

# 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)<sub>2</sub>) 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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**Keywords:** Kinetic resolution; Sulfonato-Mn(salen) complex (R,R)-1; Resin; PhI(OAc)<sub>2</sub>; Enantioselectivity (ee)

## 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 enantioselectivities (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)<sub>2</sub> 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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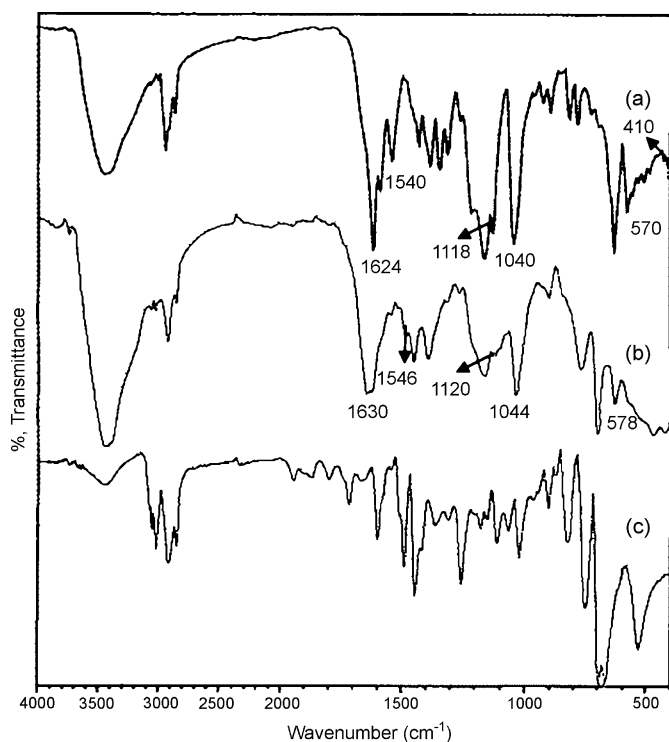


Fig. 1. FTIR spectra of: (a) homogeneous sulfonato-Mn(salen) complex (R,R)-1; (b) resin supported (R,R)-1; and (c) Merrifield's resin.

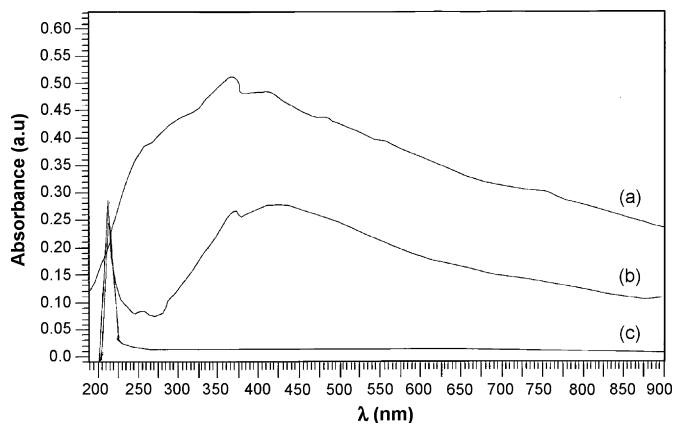
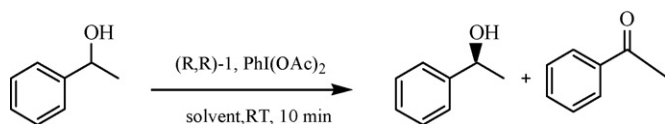


Fig. 2. UV-Vis-DRS spectra of: (a) homogeneous sulfonato-Mn(salen) complex (R,R)-1; (b) resin supported (R,R)-1; and (c) Merrifield's resin.

but no ee was obtained. Then we examined the influence of solvent on the kinetic resolution of (±)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 (±)1-phenylethanol.

Table 1

The effect of solvent on oxidative kinetic resolution of (±)1-phenylethanol

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

Reaction conditions: (R,R)-1 (1 mol%), (±)1-phenylethanol (1 mmol), PhI(OAc)<sub>2</sub> (0.7 mmol), solvent (3 mL), 10 min, and rt.

<sup>a</sup> Conversion was determined by <sup>1</sup>H NMR.

<sup>b</sup> 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 (±)1-phenylethanol

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

Reaction conditions: (R,R)-1 (1 mol%), (±)1-phenylethanol (1 mmol), PhI(OAc)<sub>2</sub> (0.7 mmol), solvent (1 mL), H<sub>2</sub>O (2 mL) 10 min, and rt.

<sup>a</sup> Conversion was determined by <sup>1</sup>H NMR.

<sup>b</sup> 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 (±)1-phenylethanol

Entry	Solvent	Additive	Conversion (%) <sup>a</sup>	ee (%) <sup>b</sup>	<i>K</i> <sub>rel</sub> <sup>c</sup>
1	H <sub>2</sub> O	–	55.0	37.8	2.7
2	H <sub>2</sub> O	N(CH <sub>3</sub> ) <sub>4</sub> Br	57.0	52.0	3.7
3	H <sub>2</sub> O	N(C <sub>2</sub> H <sub>5</sub> ) <sub>4</sub> Br	60.0	53.0	3.4
4	H <sub>2</sub> O	KBr	61.0	55.3	3.5
5	H <sub>2</sub> O	KCl	52.0	35.0	2.7
6	H <sub>2</sub> O	KI	50.0	35.0	2.8
7	H <sub>2</sub> O	NaBr	55.0	50.0	3.8

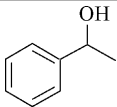
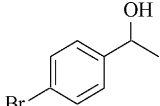
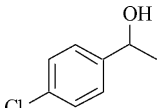
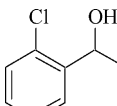
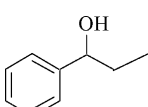
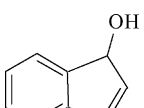
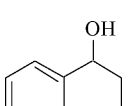
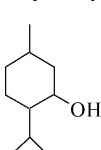
Reaction conditions: (R,R)-1 (1 mol%), (±)1-phenylethanol (1 mmol), PhI(OAc)<sub>2</sub> (0.7 mmol), additive (4 mol%), H<sub>2</sub>O (3 mL), and rt.

<sup>a</sup> Conversion (C) was determined by <sup>1</sup>H NMR.

<sup>b</sup> Ee was determined by chiral HPLC analysis using CHIRALCEL OJ-H column.

<sup>c</sup> *K*<sub>rel</sub> = ln[(1 - C)(1 - ee)]/ln[(1 - C)(1 + ee)].

Table 4  
Asymmetric kinetic resolution of racemic secondary alcohols

Entry	Substrate	Conversion (%) <sup>a</sup>		ee (%) <sup>b</sup>		$K_{rel}$ <sup>c</sup>	
		A	B	A	B	A	B
1		61.0	57.0	55.3	53.9	3.5	2.4
2		63.0	59.0	58.1	55.3	3.5	3.7
3		61.0	60.0	42.9	41.5	3.6	2.5
4		25.0	23.0	19.8	18.0	4.7	4.8
5		53.0	50.0	35.9	33.5	2.7	2.7
6		65.0	63.0	79.7	77.3	5.7	6.0
7		67.0	65.0	96.0	92.5	9.3	9.2
8		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)<sub>2</sub> (0.7 mmol), KBr (4 mol%), H<sub>2</sub>O (3 mL), and rt; (B) resin (R,R)-1 (1 mol%), substrate (1 mmol), PhI(OAc)<sub>2</sub> (0.7 mmol), KBr (4 mol%), H<sub>2</sub>O (4 mL), and rt.

<sup>a</sup> Conversion (C) was determined by <sup>1</sup>H NMR.

<sup>b</sup> ee was determined by chiral HPLC analysis using CHIRALCEL OJ-H and OD-H columns.

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

the reaction decreased sharply (Table 4, entry 5). Menthol, 1-indanol 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 <sup>a</sup>	ee (%) <sup>b</sup>	$K_{rel}$ <sup>c</sup>
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)<sub>2</sub> (0.7 mmol), KBr (4 mol%), H<sub>2</sub>O (4 mL), and rt.

<sup>a</sup> Conversion was determined by <sup>1</sup>H NMR.

<sup>b</sup> The ee was determined by chiral HPLC analysis using CHIRALCEL OJ-H column.

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

### 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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