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A new efficient chiral iridium catalyst for asymmetric transfer hydrogenation of ketones

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Abstract

The interaction of $[Ir(COD)Cl]_2$ with chiral tetradentate diaminodiphosphine ligands gave chiral diaminodiphosphine-Ir(I) complexes, which were characterized by IR, NMR and CD. The new chiral iridium(I) complex catalysts were applied to asymmetric transfer hydrogenation of various aromatic ketones using 2-propanol as a source of hydrogen. The results showed that the corresponding chiral alcohols could be obtained with high activity (up to 99.4% yield) and excellent enantioselectivities (up to 99.0% ee) under mild conditions. Propiophenone was a preferred substrate with respect to catalytic activity and enantioselectivity in the presence of base. The catalytic turnover reached 4780 mol product/mol iridium and the turnover frequency was as high as 1593 h^{-1} at 55°C.

Keywords: Chiral ligand; Chiral iridium complex; Asymmetric transfer hydrogenation; Aromatic ketone; Chiral alcohol

1. Introduction

For the past 10 years, the catalytic asymmetric transfer hydrogenation of prochiral ketones to optically active secondary alcohols has been developed with great successes [1–11]. The design and synthesis of new chiral ligands for transition metals have played a significant role in the development of the asymmetric transfer reactions. Chiral biphosphine and *N,N*-chelation ligands have attracted considerable attention as chiral ligands for metal-catalyzed asymmetric transfer reactions. Recently, the synthesis and application of chiral phosphine and nitrogen ligands have been further extended by a combination phosphorous centers and nitrogen donor atoms in PN [12], NPN [13], PNP [14,15] or PNNP [16–18] mixed type ligands. In the past several years, we have been interested in the construction and their application of chiral tetradentate PNNP ligands possessing the dual property of two "soft" phosphorus atoms and two "hard" nitrogen donor atoms. These polydentate ligands have the ability to stabilize metal center and provide special chiral coordination environments, easily modifying the steric and electronic properties of the resulting complexes. Therefore, the metal complexes with these ligands improved the catalytic activity and selectivity. Based on these ligands, a new type of chiral Ru(II) and Rh(I) complexes containing PNNP ligands were prepared, characterized and tested in the asymmetric transfer hydrogenation of aromatic ketones with high enantioselectivity [8,19–21]. As an extension of this work, we have investigated the synthesis of new chiral iridium–PNNP complexes and discovered the complexes to be very effective catalysts for enantioselective transfer hydrogenation of ketones using propan-2-ol as hydrogen donor with up to 99% ee and the molar ratio of ketone to catalyst up to 5000:1 (Schemes 1 and 2).

2. Experimental

All experiments were carried out in a nitrogen atmosphere with Schlenk and syringe techniques. All solvents were dried

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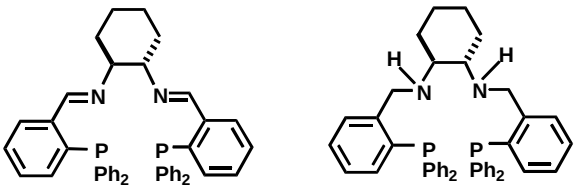
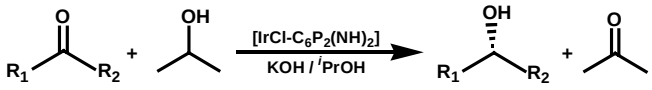


Scheme 1. Chiral ligands.



Scheme 2. Asymmetric transfer hydrogenation of ketones.

and purified according to the standard methods before use. IR spectra were recorded on a PE-Spectroy 2000 spectrophotometer. NMR spectra were recorded on a Varian Unity-500 spectrometer. ^{1}H NMR chemical shifts were reported in ppm relative to TMS. ^{31}P spectra were referenced to 85% H_3PO_4 as an external standard. The element analyses were carried out on a Fisons EA 1110. All melting points were measured in sealed tubes and were not corrected. CD spectra were measured with a JASCO J-810 spectrophotometer.

2.1. Synthesis and characterization of chiral diaminodiphosphine-iridium(I) complexes

The chiral ligands (*S*, *S*)-**1** and (*S*, *S*)-**2** were synthesized as in our previous work. The chiral diiminodiphosphine ligand (*S*, *S*)-**1** was prepared by the condensation of *o*-(diphenylphosphino)benzylaldehyde and (*S*, *S*)-diaminocyclohexane in dichloromethane using anhydrous Na_2SO_4 as a dehydrating agent. Reduction of the ligand [(*S*, *S*)-**1**] with excess $NaBH_4$ was carried out in refluxing ethanol to afford the corresponding chiral diaminodiphosphine ligand [(*S*, *S*)-**2**].

To a mixture of (*S*, *S*)-**2** (1.32 g, 2.0 mmol) and $[Ir(COD)Cl]_2$ (0.67 g, 1.0 mmol) were added benzene (20 ml) and methanol (20 ml). The mixture was stirred at room temperature for 24 h. After removal of the solvent, the residue was dissolved in dichloromethane and precipitated by addition of *n*-hexane. The precipitate was further purified by column chromatography (acetone as eluent) to afford [IrCl-(*S*, *S*)-**2**] as a yellow solid (0.98 g, 56% yield). m.p. 258–259 °C (dec.). IR (KBr pellet, υ (cm^{-1})): 3412m, 3054m, 2932m, 2859w, 1629m, 1593w, 1480m, 1436s, 1162w, 1072s, 751m, 698vs, 524vs, 468w. ^{31}P NMR ($CDCl_3$): δ 33.97, 32.39, 16.51, 13.22, 5.65. Anal. Calc. for $C_{44}H_{44}ClN_2P_2Ir$: C, 55.95; H, 5.35; N, 2.97; found C, 55.80; H, 5.30; N, 2.98.

The complex [IrCl-(*R*, *R*)-**2**] was also synthesized by a similar procedure.

2.2. Experimental procedure for asymmetric transfer hydrogenation of ketones catalyzed by chiral diaminodiphosphine-Ir(I) complexes

Typical procedure for asymmetric transfer hydrogenation of ketones was as follows: the catalyst (0.0025 mmol) was added to a Schlenk tube and 2-propanol and KOH/*iso*-PrOH solution were introduced under nitrogen. After the mixture was stirred for 20 min, substrate was added. The solution was stirred at the desired temperature for the required reaction time. The chemical yield and ee of products were determined by GLC (Chrompack CP-cyclodextrin-β-236-M-19 column).

2.3. Preparative experiment using propiophenone as typical substrate

A preparative experiment using 12.5 mmol of propiophenone (S/C = 5000) was performed as follows: the catalyst [IrCl-(*R*, *R*)-**2**] (2.2 mg, 0.0025 mmol) was added to a Schlenk tube and 2-propanol (250 ml) and KOH/*iso*-PrOH solution were introduced under nitrogen. The mixture was stirred for 20 min, 1.7 ml of propiophenone was added. The solution was stirred at 55 °C for 3 h, neutralized with 0.1 M acetic acid and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane as eluent) to afford (*S*)-1-phenylpropyl alcohol. Yield: 1.5 g (90%, 88% ee).

3. Results and discussion

The interaction of $[Ir(COD)Cl]_2$ with two equivalents (*S*, *S*)-**2** or (*R*, *R*)-**2** in a 1:1 mixture of benzene-methanol for 24 h at room temperature gave chiral diaminodiphosphine-Ir(I) complexes [IrCl-(*S*, *S*)-**2**] and [IrCl-(*R*, *R*)-**2**], respectively. The complexes are yellow solids, and are stable with respect to air and water. The ^{31}P NMR spectrum exhibited multiplet peaks at δ 33.97, 32.39, 16.51, 13.22, 5.65, which indicated that the phosphino groups of the complexes were coordinated to iridium center (the ^{31}P NMR spectrum of the diaminodiphosphine ligand appears as a singlet at δ-15.69), but suggested that this complex was a mixture of several isomers. Recently, Stoop et al. also prepared a mixture of the *trans* and *cis* isomers by reacting $[RuCl_2(PPh_3)_3]$ and chiral tetradentate PNNP ligands in CH_2Cl_2 at room temperature [22]. The CD spectra of chiral diaminodiphosphine ligands and corresponding Ir(I) complexes have been measured in methanol as solvent (Figs. 1 and 2). It can be seen that the CD spectra of (*S*, *S*)-**2** and (*R*, *R*)-**2** bear a mirror–image relationship with $\Delta\varepsilon_{max}$ at 235 nm. Similarly, the CD spectra of chiral iridium complexes also exhibit the mirror–image relationship, while the $\Delta\varepsilon_{max}$ is shifted toward about 250 nm, indicating the center metal chelated with the chiral ligands.

The chiral diaminodiphosphine-Ir(I) complexes as catalyst precursors for the asymmetric transfer hydrogenation

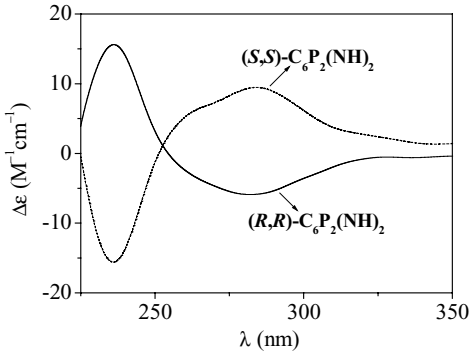


Fig. 1. The CD spectra of chiral diaminodiphosphine ligands.

of aromatic ketones have been examined and typical results are summarized in Table 1. It can be seen from the data that the chiral iridium complexes can efficiently catalyze the asymmetric reduction of several aromatic ketones under mild conditions. Very good enantioselectivities (81.9–99.0% ee) have been observed. As the bulkiness of the alkyl group increases from methyl to isopropyl, the extent of the enantioselectivity is increasing (entries 1–3). Reaction of *tert*-butyl phenyl ketone possessing a bulky alkyl substituent proceeded rather slowly with somewhat lower enantioselectivity (entry 4). Notably, for 1,1-diphenylacetone the corresponding chiral alcohols could be obtained with 99.4% yield and 99.0% ee (entry 9).

This new catalyst is characterized by high reactivity. Table 2 outlines the results of asymmetric reduction with propiophenone as a typical substrate and the chiral iridium complex [IrCl-(*R*, *R*)-**2**] as the catalyst. The catalytic turnover reached 4780 mol product/mol iridium and the turnover frequency was as high as 1593 h^{-1} with 88.4% ee at 55 °C (entry 6). These results would provide a useful index for further designing practical chiral catalytic systems.

When other dialkyl ketones were used as substrates, chiral diaminodiphosphine-Ir(I) catalyst did not give a similar high enantioselectivity as found for aromatic ketones. In the presence of base, the enantiomeric excesses were obtained

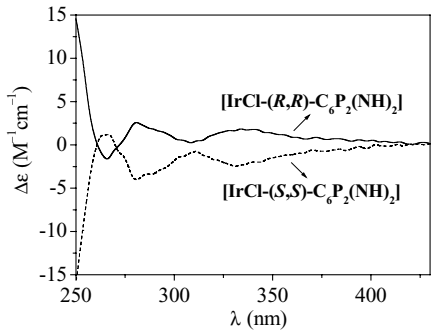
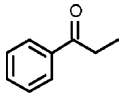
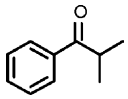
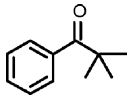
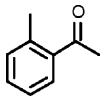
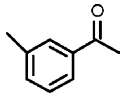
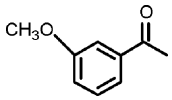
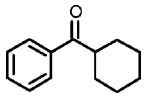
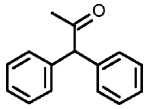


Fig. 2. The CD spectra of chiral iridium complexes.

Table 1
Asymmetric transfer hydrogenation of aromatic ketones catalyzed by chiral diaminodiphosphine-Ir(I) complexes[a]

Entry	Substrate	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1		[IrCl-(*S*, *S*)-**2**]	2.0	96.8	82.6
2		[IrCl-(*R*, *R*)-**2**]	4.5	97.3	93.7
3		[IrCl-(*R*, *R*)-**2**]	4.0	86.1	99.0
4		[IrCl-(*R*, *R*)-**2**]	2.0	26.3	81.9
5		[IrCl-(*R*, *R*)-**2**]	3.0	41.7	99.0
6		[IrCl-(*R*, *R*)-**2**]	3.0	94.1	84.9
7		[IrCl-(*R*, *R*)-**2**]	4.0	93.9	82.5
8		[IrCl-(*S*, *S*)-**2**]	4.0	98.8	98.1
9		[IrCl-(*S*, *S*)-**2**]	4.0	99.4	99.0

[a] The reaction was carried out at 25 °C using 0.0025 mmol catalyst in 10 ml 2-propanol. Ketone:catalyst:KOH = 200:1:2.
[b] GLC analysis.
[c] Capillary GLC analysis using a chiral Chrompack CP-cyclodextrin-β-236-M-19 column.

for different substrates: cyclohexyl methyl ketone (20.5% ee, 32.4% conversion); cyclohexyl ethyl ketone (27.4% ee, 42.5% conversion); isopropyl methyl ketone (10.3% ee, 41.7% conversion); isobutyl methyl ketone (28.3% ee, 83.6% conversion). The results show that the activity and enantioselectivity of the chiral iridium catalyst are very sensitive to the substrate structure.

The chiral iridium(I) complex containing diiminodiphosphine ligand was also prepared. The asymmetric transfer hydrogenation of acetophenone catalyzed by [IrCl-(*S*, *S*)-**1**] proceeded very slowly. Under the same conditions as in Table 1, (*R*)-1-phenylethnnol was obtained in only 39.8% yield and in 39.5% ee after 48 h. These results are similar to those of earlier studies [4,8,23], indicating that the NH functions in the ligands are responsible for the high activity and the NH linkage possibly can stabilize a catalytic transition state [24,25].

Table 2
Asymmetric transfer hydrogenation of propiophenone catalyzed by chiral diaminodiphosphine-Ir(I) complexes[a]

Entry	S:C:KOH (mole ratio)	Solvent (ml)	Temperature (°C)	Time (h)	TOF (h^{-1})	Yield (%)[b]	ee (%)[c]
1	200:1:2	10	25	4.5	43.2	97.3	93.7
2	400:1:2	20	28	3.0	128.4	96.3	92.4
3	1000:1:3	50	28	4.0	212.0	84.8	92.7
4	2000:1:4	100	28	4.0	479.0	95.8	89.7
5	5000:1:3	250	28	2.0	1535.0	61.4	91.0
6	5000:1:3	250	55	3.0	1593.3	95.6 (90.0)[d]	88.4

[a] Reaction conditions: catalyst [IrCl-(*R*,*R*)-**2**], 0.0025 mmol; S:C:KOH = [ketone]:[Ir]:[KOH].
[b] GLC analysis.
[c] Capillary GLC analysis using a chiral Chrompack CP-cyclodextrin-β-236-M-19 column.
[d] Isolated yield.

4. Conclusions

The interaction of $[Ir(COD)Cl]_2$ with chiral diaminodiphosphine ligands in a 1:1 mixture of benzene-methanol at room temperature gives chiral diaminodiphosphine-Ir(I) complex, which is a mixture containing different isomers. This mixture is an effective catalyst for the asymmetric transfer hydrogenation of a variety of aromatic ketones under mild conditions, leading to optically active alcohols in up to 99.4% yield and 99.0% ee. Best result is obtained with 1,1-diphenylacetone as the substrate. Other experiments are in progress to gain further understanding.

Acknowledgements

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