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Oxidative kinetic resolution of racemic secondary alcohols catalyzed by resin supported sulfonato-Mn(salen) complex in water

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Abstract

The oxidative kinetic resolution of racemic secondary alcohols catalyzed by resin supported sulfonato-Mn(salen) complex (R,R)-1 with good to excellent ee's in water in the presence of diacetoxyiodobenzene (PhI(OAc)₂) is described. The resin supported (R,R)-1 was recovered quantitatively by simple filtration and reused for three times with consistent activity.

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1. Introduction

Enantiomerically pure secondary alcohols are useful chiral auxiliaries and key synthetic intermediates in pharmaceutical, agrochemical and fine chemical industries [1]. One of the most important methods for the preparation of optically pure enantiomers is the resolution of racemic compounds. Enzyme catalysts are generally used for kinetic resolutions, which react selectively with one of the enantiomers, enabling physical separation after the reaction [2–7]. Recently, the non-enzymatic kinetic resolution has attracted much attention in asymmetric synthesis, especially in the search for versatile and selective chiral catalysts [8,9].

The kinetic resolution of secondary alcohols has been accomplished through acylation [10–20] and oxidation [21–31]. Binol-derived Ru(salen) complexes were used as catalysts in the photoinduced aerobic oxidation of racemic secondary alcohols by Katsuki and co-workers [21]. In spite of the high enantiose-lectivities (ee's) reported, the reaction times are generally long. Later, they reported the asymmetric oxidation of alcohols in the presence of catalytic binol-derived Mn(salen) complexes with PhIO as the oxidant with low yields and moderate ee's [22].

Adam et al. reported that Cr(salen) complexes were effective catalysts for the oxidation of secondary alcohols to ketones [32,33]. Recently Xia and co-workers described the oxidative kinetic resolution of secondary alcohols with excellent ee's using chiral Mn(salen) complex in the presence of PhI(OAc)₂ as the oxidant [34,35]. Although the homogeneous catalysts have been recovered using chromatography, it is envisaged that this process for recycling is uneconomical. Moreover, from the standpoint of green chemistry, the development of more environmentally benign reaction media, which allows water instead of organic solvents, would be desirable.

There is considerable interest in the immobilization of catalysts on solid supports, since the active materials thus prepared are easy to handle and recycle compared to their homogeneous counterparts. Reger and Janda reported the asymmetric epoxidation of unfunctionalised olefins by using polymer supported Jacobsen's catalyst [36] and the kinetic resolution of racemic secondary alcohols by using a proline based diamine catalyst [37] with moderate to excellent ee's. Smith and Liu described the asymmetric epoxidation of 1,2-dihydronaphthalene by using the resin supported Katsuki type catalyst [38]. Recently, we reported the asymmetric epoxidation of unfunctionalised olefins using silica, LDH and resin supported sulfonato-Mn(salen) complex (R,R)-1 (Scheme 1) [39]. During the course of working on sulfonato-Mn(salen) complex for various organic transformations, we found that resin (R,R)-1 as an efficient and reusable catalyst for the oxidative kinetic resolution of racemic secondary

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Scheme 1. Schematic representation of catalysts (R,R)-1 and resin (R,R)-1.

alcohols in water. The resin (R,R)-1 catalyst can be recovered by simple filtration and reused with consistent activity.

2. Experimental

2.1. Materials and methods

All chemicals were purchased from Aldrich and were used as received. All solvents used were analytical grade and used as received from Merck India Pvt. Ltd. ¹H NMR spectra were recorded on a Varian-Gemini 200 MHz spectrometer. Chemical shifts (δ) were reported in ppm, using TMS as internal standard for ¹H NMR. IR spectra were recorded on BIORAD 175C FTIR spectrometer for samples as KBr pellets. UV-Vis-DRS spectra were recorded on a CINTRA 10e GBC UV-Visible Spectrometer. High-performance liquid chromatography (HPLC) was performed using an Agilent-1100 series liquid chromatograph equipped with a single pump and UV detector (fixed at 216 nm) using a CHIRACEL-OD-H and CHIRACEL-OJ-H capillary column with 2-propanol/hexane as eluting agent. ACME silica gel (100-200 mesh) was used for column chromatography and thin layer chromatography was performed on Merck precoated silica gel 60-F254 plates. ICP-AES analyses were performed on IRIS Intrepid II XDL ICP-AES (Thermo Electron Corporation).

2.2. Preparation of resin supported sulfonato-Mn(salen) complex

The resin was obtained by quaternisation of triethylamine (1.05 mL) with 0.5 g of chloromethylated styrene– divinylbenzene copolymer (Merrifield resin, 2% cross-linked, 200–400 mesh, ca. 2 mmol g⁻¹ Cl, Aldrich) in chloroform (10 mL) under reflux for 24 h. Quaternary ammonium resin (0.5 g) was suspended in 10 mL of water containing 100 mg of (R,R)-1. This mixture was stirred at 25 °C for 12 h under a nitrogen atmosphere. The solid catalyst was filtered, washed thoroughly with 100 mL of water, 50 mL of acetonitrile, and 10 mL of methanol and finally vacuum-dried to obtain resin (R,R)-1 (Scheme 2). The Mn content was found to be 0.1 mmol g⁻¹ by AAS.



Scheme 2. Schematic representation of resin (R,R)-1 preparation.

2.2.1. General procedure for kinetic resolution of racemic secondary alcohols under homogeneous conditions

A mixture of $(\pm)1$ -phenylethanol (1 mmol, 0.122 g), (R,R)-1 (1 mol%, 0.008 g), KBr (4 mol%, 0.005 g) and water (3.0 mL) was stirred in a 25 mL round-bottomed flask for few minutes at room temperature. The oxidant PhI(OAc)₂ (0.7 mmol, 0.224 g) was then added and the reaction mixture was stirred for another 10 min. Then the reaction mixture was extracted with ethyl acetate and the organic layer was dried over sodium sulfate and concentrated under vacuum. The unreacted alcohol in the reaction mixture was determined by column chromatography and the ee was determined by chiral HPLC.

2.2.2. General procedure for kinetic resolution of racemic secondary alcohols under heterogeneous conditions

A mixture of $(\pm)1$ -phenylethanol (1 mmol, 0.122 g), resin (R,R)-1 (1 mol%, 0.050 g), KBr (4 mol%, 0.005 g) and water (4.0 mL) was stirred in a 25 mL round-bottomed flask for few minutes at room temperature. The oxidant PhI(OAc)₂ (0.7 mmol, 0.224 g) was then added and the reaction mixture was stirred for another 30 min. Then the reaction mixture was filtered to separate the catalyst, which was reused for another cycle. The filtrate was diluted with ethyl acetate and the organic layer was dried over sodium sulfate and concentrated under vacuum. The unreacted alcohol in the reaction mixture was separated by column chromatography and the ee was determined by chiral HPLC.

3. Results and discussion

3.1. Characterization of resin (R,R)-1

3.1.1. FTIR spectroscopy

The homogeneous (R,R)-1 exhibits IR bands at 1040 cm^{-1} and 1118 cm^{-1} associated with the symmetric and antisymmetric stretching modes of the SO₃⁻ moiety, together with other IR bands at 1624 cm^{-1} (CH=N), 1540 cm^{-1} (C–O), 570 cm^{-1} (Mn–O) and 410 cm^{-1} (Mn–N), which were retained in the resin (R,R)-1 with slight displacements, confirming the successful immobilization of (R,R)-1 on resin support (Fig. 1) [40].

3.1.2. UV–Vis–DRS spectroscopy

The UV–Vis–DRS spectra of the free sulfonato-Mn(salen) complex (R,R)-1 are similar to the resin (R,R)-1 revealing that the complex (R,R)-1 is loaded on the resin support (Fig. 2). Main absorptions appear near 363, 430 and 490 nm. They are probably due to charge-transfer transitions [41,42] and d-d transitions in the Mn ions [43,44], respectively (Fig. 2).

3.2. Catalytic activity of resin (R,R)-1 in the resolution of racemic secondary alcohols

The catalyst (R,R)-1 was synthesized according to our earlier procedure [39]. Its catalytic activity was initially assessed by the oxidation of $(\pm)1$ -phenylethanol in CH₃CN at RT. As the resolution of $(\pm)1$ -phenylethanol with (R,R)-1 occurs within 10 min

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Fig. 1. FTIR spectra of: (a) homogeneous sulfonato-Mn(salen) complex (R,R)-1; (b) resin supported (R,R)-1; and (c) Merrifield's resin.



Fig. 2. UV–Vis–DRS spectra of: (a) homogeneous sulfonato-Mn(salen) complex (R,R)-1; (b) resin supported (R,R)-1; and (c) Merrifield's resin.

but no ee was obtained. Then we examined the influence of solvent on the kinetic resolution of $(\pm)1$ -phenylethanol at room temperature (Scheme 3). In terms of enantioselectivity, water was the best solvent for our catalytic system (Table 1). We have carried out the kinetic resolution experiments in water/organic biphasic system as reported by Li et al. [35] but the ee's are very



Scheme 3. Oxidative kinetic resolution of (\pm) 1-phenylethanol.

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The effect of solvent on oxidative kinetic resolution of $(\pm)1$ -phenylethanol

Entry	Solvent	Conversion (%) ^a	ee (%) ^b
1	CH ₃ CN	50.0	8.0
2	MeOH	65.0	0
3	H ₂ O	55.0	37.8
4	THF	50.0	0
5	Toluene	52.0	0

Reaction conditions: (R,R)-1 (1 mol%), (\pm)1-phenylethanol (1 mmol), PhI(OAc)₂ (0.7 mmol), solvent (3 mL), 10 min, and rt.

^a Conversion was determined by ¹H NMR.

 $^{\rm b}$ Ee was determined by chiral HPLC analysis using CHIRALCEL OJ-H column.

Table 2

The effect of water/organic biphasic system on oxidative kinetic resolution of $(\pm)1$ -phenylethanol

Entry	Solvent	Additive	Conversion (%) ^a	ee (%) ^b
1	CH ₃ CN/H ₂ O	_	35.0	0
2	CH ₃ CN/H ₂ O	KBr	53.0	9.0
3	THF/H ₂ O	_	30.0	0
4	THF/H ₂ O	KBr	50.0	3
5	Toluene/H ₂ O	_	15.0	0
6	Toluene/H ₂ O	KBr	55.0	0

 $\label{eq:Reaction conditions: (R,R)-1 (1 mol\%), (\pm)1-phenylethanol (1 mmol), PhI(OAc)_2 (0.7 mmol), solvent (1 mL), H_2O (2 mL) 10 min, and rt.$

^a Conversion was determined by ¹H NMR.

^b Ee was determined by chiral HPLC analysis using CHIRALCEL OJ-H column.

low (Table 2). The nature of additive has a pronounced effect in the kinetic resolution reactions. This enabled us to carry out the reaction with different additives as shown in Table 3. The ee of the product was more using a cheap and inexpensive additive, KBr.

Next, the substrate scope of the oxidative kinetic resolution was evaluated (Table 4). It can be seen that α -methylbenzyl alcohols with a substituent at the 4-position (Table 4, entries 2 and 3) gave higher ee's compared to the substituent at the 2-position (Table 4, entry 4). However, when the 'R' group of the substrate was changed from methyl to ethyl, the ee of

Table 3	
The effect of additives on oxidative kinetic resolution of (\pm) 1-phenyle	thanol

Entry	Solvent	Additive	Conversion (%) ^a	ee (%) ^b	$K_{\rm rel}^{\rm c}$
1	H ₂ O	_	55.0	37.8	2.7
2	H_2O	N(CH ₃) ₄ Br	57.0	52.0	3.7
3	H_2O	N(C ₂ H ₅) ₄ Br	60.0	53.0	3.4
4	H_2O	KBr	61.0	55.3	3.5
5	H_2O	KCl	52.0	35.0	2.7
6	H_2O	KI	50.0	35.0	2.8
7	H_2O	NaBr	55.0	50.0	3.8

^a Conversion (C) was determined by ¹H NMR.

^b Ee was determined by chiral HPLC analysis using CHIRALCEL OJ-H column.

^c $K_{\text{rel}} = \ln[(1 - C)(1 - \text{ee})]/\ln[(1 - C)(1 + \text{ee})].$

Table 4
Asymmetric kinetic resolution of racemic secondary alcohols

Entry	Substrate	Conversion	Conversion (%) ^a		ee (%) ^b		$K_{\rm rel}{}^{\rm c}$	
		A	В	A	В	A	В	
1	OH	61.0	57.0	55.3	53.9	3.5	2.4	
2	OH Br	63.0	59.0	58.1	55.3	3.5	3.7	
3	OH CI	61.0	60.0	42.9	41.5	3.6	2.5	
4	Cl OH	25.0	23.0	19.8	18.0	4.7	4.8	
5	OH	53.0	50.0	35.9	33.5	2.7	2.7	
6	ОН	65.0	63.0	79.7	77.3	5.7	6.0	
7	OH	67.0	65.0	96.0	92.5	9.3	9.2	
8	ОН	63.0	59.0	76.9	73.7	5.8	6.6	

Reaction conditions: (A) (R,R)-1 (1 mol%), substrate (1 mmol), PhI(OAc)₂ (0.7 mmol), KBr (4 mol%), H₂O (3 mL), and rt; (B) resin (R,R)-1 (1 mol%), substrate (1 mmol), PhI(OAc)₂ (0.7 mmol), KBr (4 mol%), H₂O (4 mL), and rt.

^a Conversion (C) was determined by ¹H NMR.

^b ee was determined by chiral HPLC analysis using CHIRALCEL OJ-H and OD-H columns.

^c $K_{\text{rel}} = \ln[(1 - C)(1 - \text{ee})]/\ln[(1 - C)(1 + \text{ee})].$

the reaction decreased sharply (Table 4, entry 5). Menthol, 1indanol and 1,2,3,4-tetrahydro-1-naphthol (Table 4, entries 6–8) gave higher ee's. We observed slightly lower ee's with resin (R,R)-1 compared to its homogeneous counterpart. While the selectivity factor K_{rel} remains modest in many cases, ranging from 2.4 to 9.3, the reusability of the resin (R,R)-1 was appreciable. As mentioned in the literature [34,35] the steric hindrance at the 5,5' position was favorable for the catalytic activity of the Jacobsen's Mn(salen) complex. Substitution of the bulkier *tert*-butyl groups at 5,5' position with $-SO_3Na$ groups may be the reason for the low ee's in our catalytic system.

Table 5	
Reusability study of the catalyst	

Run	Conversion ^a	ee (%) ^b	$K_{\rm rel}^{\rm c}$	
1	61.5	55.3	3.4	
2	61.0	55.0	3.4	
3	61.0	54.5	3.4	
4	60.0	54.0	3.5	

Reaction conditions: resin (R,R)-1 (1 mol%), substrate (1 mmol), $PhI(OAc)_2$ (0.7 mmol), KBr (4 mol%), H_2O (4 mL), and rt.

^a Conversion was determined by ¹H NMR.

^b The ee was determined by chiral HPLC analysis using CHIRALCEL OJ-H column.

^c $K_{\text{rel}} = \ln[(1 - C)(1 - \text{ee})]/\ln[(1 - C)(1 + \text{ee})].$

3.3. Reusability study of the catalyst

The catalyst was recovered by simple filtration and washed with THF and air-dried. The recovered catalyst was reused and consistent activity was noticed even after third cycle (Table 5). When a fresh reaction was conducted with the filtrate obtained at the end of the reaction, almost no catalytic activity of the filtrate was observed. Moreover, the absence of Mn in the filtrate was determined by ICP-AES analysis.

4. Conclusion

In conclusion, we found that sulfonato-Mn(salen) complex is an efficient catalyst for the resolution of racemic secondary alcohols. Although the selectivity factor K_{rel} remains modest in many cases, the resin (R,R)-1 catalyst can be recycled for three times with consistent activity.

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