

Highly efficient chiral PNNP ligand for asymmetric transfer hydrogenation of aromatic ketones in water

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Abstract—Chiral PNNP ligand **II** and $[\text{IrHCl}_2(\text{COD})]_2$ were applied for the first time in the asymmetric transfer hydrogenation of aromatic ketones with HCOONa in water, giving the corresponding optical alcohols in high yield and excellent enantioselectivity (up to 99% ee). Particularly, the reduction of propiophenone proceeded smoothly at a substrate to catalyst molar ratio of 8000, without compromising the ee values obtained.

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Asymmetric transfer hydrogenation (ATH) of ketones has emerged as an attractive method for the production of chiral alcohols due to its operational simplicity and easy availability of hydrogen sources.¹ The solvent for ATH is usually 2-propanol,² $\text{HCOOH-Et}_3\text{N}$,³ or water.^{4,5} Among these solvents, involvement of 2-propanol in ketone/alcohol equilibrium deteriorates the enantioselectivity and prevents a complete conversion,^{4f} while using $\text{HCOOH-Et}_3\text{N}$ as an organic solvent is harmful and contaminates the environment.⁶ In the context of using alternative solvents for green synthesis, water is certainly the most outstanding solvent.⁷ Recently, some effective chiral ligands of N,N-⁴ and N,O-type⁵ have been applied in ATH using HCOONa as hydrogen source in water. However, chiral polydentate PNNP ligands have found little utility for ATH in water.⁵

In the earlier studies, we reported the synthesis and catalytic property of the well-designed PNNP-type ligand **II**⁸ (Fig. 1), which exhibited high enantioselectivity and activity in ATH of ketones using 2-propanol as solvent and hydrogen source.⁹ Recently, we found that this chiral ligand could also be applied in ATH using HCOONa as the reductant in aqueous media.

Initially, various conditions were trailed to determine the potential applicability of chiral PNNP-type ligands for ATH of propiophenone (Scheme 1). The chiral diiminodiphosphine ligand **I** exhibited good catalytic activity (85% yield) but low enantioselectivity (34% ee), while the chiral diaminodiphosphine ligand **II** having two NH groups gave good to excellent results (Table 1, entry 1). This suggests that the NH function plays a crucial role for the high conversion and good ee. These results are similar to the case where 2-propanol is used as solvent.^{8,9} When ligand **II** was used, increasing the amount of HCOONa from 5 to 10 equiv had little effect (entry 2). The effect of temperature was investigated; a temperature change from 60 to 40 °C greatly decreased

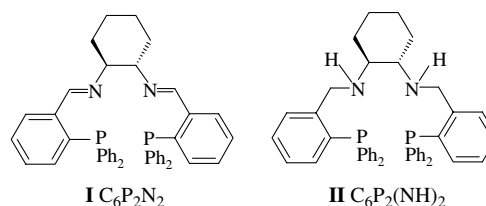
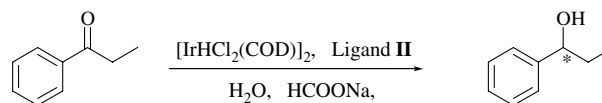


Figure 1.



Scheme 1.

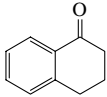
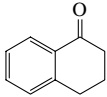
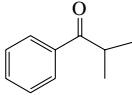
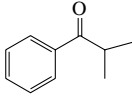
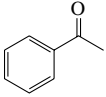
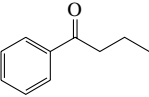
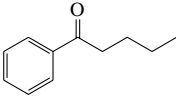
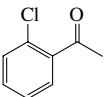
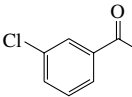
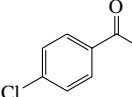
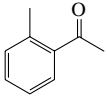
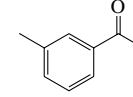
Keywords: Chiral ligand; Aromatic ketone; Asymmetric transfer hydrogenation.

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Table 1. Asymmetric transfer hydrogenation of propiophenone catalyzed by $[\text{IrHCl}_2(\text{COD})]_2/\text{ligand II}$ system in aqueous media¹⁰

Entry	S/C	HCOONa (equiv)	Temp (°C)	Time (h)	Yield ^a (%)	ee (%) ^a
1	100/1	5	60	9	99	88
2	100/1	10	60	9	99	87
3	100/1	5	40	60	40	85
4	200/1	5	60	21	98	88
5 ^b	200/1	5	60	39	92	89
6 ^c	200/1	5	60	51	99	88
7	4000/1	5	60	77	99(95 ^d)	86
8	8000/1	5	60	101	88(80 ^d)	85

^a Determined by GC analysis on a G-TA column.^b Carried out in air.^c Water was not degassed.^d Isolated yield.**Table 2.** Asymmetric transfer hydrogenation catalyzed by $[\text{IrHCl}_2(\text{COD})]_2/(R,R)$ - or (S,S) - $\text{C}_6\text{P}_2(\text{NH})_2$ systems in aqueous media^a

Entry	Substrate	Ligand	Time (h)	Yield ^b (%)	ee ^b (%)	Conf. ^c
1		(<i>S,S</i>)	33	99	99	<i>R</i>
2		(<i>R,R</i>)	30	95	99	<i>S</i>
3		(<i>S,S</i>)	50	99	96	<i>R</i>
4		(<i>R,R</i>)	39	85	92	<i>S</i>
5		(<i>R,R</i>)	47	99	62	<i>S</i>
6		(<i>R,R</i>)	39	86	88	<i>R</i>
7		(<i>R,R</i>)	36	99	82	<i>R</i>
8		(<i>R,R</i>)	33	98	51 ^d	<i>S</i>
9		(<i>S,S</i>)	47	98	55	<i>R</i>
10		(<i>R,R</i>)	34	48	76	<i>S</i>
11		(<i>S,S</i>)	39	95	82	<i>S</i>
12		(<i>R,R</i>)	39	98	64	<i>R</i>

^a The reactions were carried out at 60 °C with 5 mol % of PPNCI and a S/C/HCOONa ratio of 100/1/500.^b Determined by GC equipped with a G-TA column (25 m) unless otherwise noted.^c The configurations were determined by comparison of the GC retention times for product mixtures with known literature values.^d Determined by HPLC analyses with a Chiralcel OD column.

the yield without loss of enantioselectivity (entries 3 and 4). When the catalytic reaction was carried out in air, the activity slowed down but did not affect the ee value (89% ee, entry 5). Interestingly, if water was not degassed, the reaction time would be dramatically prolonged from 21 to 51 h in order to obtain the same yield (entry 6). The reaction, notably, was also feasible at a higher substrate to catalyst molar ratio (S/C) of 8000 (To the best of our knowledge, the highest S/C ratio reported to date does not exceed 2000.^{4a,d,e}), with high isolated yield and good enantioselectivity (entry 8), which allows for potential practical application.

Encouraged by the results obtained with $[\text{IrHCl}_2(\text{COD})]_2/\text{C}_6\text{P}_2(\text{NH})_2$, we then applied this system to a wide range of aromatic ketones (Table 2). When the reactions were performed in water without any

additives, only very low conversions were obtained in 60–72 h. In order to overcome this drawback, several phase transfer catalysts (PTC), such as tetrabutyl ammonium bromide (TBAB), cetyltrimethyl ammonium bromide (CATB), and bis(triphenylphosphoranyl)idene)ammonium chloride (PPNCI), were investigated. We were pleased to discover that the enantioselectivities and reactivities of the transfer hydrogenation were enhanced highly in the presence of PPNCI. Generally, the enantiomeric excess and the reaction rate in the reduction of alkyl aryl ketones have been found to be dependent on both steric and electronic factors.^{9b} The ee value was noticeably increased by increasing the steric hindrance of ketones (entries 1–4). The best results (99% yield and 99% ee, entries 1 and 2) were obtained in the asymmetric reduction of 1-tetralone (2). ATH of alkyl aryl ketones 5 and 6 proceeded rapidly to the

corresponding chiral alcohols in good ee's (entries 6 and 7). The introduction of electron-withdrawing substituents, such as –Cl in the *ortho*- or *meta*-position of the aryl ketone, resulted in higher rates but slightly lower enantioselectivities compared with *para*-substituted substrates (entries 8–10). The reactivity was also delicately influenced by electron-donating substituents on the aromatic ring, with the enantioselectivity for *ortho*-substitution being higher than that for *meta*-substituted ketones (entries 11 and 12).

In summary, this work demonstrates that the catalytic system generated in situ from $[\text{IrHCl}_2(\text{COD})]_2$ and PNNP ligand is an excellent catalyst for the asymmetric transfer hydrogenation of various aromatic ketones using HCOONa in water. The best result was obtained in the reduction of 1-tetralone, giving 99% yield and 99% ee. In addition, even with a molar ratio of propiophenone to catalyst of up to 8000/1, the reduction proceeded smoothly in excellent enantioselectivity. These experimental results provide an attractive method for conducting ATH in a less costly, simpler and 'greener' manner.

Acknowledgements

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- General procedure for the asymmetric transfer hydrogenation of ketones: $[\text{IrHCl}_2(\text{COD})]_2$ (1.9 mg, 0.0025 mmol) and (*R,R*)-ligand **II** (5.0 mg, 0.0055 mmol) were dissolved in 2 ml of degassed water under a N_2 atmosphere. The mixture was stirred at 60 °C for 1 h, HCOONa (130 mg, 1.25 mmol) was then added to the solution. After the solution was stirred for a further 10 min, propiophenone (0.033 ml, 0.25 mmol) was introduced and the resulting solution allowed to react for the predetermined reaction time. At the end of the experiment, the reaction products were extracted by a mixed solvent (3 × 5 ml) of *n*-hexane and diethyl ether (v/v, 5:1). The extracted liquor was dried over Na_2SO_4 and analyzed by GC.