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The novel water-soluble chiral PNNP-type ligand for the enantioselective reduction of ketones in aqueous media

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Abstract

The condensation of *o*-(diphenylphosphino)benzaldehyde and (*R*,*R*)-1,2-diaminocyclohexane in dichloromethane gives a diiminodiphosphine ligand, which is reduced with excess $NaBH_4$ in refluxing ethanol to afford the corresponding diaminodiphosphine ligand [(*R*,*R*)-$C_6P_2(NH)_2$]. The novel water-soluble PNNP-type tetradentate diaminodiphosphine ligand [(*R*,*R*)-$C_6P_2(NH)_2(SO_3Na)_4$] has been prepared by the sulfonation of the chiral ligand [(*R*,*R*)-$C_6P_2(NH)_2$] and also characterized by IR, NMR and CD. The water-soluble iridium catalyst is generated in situ from [IrCl(COD)(Ph_3P)] and water-soluble ligand [(*R*,*R*)-$C_6P_2(NH)_2(SO_3Na)_4$] in a mixture solvent of 2-propanol and water. This water-soluble iridium catalytic system has been examined for asymmetric transfer hydrogenation of various aromatic ketones in aqueous media, giving the corresponding optically active alcohols in high yield and excellent enantioselectivity. Even those ketones having a great bulkiness of the alkyl group, such as isobutyrophenone, phenyl cyclohexyl and 1,1-diphenylacetone, are smoothly converted to optically active alcohols in up to 99% ee.

Keywords: PNNP-type diaminodiphosphine; Water-soluble chiral ligand; Asymmetric transfer hydrogenation; Aromatic ketone; Chiral alcohols

1. Introduction

The catalytic enantioselective reduction of ketones has been extensively studied with a great success during the last decade [1–4]. A particularly useful method is the asymmetric transfer hydrogenation catalyzed by metal complexes associated with various chiral ligands and using 2-propanol or HCOOH/Et_3N as a hydrogen source [5–12]. Amongst the used chiral ligands, bifunctional aminophosphine ligands have emerged as very effective ligands for the enantioselective reduction reaction [13–16] as well as for epoxidation [17,18] and cyclopropanation [19–21].

However, with the increasing demand for environmentally friendly methods [22], the asymmetric transfer hydrogenation performed in water is now of great interest. Therefore, there is increasing interest in developing water-soluble chiral catalytic systems which allow asymmetric transfer reaction to be carried out in water [23–25]. Among the water-soluble chiral catalysts used in this field, the most notable catalytic systems are Ru(II)-sulfonated-TsDPEN and its supported derivatives [26–30]. Ru(II)-TsDPEN [TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylene diamine] is first invented by Noyori and co-workers [31]. Ru(II)-sulfonated-BINAP [32,33] and Ru(II)-chiral amino amides [34,35] as water-soluble catalysts are also used in asymmetric hydrogenation in aqueous solution. There are relatively few reports on using iridium-based water-soluble chiral aminophosphine system as catalyst [36].

In our previous studies, we have synthesized a series of C_2-symmetrical chiral diaminodiphosphine ligands (PNNP-type), which have been proved to be very efficient for the asymmetric transfer hydrogenation of ketones in 2-propanol [37–42]. However, 2-propanol as solvent and the hydrogen donor still needs distillation and degassing. Herein we describe a novel catalytic system generated in situ from the water-soluble chiral PNNP-type ligand and iridium complex to catalyze the asymmetric transfer hydrogenation of ketones in aqueous media. Good to excellent enantioselectivity has been obtained and the catalytic experiments are greatly simplified.

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2. Experimental

2.1. General methods

All experiments were carried out in a nitrogen atmosphere with a Schlenk tube. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrophotometer. NMR spectra were recorded on a Varian Unity-500 spectrometer. ^{31}P spectra were referenced to 85% H_3PO_4 as external standard. ^{1}H NMR chemical shifts were reported in ppm relative to TMS. The element analysis was carried out on a CARLO ERBA 1110 elemental analyzer. All melting points were determined on a X-4 digital melting point apparatus and were uncorrected. CD spectra were measured with a JASCO J-810 spectrophotometer.

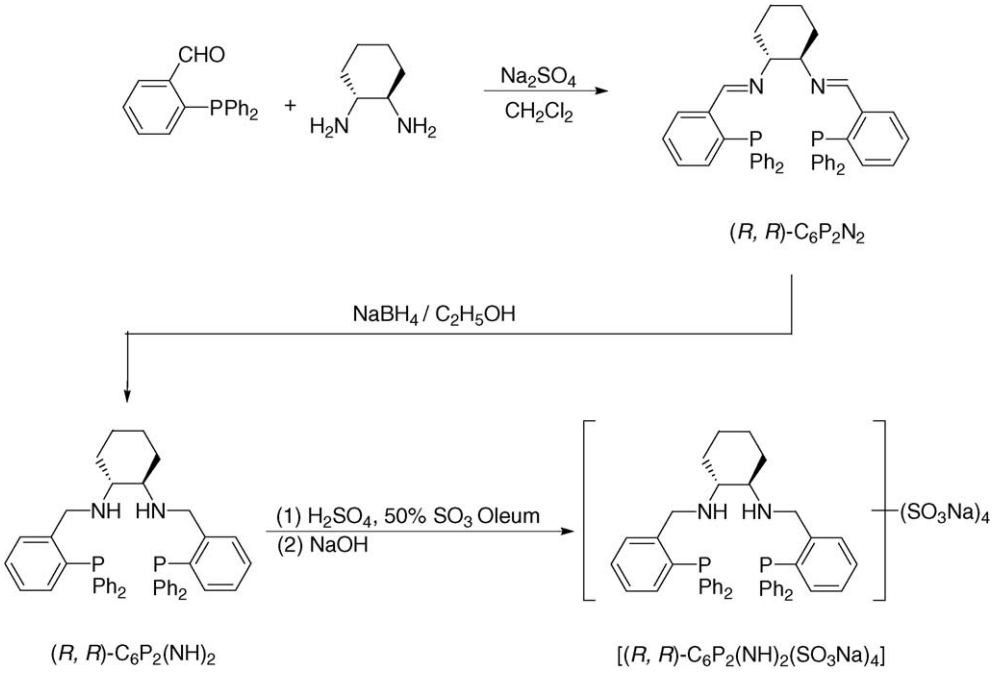
2.2. Synthesis and characterization of water-soluble chiral ligand [(R,R)-$C_6P_2(NH)_2(SO_3Na)_4$]

A chiral PNNP-type ligand, (*R,R*)-$C_6P_2(NH)_2$ was prepared according to our previous reported procedure [31]. (*R,R*)-$C_6P_2(NH)_2$ (1 g, 1.52 mmol) was dissolved in concentrated sulphuric acid (5 mL) with slowly dropwise addition of 50% SO_3 oleum (15 mL), and the mixture was stirred at 0–5 °C. The solution was tested at intervals by adding one drop to water (~3 mL) until a test drop gave a clear aqueous solution (about 2 days). The mixture was poured very slowly into 100 mL of ice-cooled water and neutralized with 50% sodium hydroxide at 0 °C until the pH reached 8–9. Then the solution was poured into 100 mL of methanol to precipitate any sodium sulphate. The filtered solution of methanol and water was evaporated and sulfonated (*R,R*)-$C_6P_2(NH)_2(SO_3Na)_4$ was obtained as pale yellow solid (1.74 g, 89.6% yield). Mp.: 238 °C (dec.) IR (KBr): 3448vs, 3055m, 2926s, 2854m, 1634m, 1442s, 1196vs, 1144s, 1038s, 791m, 752m, 692s, 622vs and 516m cm^{-1}. ^{1}H NMR (D_2O): δ 0.75 (S, 2H, $–CH_2–$), 0.96 (m, 2H, $–CH_2–$), 1.32 (t, 2H, $–CH_2–$), 1.67 (m, 2H, $–CH_2–$), 1.77 (m, 2H, –NH–), 2.08 (S, 2H, –CH–), 3.72 (d, 2H, J = 15.0 Hz, $ArCH_2–$), 3.79 (d, 2H, J = 10 Hz, $ArCH_2–$), 6.69–7.72 (m, 28 H, Ar–). ^{31}P NMR (D_2O): δ −15.68 ppm. Anal. Calc. for (*R,R*)-$C_6P_2(NH)_2(SO_3Na)_4 \cdot 4H_2O$: C, 46.23; H, 4.23; N, 2.45. Found: C, 45.90; H, 4.15; N, 2.40%.

The ligand (*S,S*)-$C_6P_2(NH)_2(SO_3Na)_4$ was also synthesized by the above mentioned procedure.

2.3. Typical procedure for asymmetric transfer hydrogenation of ketones catalyzed by water-soluble chiral iridium catalytic system using 2-propanol as hydrogen source

A water-soluble chiral ligand (0.0038 mmol) and iridium complex [IrCl(COD)(PPh_3)] (0.0025 mmol) were added to a Schlenk tube, and then 2-propanol (10 mL) and H_2O (5 mL) were introduced under nitrogen without purification. After stirring for 20 min, KOH/H_2O (2.0 M, 1 mL) was added to the mixture which kept stirring for 15 min. Then the ketone substrate was added, and the solution was stirred at desired temperature for the required reaction time. At the end of experiment, a mixed solvent (5 mL) of *n*-hexane and diethyl ether (V:V; 10:1) was added to extract organic materials. After dried over anhydrous Na_2SO_4, the chemical yield and the enantioselectivity of product were determined by GLC analysis using a Chiral Chrompack CP-cyclodextrin-β-236-M-19 column.



Scheme 1. The synthesis of water-soluble chiral ligand.

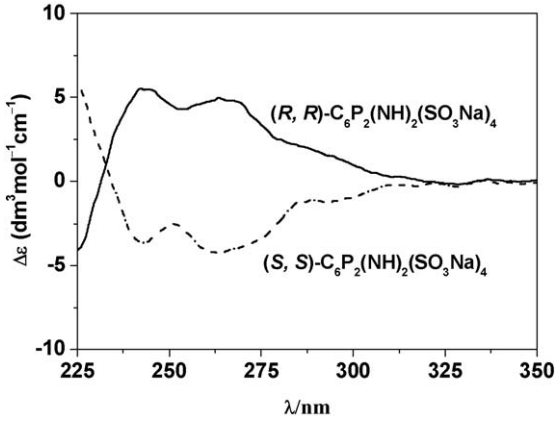


Fig. 1. The CD spectra of (*R*,*R*), (*S*,*S*)-$C_6P_2(NH)_2(SO_3Na)_4$.

3. Results and discussion

3.1. Preparation and characterization of water-soluble chiral PNNP-type ligands

A chiral PNNP-type ligand, (*R*,*R*)-$C_6P_2N_2$, was prepared by the condensation of *o*-(diphenylphosphino)benzylaldehyde and (*R*,*R*)-1,2-diaminocyclohexane in dichloromethane using anhydrous Na_2SO_4 as a dehydrating agent. Reduction of (*R*,*R*)-$C_6P_2N_2$ with excess $NaBH_4$ was carried out in refluxing ethanol to afford the corresponding (*R*,*R*)-*N*,*N*′-bis[*o*-(diphenyldiphosphino)benzylidene]-cyclohexane-1,2-diamine [(*R*,*R*)-$C_6P_2(NH)_2$], in 75–80% yield [32]. The chiral PNNP-type ligand (*R*,*R*)-$C_6P_2(NH)_2$ was further sulfonated by using 50% SO_3 oleum to give a water-soluble chiral ligand [(*R*,*R*)-$C_6P_2(NH)_2(SO_3Na)_4$] (Scheme 1). The ^{31}P NMR spectrum of (*R*,*R*)-$C_6P_2(NH)_2(SO_3Na)_4$ exhibited a singlet at −15.68 ppm, suggesting that two phosphorus centres of sulfonated (*R*,*R*)-$C_6P_2(NH)_2(SO_3Na)_4$ are equivalent and the molecule has C_2-symmetry. Water-soluble ligand (*S*,*S*)-$C_6P_2(NH)_2(SO_3Na)_4$ was also prepared by a similar procedure. The CD spectra of the (*R*,*R*)-$C_6P_2(NH)_2(SO_3Na)_4$ and (*S*,*S*)-$C_6P_2(NH)_2(SO_3Na)_4$ give a mirror-image relationship with $\Delta\varepsilon_{max}$ at 242 nm (Fig. 1).

3.2. Asymmetric transfer hydrogenation of ketones carried out in water using 2-propanol as hydrogen source

In the studies of asymmetric transfer hydrogenation of ketones, a mixture of [IrCl(COD)(Ph_3P)] and the water-soluble ligand (*R*,*R*)-$C_6P_2(NH)_2(SO_3Na)_4$ as catalytic precursor has been examined in water. Although the catalyst is highly soluble in water, the catalytic reaction cannot proceed well without adding 2-propanol as a source of hydrogen. Therefore, the reaction has been carried out in 2-propanol/H_2O mixture solvent (Scheme 2).

Table 1
Effect of water in asymmetric transfer hydrogenation of propiophenone with water-soluble catalyst[a]

Entry	Solvent (mL)		S/C/OH⁻	Time (h)	Alcohol	
	2-propanol	H_2O			Yield (%)[b]	ee (%)[c]
1	10	0	200:1:2	3	95	88
2	10	0.5	200:1:8	3	91	89
3	10	1.0	200:1:10	6	83	92
4	10	2.5	200:1:100	22	83	93
5	10	4.5	200:1:200	22	73	91
6	10	9.0	200:1:400	51	73	92
7	10	12.5	200:1:1000	46	92	93

[a] Conditions: [IrCl(COD) (PPh_3)], 0.0025 mmol; [(*R*,*R*)-$C_6P_2(NH)_2(SO_3Na)_4$], 0.0038 mmol. The reaction was carried out at 25 °C in 2-propanol and H_2O.
[b] Yield was determined by GLC.
[c] Determined by capillary GLC analysis using a Chiral Chrompack CP-cyclodextrin-β-236-M-19 Column.

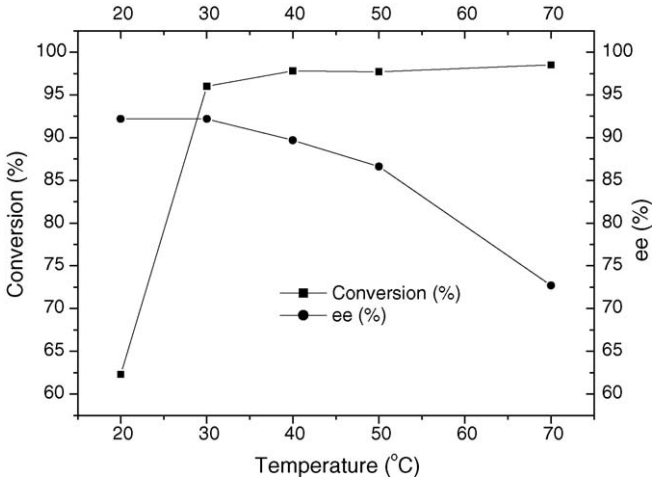
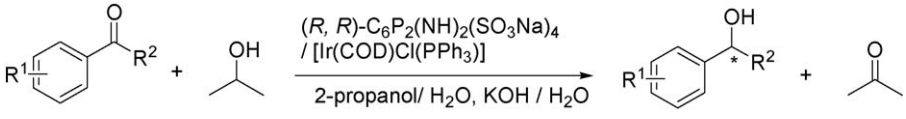


Fig. 2. Effect of reaction temperature on the conversion and the enantioselectivity. Reaction conditions, catalyst, [Ir(COD)Cl(PPh_3)], 0.0025 mmol; ligand, [(*R*,*R*)-$C_6P_2(NH)_2(SO_3Na)_4$], 0.0038 mmol; solvent, 5 mL 2-propanol and 5 mL H_2O; [propiophenone]:[Ir]:ligand:KOH = 200:1:1.5:800 (mole ratio); 23 h; The products were determined by GLC analysis using a chiral chrompack CP-cyclodextrin-β-236-M-19 Column.

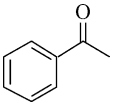
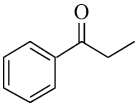
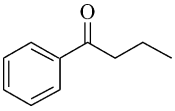
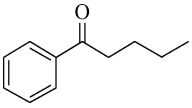
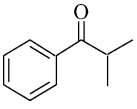
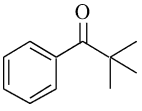
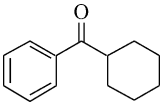
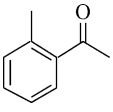
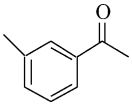
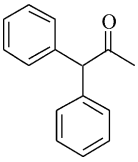
The effect of water was examined by increasing water concentration in the mixture solvent (Table 1). When the catalytic reaction was carried out in pure 2-propanol, the reaction proceeded more smoothly with moderate ee (entry 1). With increasing amount of water from 0.5 to 9.0 mL, a slight enhancement in enantiomeric excess was observed. However, the reaction activity dropped sharply even though the reaction time as well as the concentration of base increased correspondingly (entries



Scheme 2. Asymmetric transfer hydrogenation of ketones.

2–6). Although adding too much base in the reaction gave no good experimental result, a large excess amount of base actually increased the reaction rate dramatically (entry 7). Thus base acted as an important co-catalyst in the reduction.

Table 2
Asymmetric transfer hydrogenation of aromatic ketones catalyzed by water-soluble iridium system in aqueous media[a]

Entry	Ketone substrate	Alcohol		
		Yield (%)[b]	ee (%)[c]	Configuration[d]
1		99	84	*S*
2		98	92	*S*
3		75	94	*R*
4		85	93	*R*
5		89	99	*S*
6		21	93	*R*
7		93	99	*R*
8		95	89	*S*
9		98	85	*S*
10		97	98	*R*

[a] Conditions: [IrCl(COD) (PPh_3)], 0.0025 mmol; [(*R,R*)-$C_6P_2(NH)_2(SO_3Na)_4$], 0.0038 mmol. The reaction was carried out at 30 °C for 24 h in 2-propanol (10 mL) and H_2O (5 mL). Ketone:Ir:ligand:KOH = 200:1:1.5:800.

[b] Yield was determined by GLC.

[c] Determined by capillary GLC analysis using a Chiral Chrompack CP-cyclodextrin-β-236-M-19 Column.

[d] Determined by comparison of the retention times of the enantiomers on the GLC traces with literature values.

Then the effect of reaction temperature using propiophenone as substrate has been investigated and the results are shown in Fig. 2. The catalytic activity was remarkably increased with good enantioselectivity when temperature changed from 20 to 30 °C. However, with further increasing temperature, the activity was slightly improved but ee decreased. According to this observation, reaction temperature of 30 °C was employed for investigating asymmetric transfer hydrogenation of various aromatic ketones.

The water-soluble iridium catalytic system was prepared in situ from [IrCl(COD)(Ph_3P)] and (*R,R*)-$C_6P_2(NH)_2(SO_3Na)_4$ in a mixture solvent of 2-propanol and water, which was employed for reduction of ketones without further purification. Asymmetric transfer hydrogenation of various aromatic ketones in water has been examined and the results are summarized in Table 2.

A variety of simple alkyl ketones can be transformed to the corresponding secondary alcohols with high enantiomeric purity. The reaction rate and enantioselectivity are delicately affected by the steric and electronic properties of ketones. Although the reactivity gradually decreased by increasing the bulkiness of alkyl groups (methyl < ethyl < butyl < pentyl < tert-butyl) (entries 1–6), good to excellent enantioselectivity was still observed, except for the *n*-butyrophenone. Furthermore, the absolute configuration of chiral aromatic alcohols listed in Table 1 was variable depending on the bulkiness of the alkyl groups in the aromatic ketones. Under the experimental conditions, when the chiral ligand was (*R*)-enantiomer, (*S*)-enantiomers of the aromatic alcohols were obtained. However, for the ketones more congested in the alkyl group, the absolute configuration reversed from *S* to *R* was observed (entries 3, 4, 6 and 7). Although isobutyrophenone and pivalophenone had similar steric factors, pivalophenone was more congested, and so the absolute configuration reversed from *S* to *R* was obtained (entries 5 and 6). These results were similar to the case when a chiral diaminodiphosphine ruthenium complex as catalyst was used [43]. *Ortho* and *m*-substituted methylacetophenones were reduced smoothly with good enantioselectivity (entries 8, 9). Phenyl cyclohexyl ketone and 1,1-diphenylacetone are good substrates (entries 7 and 10), which are convertible to the corresponding alcohols with high conversion and excellent enantioselectivity.

4. Conclusion

In summary, we have synthesized a new water-soluble chiral PNNP-type ligand by sulfonation of a diaminodiphosphine ligand. The new water-soluble ligands are stable to air and water. A water-soluble iridium catalyst was prepared in situ from the water-soluble ligand and iridium complex [IrCl(COD)(Ph_3P)] in a mixture solvent of 2-propanol and water, which was employed in asymmetric transfer hydrogenation of various ketones and the high catalytic activity and good to excellent enantiomeric purity have been obtained. The discovery of these new water-soluble chiral ligands provides an efficient method for the catalytic transfer hydrogenation using 2-propanol as hydride source. The reduction reaction was carried out

in aqueous media and catalytic experiments were greatly simplified.

Acknowledgements

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