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COMMUNICATION

Oxidative kinetic resolution of racemic secondary alcohols in water with chiral PNNP/Ir catalyst†

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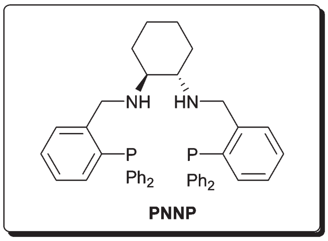
Using water as solvent, the oxidative kinetic resolution of a wide range of racemic secondary alcohols with a chiral PNNP/Ir catalyst was investigated. The catalytic reaction proceeded smoothly with excellent enantioselectivity (up to 97% ee) under mild conditions, providing an environmentally benign process to achieve optically active alcohols.

Introduction

Optically active alcohols are important for pharmaceutical and agrochemical industries. In past decades, the highly efficient asymmetric reduction of prochiral ketones catalyzed by transition metal complexes to attain chiral alcohols has made great progress.[1] In 1996, we firstly synthesized a series of C_2-symmetric chiral diimino- and diaminodiphosphine ligands (PNNP-type, Scheme 1). Since then, a new class of chiral Ru, Rh, Fe and Ir complexes with PNNP-type ligands have been synthesized and successfully used as catalysts in the asymmetric transfer hydrogenation of aromatic ketones, leading to corresponding chiral alcohols with up to 99% ee and the molar ratio of substrate : catalyst up to 10 000 : 1.[2] Among the successful methods used to obtain chiral alcohols, oxidative kinetic resolution (OKR) of racemic alcohols—a process where the two enantiomers of a racemate are transformed to products at different reaction rates—is another classical and efficient method.[3] In some cases, the variety and abundance of racemic alcohols even make the OKR method more efficient, and thus, more important than the reduction of ketones for the production of chiral alcohols. Recently, several effective non-enzymatic catalysts for the OKR of racemic alcohols have been developed. Sigman's and Stoltz's groups intensively studied aerobic OKR of secondary alcohols catalyzed by (−)-sparteine/Pd(II) to conveniently access enantiomerically enriched secondary alcohols.[4,5] Katsuki *et al.* investigated iron-catalyzed aerobic OKR of secondary alcohols with good to high enantioselectivity.[6] Xia *et al.* reported chiral Mn (salen)-complex catalyzed kinetic resolution of secondary alcohols with excellent enantioselectivity (up to 98% ee) in water.[7]



Scheme 1 Chiral diaminodiphosphine ligand.

In view of sustainable development, green chemistry has attracted more and more attention. Compared with other organic solvents, water is abundant and ubiquitous on the earth as well as being a clean, safe, and easy-to-handle solvent. However, most organic reactions are carried out in organic solvents, which results in about 80% of chemical pollution.[8] In the past few years, chemists have devoted themselves to investigating organic reactions using water as a solvent.[9] Compared with the extensive research being achieved in asymmetric transfer hydrogenation using water as solvent,[9b] there are fewer examples on the OKR method carried out in water.[7,8] To our delight, superior to most transition metal catalysts which are sensitive to moisture, the PNNP/Ir catalyst shows good water tolerance.[9d] Therefore, following our previous research on OKR,[3f] herein we report for the first time the OKR of racemic secondary alcohols with PNNP/Ir catalyst in water, which gives chiral alcohols with excellent enantioselectivity under mild conditions.

Results and discussion

In the initial experiment, the racemic 1-phenylpropanol was chosen as a model substrate. The enantioselective oxidation was carried out in water, using catalyst prepared *in situ* from the chiral ligand (*S*,*S*)-PNNP and metal precursors. We examined the OKR of racemic 1-phenylpropanol catalyzed by the chiral PNNP ligand coupled with various Ru(II), Rh(I), or Ir(I) complexes and the results are summarized in Table 1. It can be seen that both the Ru- and Rh-based catalysts were almost inert to the enantioselective oxidation of 1-phenylpropanol. Under the same reaction conditions, the Ir-based catalysts exhibited high catalytic activity and enantioselectivity. With the (*S*,*S*)-PNNP/Ir catalyst, (*R*)-1-phenylpropanol is fast transferred to propiophenone while

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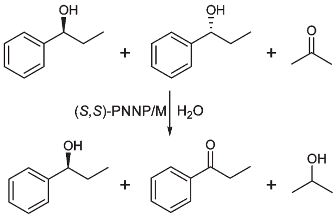
Table 1 OKR of racemic 1-phenylpropanol catalyzed by the chiral PNNP ligand and various metal complexes in water[a]



Entry	Metal complexes	Conv.[b] [%]	ee[b] [%]
1	$RuCl_2(PPh_3)_3$	—	—
2	$Ru(DMSO)_4Cl_2$	—	—
3	$RuH_2(PPh_3)_4$	—	—
4	$RhCl(PPh_3)_3$	2	—
5	$RhH(CO)(PPh_3)_3$	—	—
6	$IrH(CO)(PPh_3)_3$	0.3	—
7	$[IrCl(COD)]_2$	62	93
8	$[IrHCl_2(COD)]_2$	53	90
9	$IrCl(CO)(PPh_3)_2$	1	—

[a] Reaction conditions: racemic 1-phenylpropanol (1 mmol); catalyst (0.005 mmol); solvent: water (8 mL); oxidant: acetone (2.2 mL); additive: PPNCl (0.05 mmol); sub.–cat.–KOH = 200 : 1 : 2; room temperature; time: 21 h. [b] Conversions and enantiomeric excesses were determined by GC analysis using a CP-Chirasil-Dex CB column.

(*S*)-1-phenylpropanol—reacting slowly—is left. The ketone and the final chiral alcohol are key building blocks in organic synthesis; no waste is produced. Notably, the catalyst generated *in situ* from chiral PNNP ligand and $[IrCl(COD)]_2$ gave 62% conversion and 93% ee at room temperature (Table 1, entry 7). Therefore, $[IrCl(COD)]_2$ was used as the metal precursor for further study.

In kinetic resolutions, enantiomers of a racemic substrate react at different rates to form a product. If the kinetic resolution is efficient, one of the enantiomers of the racemic mixture is transformed into the product while the other is recovered unchanged.[3a,l] Thus, conversion around 50% based on racemic starting material is a preferred result, which means a maximum yield of enantiopure compound. To obtain the best resolution efficiency, the optimal reaction time is a vital factor. The influence of reaction time on the OKR of racemic 1-phenylpropanol with chiral PNNP/Ir catalyst was examined and the results are shown in Fig. 1. It indicates that the reaction proceeds rapidly at the beginning and then slows down. The highest ee value was obtained after 16 h at 28 °C, and the corresponding conversion was 61%.

As the substrate and catalyst are insoluble in water, the addition of a phase transfer catalyst (PTC) is necessary. The effects of different PTCs, such as sodium dodecyl sulfate (SDS), tetrabutyl ammonium bromide (TBAB), and bis(triphenylphosphoranylidene)ammonium chloride (PPNCl) on the OKR of racemic 1-phenylpropanol were investigated (Table 2). When PPNCl was introduced to the OKR of racemic 1-phenylpropanol, the catalytic reaction proceeded smoothly with excellent enantioselectivity (97% ee, Table 2, entry 7).

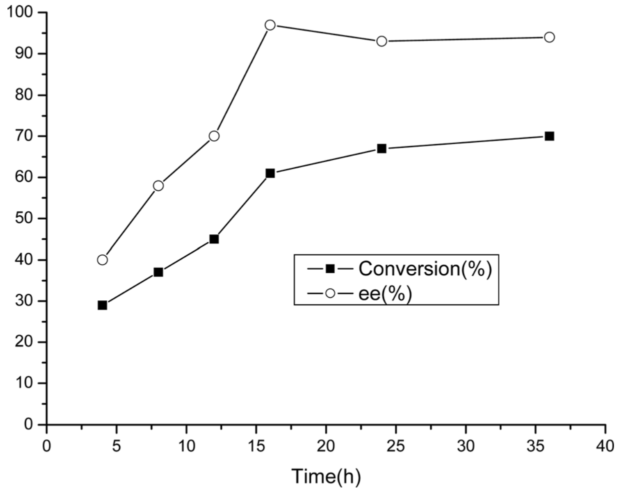


Fig. 1 Effect of time on the OKR of racemic 1-phenylpropanol with chiral PNNP/Ir catalyst. Reaction conditions: racemic 1-phenylpropanol (1 mmol); catalyst (0.005 mmol); solvent: water (8 mL); oxidant: acetone (2.2 mL); additive: PPNCl (0.05 mmol); sub.–cat.–KOH = 200 : 1 : 2; temperature: 28 °C.

Table 2 Effect of PTC on the OKR of racemic 1-phenylpropanol with chiral PNNP/Ir catalyst[a]

Entry	Additive	Conv.[b] [%]	ee[b] [%]
1	Hexadecyltrimethylammonium bromide	45	79
2	Sodium dodecylbenzenesulfonate	3	—
3	Tetramethylammonium bromide	43	77
4	Benzyltriethylammonium chloride	46	84
5	Sodium dodecyl sulfate	11	22
6	Tetrabutylammonium bromide	40	62
7	Bis(triphenylphosphoranylidene) ammonium chloride	61	97
8	Tetrabutylammonium iodide	1	—

[a] Reaction conditions: racemic 1-phenylpropanol (1 mmol); catalyst (0.005 mmol); PTC: (0.05 mmol); solvent: water (8 mL); oxidant: acetone (2.2 mL); sub.–cat.–KOH = 200 : 1 : 2; temperature: 28 °C; time 16 h. [b] Conversions and enantiomeric excesses were determined as shown in Table 1.

Table 3 Effect of the amount of base on the OKR of racemic 1-phenylpropanol with chiral PNNP/Ir catalyst[a]

Entry	Sub.–cat.–KOH	Conv.[b] [%]	ee[b] [%]
1	200 : 1 : 0	—	—
2	200 : 1 : 1	45	66
3	200 : 1 : 2	62	93
4	200 : 1 : 4	75	87
5	200 : 1 : 8	85	66

[a] Reaction conditions: racemic 1-phenylpropanol (1 mmol); catalyst (0.005 mmol); solvent: water (8 mL); oxidant: acetone (2.2 mL); additive: PPNCl (0.05 mmol); room temperature; time: 21 h. [b] Conversions and enantiomeric excesses were determined as shown in Table 1.

Adding a base is known to be crucial to the OKR of racemic alcohols on reactivity and enantioselectivity.[3f] Table 3 presents the effect of bases on the OKR of racemic 1-phenylpropanol. It shows that no reaction occurred if the base was absent. Both the reaction rate and ee increased dramatically with the addition of KOH. With 2 eq. (related to catalyst) of KOH, the OKR afforded the best ee (Table 3, entry 3). However, excess base decreased

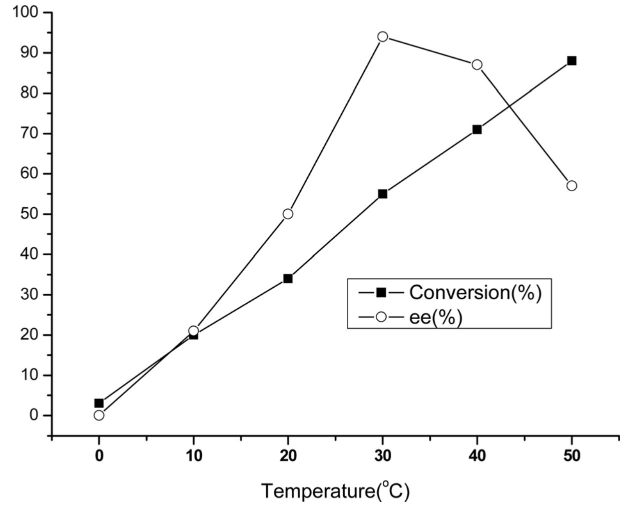
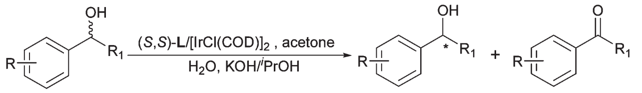
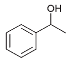
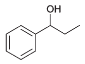
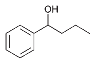
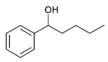
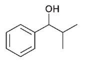
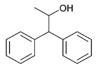
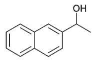
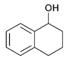
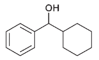
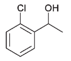
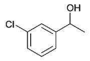
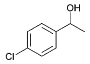
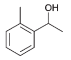
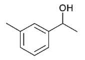
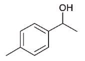
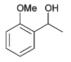
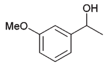
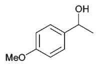


Fig. 2 Effect of temperature on the OKR of racemic 1-phenylpropanol with chiral PNNP/Ir catalyst. Reaction conditions: racemic 1-phenylpropanol (1 mmol); catalyst (0.005 mmol); solvent: water (8 mL); oxidant: acetone (2.2 mL); additive: PPNCl (0.05 mmol); sub.–cat.–KOH = 200 : 1 : 2; time: 15 h.

Table 4 The OKR of various racemic secondary alcohols with chiral PNNP/Ir catalyst in water[a]



Entry	Substrate	Temp. [°C]	Time [h]	Conv.[b] [%]	ee[b] [%]
1		28	10	65	90
2		28	16	61	97
3		28	24	56	97
4		28	24	58	97
5		40	44	51	89
6		45	32	45	80
7		28	15	65	80
8		28	5	61	84
9		28	33	53	97
10		28	24	—	—
11		18	6	54	64
12		18	6	54	62
13		28	5	1	—
14		28	4.5	59	94
15		28	5	68	97
16		28	22	1	—
17		28	6.5	59	91
18		28	5.5	63	93

[a] Reaction conditions: racemic secondary alcohol (1 mmol); catalyst (0.005 mmol); solvent: water (8 mL); oxidant: acetone (2.2 mL); additive: PPNCl (0.05 mmol); sub.–cat.–KOH = 200 : 1 : 2. [b] Conversions were determined by GC analysis and enantiomeric excesses were determined by GC analysis using a CP-Chirasil-Dex CB column or HPLC analysis using a Daicel Chiralcel OD column.

the enantioselectivity although the conversion increased (Table 3, entries 4, 5). The role of the base is considered to be increasing the concentration of the 2-propoxide ion, which coordinates with M and then β-eliminates, forming a reducing M–H species and acetone.[1l] In our previous study, we observed that excess base initiated the aldol condensation of acetone, which could hamper the catalytic cycle.[3f] These results are also in accordance with Noyori's study of OKR with chiral Ru–TsDPEN complexes in acetone.[3n]

Moreover, we also investigated the correlation between conversion, enantioselectivity and temperature of the OKR on racemic 1-phenylpropanol. As shown in Fig. 2, the reaction rate accelerated when the reaction temperature increased. However, at higher temperatures, the ee dropped quickly. Therefore, it is vital to carry out the OKR reaction under proper temperature.

With the optimized conditions in hand, we next screened the OKR of various racemic secondary alcohols in water with the catalyst generated *in situ* from chiral PNNP ligand and $[IrCl(COD)]_2$. As shown in Table 4, using water as solvent, the catalytic reactions of racemic 1-phenylethanol and its derivatives proceeded smoothly with up to 97% ee under mild conditions. However, when the alkyl substituent of the substrate was substituted with a bulkier group, the reaction proceeded slowly with decreased enantioselectivity (Table 4, entry 5). The decrease in reactivity and enantioselectivity may be due to the steric repulsion between alcohol and catalyst. An unexpected example is 1-cyclohexyl-1-phenyl-methanol, which has bulkier substituents but affords excellent enantioselectivity (Table 4, entry 9). Furthermore, enantioselective oxidation of substituted phenylethanol in water was also investigated. Introduction of a substituent group to the *ortho* position of the aromatic ring dramatically decreases the reactivity and enantioselectivity of the reaction (Table 4, entries 10, 13, and 16). Xia *et al.* also observed that in the OKR of secondary alcohols catalyzed by chiral Mn(salen)-complex, 2′-chloro-1-phenylethanol gave the lowest conversion and enantioselectivity.[7a] The decrease in conversion may be caused by the steric hindrance of the substituent. When the chloro substituent is on the *meta* or *para* position of the aromatic ring, the activity was greatly increased, although the enantioselectivity decreased (Table 4, entries 11 and 12). However, with electron donating groups, such as a methyl- or methoxy-substituent on the *meta* or *para* position of the aromatic ring, the OKR leads to excellent results in terms of both conversion and enantioselectivity (Table 4, entries 14, 15, 17 and 18). These results show that the catalyst is highly active and enantioselective for the OKR of a wide range of racemic alcohols in water.

Conclusions

In summary, when using water as solvent, the OKR of various racemic secondary alcohols with chiral PNNP/Ir catalyst proceeded smoothly with up to 97% ee under mild conditions. Being highly efficient as well as greatly reducing the need for an organic solvent, this method presents an environmentally benign process to achieve optically active alcohols. Further studies on the mechanism are now being investigated in our laboratory.

Experimental section

General procedure for the catalytic reaction

Under a nitrogen atmosphere, the metal complex and chiral PNNP ligand were placed in a Schlenk tube equipped with a Teflon-coated magnetic stirring bar. Dichloromethane (0.5 mL) was then added and the mixture was stirred for a few minutes to generate catalyst *in situ*. Subsequently, acetone, PPNCl, and water were successively introduced. After the mixture was stirred for 1 h, an appropriate amount of KOH/^{i}PrOH solution was added. After 0.5 h, the substrate was added and the mixture was continually stirred at the desired temperature for the required reaction time. At the end of the reaction, the product was extracted with ethyl acetate and then passed through a short silica gel column. The conversion of the alcohol was determined by GC and the ee was determined by GC or HPLC.

Acknowledgements

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