyl-2-propanol, 4-phenyl-2-butanol and 2-butanol were used for resolution, this catalytic system provided the corresponding enantioenriched alcohols with 97%, 94% and 97% ee respectively (entries 12–14), which are similar to the ee obtained from **C2**/PhI(OAc)$_2$ system. It is to be noted here that NBS is able to oxidize the alcohol in the absence of a catalyst (entry 15) as was the case with PhI(OAc)$_2$.

3.1. Possible route of the catalytic reaction with PhI(OAc)$_2$

The catalytic route for the Mn–salen catalyzed oxidation of secondary alcohols was first proposed by Xia et al. on the basis of UV–vis spectroscopic analysis and ESI-MS study of the reaction. This route involved the formation of Mn(V)-oxo-salen complex by the oxidation of Mn–salen complex with the oxidant–PhI(OAc)$_2$, which in turn oxidized the secondary alcohol. Subsequently,

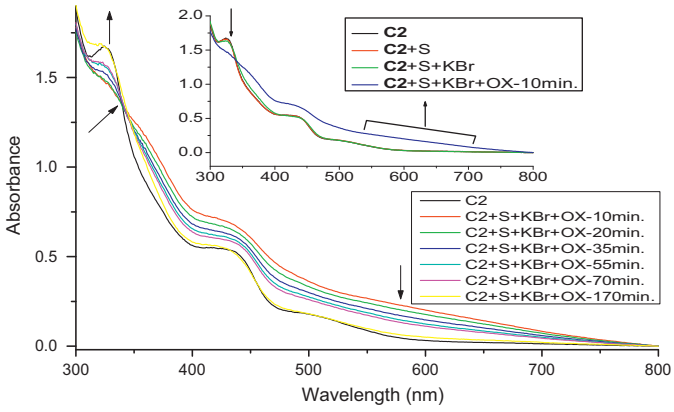
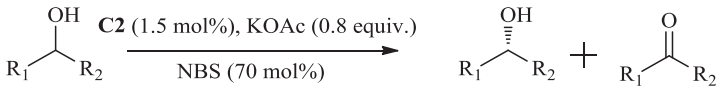


Fig. 1. UV–vis spectra of the reaction mixture after the sequential addition of 1-phenylethanol, KBr and PhI(OAc)$_2$ to the solution of **C2** (**C2**: 1-phenylethanol:KBr:PhI(OAc)$_2$ = 1:7:1:4) in $CHCl_3$ with time. 'S' stands for substrate (1-phenylethanol) and 'OX' stands for oxidant (PhI(OAc)$_2$).

Table 5
OKR of racemic secondary alcohols with **C2** using NBS as oxidant.[a]



Racemic
R_1 = Aryl/alkyl
R_2 = Alkyl

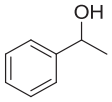
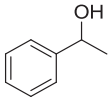
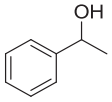
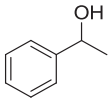
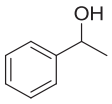
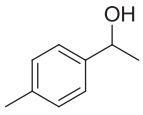
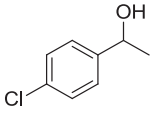
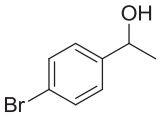
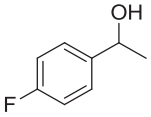
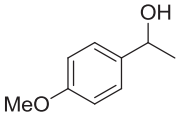
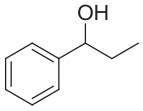
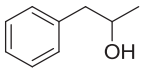
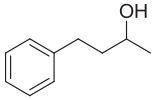
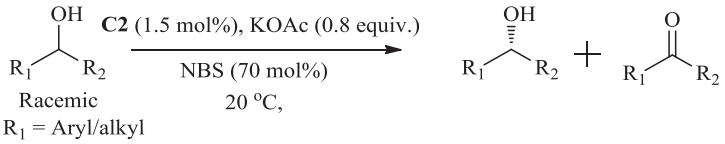
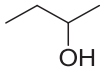
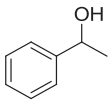
Entry	Racemic alcohol	Catalyst loading (mol%)	Solvent	Conversion (%)[b]	ee (%)[c]	k_{rel}[d]
1		0.5	CH_2Cl_2	65	77	4.51
2		1	CH_2Cl_2	67	85	6.09
3		1.5	CH_2Cl_2	64	99.3	18.02
4		2	CH_2Cl_2	65	99	15.63
5		1.5	DCE	66	97	11.44
6		1.5	CH_2Cl_2	65	96	11.32
7		1.5	CH_2Cl_2	67	98	11.79
8		1.5	CH_2Cl_2	64	97	13.18
9		1.5	CH_2Cl_2	66	96	10.59
v 10		1.5	CH_2Cl_2	64	88	8.05
11		1.5	CH_2Cl_2	66	>99.5	16.43
12		1.5	CH_2Cl_2	65	97	12.25
13		1.5	CH_2Cl_2	64	94	10.69

Table 5 (*Continued*)



Entry	Racemic alcohol	Catalyst loading (mol%)	Solvent	Conversion (%)[b]	ee (%)[c]	k_{rel}[d]
14[e]		1.5	CH_2Cl_2	67	97	10.72
15		–	CH_2Cl_2	66	–	–

[a] Reaction condition: Substrate 0.25 mmol, catalyst 1.5 mol%, KOAc 0.8 equiv., NBS 0.7 equiv. for 50 min at RT in 0.5 mL of organic and 1 mL H_2O solvent mixture.
[b] Determined by ^1H NMR measurement of alcohol and corresponding ketone relative concentration.
[c] Determined by HPLC with a chiral Daicel Chiralcel columns, using hexane/*i*-PrOH solvent mixture as eluent.
[d] Selectivity factor k_{rel} was calculated using the equation, $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$ (where the *C* is the conversion of secondary alcohol and ee is the enantiomeric excess of secondary alcohol).
[e] Determined by GC with BTA column.

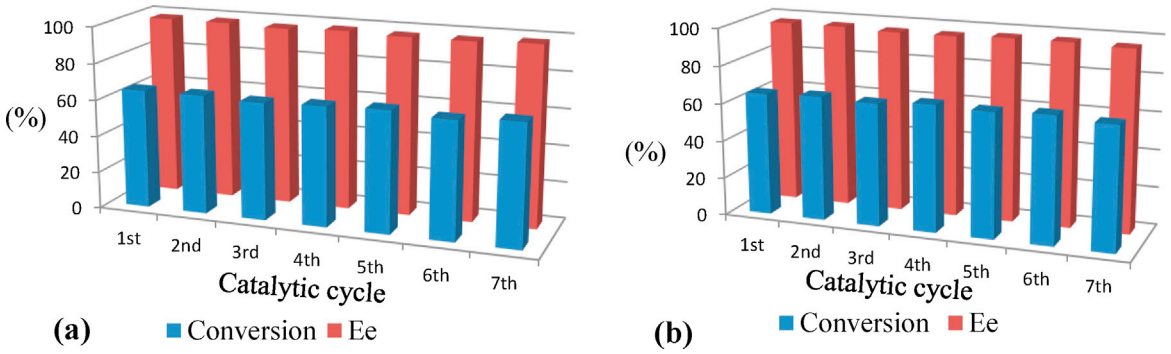


Fig. 2. Recyclability of the catalyst under the optimized reaction condition using 1-phenyl-2-propanol as substrate, (a) with $PhI(OAc)_2$ and (b) with NBS.

Corey et al., based on elaborate experimental results rejected the involvement of Mn(V)-oxo-salen complex and shown that such an enantioselective pathway with pre-transition state assembly involving binding of secondary alcohol with Mn(V)-oxo-salen complex should have given the product with opposite configuration in excess. Here, we would like to mention that in our case the reaction mixture in ESI-MS study clearly indicates the presence of several [O=Mn–salen] species (See supporting information for detail), which is further supported by UV–vis. Studies (Fig. 1, inset spectra, around 600 nm).

Based on the experimental results and spectral studies we would like to propose an alternative mechanism during catalytic OKR of secondary alcohols (Scheme 2). Accordingly, we believe that the oxo species (**II**) and (**III**) react to the preferred enantiomer of the racemic alcohol to form an intermediate (**IV**), which is eventually oxidized via a transition state (**V**).

Finally, it is important to mention that once substoichiometiric amount of oxidant used in the present OKR protocol is consumed, the original catalyst spectrum was resumed (Fig. 1). Hence it can be safely concluded that the catalyst in the present oxidative environment is resistant to oxidative degradation.

3.2. Recyclability of the catalyst

After completion of the reaction, catalyst **C2** being insoluble in hexane was precipitated out by the addition of hexane to the reaction mixture and filtered off. The precipitated complex thus obtained was washed thoroughly with hexane and dried in vacuum. This recovered catalyst was charged with fresh substrate 1-phenyl-2-propanol to check its reusability. Fig. 2 represents the recyclability of the catalyst **C2** with $PhI(OAc)_2$ (Fig. 2a) as well as with NBS (Fig. 2b) as oxidants. The catalyst **C2** seems to be very stable under the applied oxidizing reaction conditions and was recycled successfully up to 7 cycles without any loss in activity and enantioselectivity.

4. Conclusion

In conclusion, we have synthesized macrocyclic Mn(III) salen complexes and used them for OKR of benzylic and non benzylic type of racemic secondary alcohols. Excellent enantioselectivity were achieved (up to 99%) for some of the racemic secondary alcohols used in the present study with the complex **C2** and $PhI(OAc)_2$ and NBS as oxidants in the presence of KBr in dichloromethane/water solvent mixture in 30–50 min. Noticeably, NBS as an oxidant was found to be superior in terms of higher enantioselectivity for the OKR of sterically more demanding racemic secondary alcohols. Based on experimental results, the mechanism for preferential bonding of one of the enantiomer of the substrate (racemic alcohol) is proposed. This complex was found to be very stable under the oxidizing reaction condition and was reused seven times successfully.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.apcata.2013.07.055.

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