Novel Chiral PNNP-Ru Complexes: Synthesis and Application in Asymmetric Transfer Hydrogenation of Ketones

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Abstract The efficient catalytic systems generated *in situ* from $RuCl_2(PPh_3)_3$ and chiral ligands *N*,*N*-bis[2-(di-*o*-tolylphosphino)-benzyl]cyclohexane-1,2-diamine(**2**) were employed for asymmetric transfer hydrogenation of aromatic ketones, giving the corresponding optically active alcohols with high activities(up to 99% conversion) and excellent enantioselectivities(up to 96% *e.e.*) under mild conditions. The chiral ruthenium(II) complex (*R*,*R*)-**3** has been prepared and characterized by NMR and X-ray crystallography.

Keywords Chiral PNNP ligand; Ru complex; Asymmetric transfer hydrogenation; Aromatic ketone

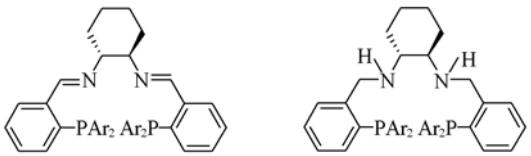
Article ID 1005-9040(2011)-02-170-04

1 Introduction

The design and application of new chiral ligands leading to high activity and enantioselectivity in metal-catalyzed asymmetric catalysis is a topic of constantly ongoing researches. Over the past two decades, a large number of chiral mixed-P, N ligands have been synthesized and applied in catalytic asymmetric synthetic reactions[1—9]. Among these ligands, the chiral tetradentate PNNP-type ligands[10,11] have received considerable attention in view of their conformational rigidity, which is expected to provide a favorable combination during a catalytic cycle[12,13].

In 1996, we synthesized C_2-symmetric chiral diimino- and diamino-diphosphine ligands[14]. Since then, a new class of chiral PNNP-type ligands has been synthesized and their catalytic performance for asymmetric hydrogenation has been studied in detail. Based on the PNNP ligands, their coordination chemistry with various metal centers, such as Ru(II), Rh(I), Ir(I), Co(II) and Fe(II), has been investigated[14—20]. The application has been extended from asymmetric transfer hydrogenation (ATH) of ketones[14—18,21—25] to oxidative kinetic resolution of racemic second alcohols[26], asymmetric epoxidation[27], asymmetric cyclopropanation[28—32], hydrovinylation of styrene[19] and so on. The chiral PNNP ligands are so versatile that they have promoted us to further study the relationship between the structure and performance of the ligands. In our previous studies, we have used different chiral 1,2-diamines to prepare a series of PNNP ligands[33]. However, another synthetic improvement is to introduce different aromatic groups on the phosphine, which has seldom been reported. Mezzetti *et al*.[30—32] synthesized the CF_3-substituted PNNP ligands and employed them in the asymmetric cyclopropanation of olefins efficiently.

Recently, we have used 2-(di-*o*-tolylphosphino)benzyldehyde, instead of *o*-(diphenylphosphino)benzaldehyde, to synthesize novel chiral tetradentate PNNP ligands *N*,*N*-bis[2-(di-*o*-tolylphosphino)-benzyl]cyclohexane-1,2-diimine(**1**) and *N*,*N*-bis[2-(di-*o*-tolylphosphino)-benzyl]cyclohexane-1,2-diamine(**2**)(Fig.1). The catalytic performance of the ligands was investigated in the ATH of aromatic ketones with high chiral efficiency[34]. Herein we reported the synthesis of chiral PNNP-Ru complexes and their application in asymmetric transfer hydrogenation of ketones.



(*R*,*R*)-**1** (*R*,*R*)-**2**

Ar=*o*-Tolyl

Fig.1 Chiral PNNP ligands (*R*, *R*)-1 and (*R*, *R*)-2

2 Experimental

2.1 General Methods

All the experiments were carried out under nitrogen atmosphere. The solvents were dried and purified according to standard methods. NMR spectra were recorded on a Bruker AV 400 instrument. Mass spectra were recorded on a Finnigan

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Received March 15, 2010; accepted June 8, 2010.

Supported by the National Natural Science Foundation of China(Nos.20423002, 20703034), the Natural Science Foundation of Fujian Province of China(No.2008J0235) and the Natural Science Foundation of Guangxi Province of China(No. 0991016).

LCQ mass spectrometer. IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer. All the melting points were measured on an X-4 digital melting point apparatus and were uncorrected. The conversions and *e.e*. values were determined by GC analysis with a CP-Chirasil-Dex CB column or HPLC using a chiralcel OD column. Optical rotations were measured with a Perkin-Elmer 341 polarimeter. X-Ray diffraction data were collected on a Bruker Smart Apex CCD diffractometer.

2.2 General Procedure for ATH of Ketones

A solution of ligand (*R*,*R*)-**2**(4.3 mg, 0.006 mmol) and $RuCl_2(PPh_3)_3$(4.8 mg, 0.005 mmol) in ^{i}PrOH(10 mL) was stirred for 20 min, KOH/^{i}PrOH solution and aromatic ketone (1 mmol) were then introduced, and the solution was stirred at the desired temperature for the required reaction time. The reaction mixture was then filtered through a pad of silica gel and analyzed by GC using a chiral CP-Chirasil-Dex CB column or HPLC using chiralcel OD column.

2.3 Synthesis of Chiral Ru Complex (*R*,*R*)-3

Complex (*R*,*R*)-**3** was synthesized by the reaction of (*R*,*R*)-**2**(0.6 g, 0.8 mmol) and *trans*-$Ru(DMSO)_4Cl_2$(0.4 g, 0.8 mmol) in refluxing toluene(40 mL) for 13 h. The resulting orange-red solution was cooled to room temperature and the solvent was removed under vacuum to leave an orange-red residue. The solid was purified by column chromatography on silica with CH_2Cl_2/acetone(20:1, volume ratio) as an eluant to give an orange-yellow solid (*R*, *R*)-**3**(0.54 g, 73% yield). m. p. 228—234 °C, $[\alpha]_D^{20}$= –13.3(*c*=0.1, $CHCl_3$). IR(KBr), $\tilde{\nu}$/cm^{-1}: 3207, 3052, 3003, 2924, 2856, 1588, 1467, 1448, 1129, 1043, 1008, 963, 752, 716, 671. ^{1}H NMR($CDCl_3$, 400 MHz), δ: 8.47—8.58(m, 1H), 7.81(s, 1H), 6.67—7.50(m, 22H), 5.72(s, 1H), 5.29(d, 1H, *J*=13.2 Hz), 4.29—4.48(m, 2H), 3.72(d, 2H, *J*=6.4 Hz), 3.31(m, 1H), 3.11—3.13(m, 2H), 2.58(d, 1H, *J*=9.2 Hz), 2.40(s, 6H), 2.08—2.17(m, 6H), 1.58(s, 6H), 1.46(d, 1H, *J*=9.6 Hz), 0.79—1.07(m, 4H). ^{31}P NMR($CDCl_3$, 162 MHz), δ: 49.65 and –29.03. Complex (*S*,*S*)-**3** was synthesized by the similar procedure.

2.4 X-Ray Crystallographic Study of (*R*,*R*)-3

Orange-yellow crystals of (*R*,*R*)-**3** suitable for X-ray diffraction were grown from ethanol/toluene. Diffraction data were collected on a Bruker Smart Apex CCD diffractometer with graphite monochromated Mo *Kα* radiation at 296 K. The structure was solved by SHELXS-97 and refined by full-matrix least-quares with anisotropic thermal parameters for all of the nonhydrogen atoms. Hydrogen atoms were located from a difference Fourier map. All the calculations were performed on a microcomputer *via* SHELXL-97 and SHELXS-97 programs[35,36].

Crystal data for compound (*R*,*R*)-**3**(CCDC 730809 contains the supplementary crystallographic data for the structure of (*R*,*R*)-**3**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif): monoclinic, *a*= 1.1701(3) nm, *b*= 1.4933(3) nm, *c*=2.8875(6) nm, *V*=5.0456(19) nm^3, *Z*=10, $\rho_{calcd.}$=1.272 g/cm^3, *T*=273(2) K, R_1=0.0476, wR_2=0.1462 [$I>2\sigma(I)$], R_1=0.0511, wR_2=0.1490 for all data.

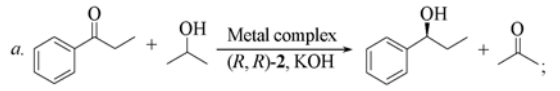
3 Results and Discussion

3.1 ATH of Propiophenone

In the initial experiment, the ATH of propiophenone was chosen as a model reaction. The catalyst systems were generated *in situ* by mixing ligand (*R*,*R*)-**2** with metal complex in ^{i}PrOH under nitrogen atmosphere. Typical results are listed in Table 1. The trinuclear ruthenium cluster $Ru_3(CO)_{12}$ combined with ligand (*R*,*R*)-**2** showed low activity(Table 1, Entry 1). While $RuCl_2(DMSO)_4$ was used, the activity was improved but the enantioselectivity was still unsatisfactory(Table 1, Entry 2). Notably, the catalytic system composed of $RuCl_2(PPh_3)_3$/(*R*,*R*)-**2** gave the best result with a conversion of 97% and an *e.e*. of 91%(Table 1, Entry 3). Although the activities were improved, low enantioselectivities were observed when Rh complexes were employed in the reactions(Table 1, Entries 4 and 5). The Ir complexes proceeded with very high activity and moderate enantioselectivities for 3 h at 30 °C(Table 1, Entries 6 and 7). Therefore, $RuCl_2(PPh_3)_3$ was chosen as metallic precursor for further study.

Table 1 ATH of propiophenone with (*R*,*R*)-2 and metal complexes as catalyst precursors[a]

Entry	Metal complex	*t*/°C	Time/h	Conv.[b](%)	*e.e*.[b](%)
1	$Ru_3(CO)_{12}$	45	5	11	65
2	$RuCl_2(DMSO)_4$	45	5	63	65
3	$RuCl_2(PPh_3)_3$	45	3	97	91
4	$RhCl(PPh_3)_3$	45	5	92	18
5	$[Rh(COD)Cl_2]_2$	45	5	90	55
6	$[IrCl(COD)]_2$	30	3	97	76
7	$IrCl(COD)PPh_3$	30	3	90	60



reaction conditions: ketone, 0.5 mmol; ^{i}PrOH, 5 mL; propiophenone: [M]:ligand:KOH=100:1:1.2:4, molar ratio; *b*. conversion and *e.e*. were determined by GC analysis on a chiral CP-Chirasil-Dex CB column.

The catalytic performance of (*R*,*R*)-**1** was also tested in the ATH of propiophenone, coupled with $RuCl_2(PPh_3)_3$, giving only a conversion of 78% with an *e.e*. of 61% over 12 h. The result is similar to our earlier studies[14], indicating that the NH functions in the ligands are responsible for the high activity and enantioselectivity.

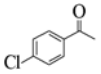
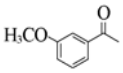
3.2 ATH of Various Ketones

The catalytic systems $RuCl_2(PPh_3)_3$/ligand **2** have been investigated for the ATH of a diverse range of aromatic ketones in ^{i}PrOH. Typical results are listed in Table 2.

A variety of aromatic ketones could be smoothly reduced to the corresponding chiral secondary alcohols under mild conditions. The activity and the enantioselectivity were highly dependent on the steric and electronic properties of ketones. With increasing the bulkiness of alkyl groups(methyl<ethyl< propyl), high conversion and excellent enantioselectivity were

obtained(Table 2, Entries 1—5). Notably, for cyclohexyl phenyl ketone, the corresponding chiral alcohols could be observed with a yield of 95% and an *e.e.* of 96%(Table 2, Entry 6). When the 1,1-diphenylacetone was used as substrate, the *e.e.* of the reaction dropped significantly(Table 2, Entry 7). The electronic properties and position of the groups in the ring substituent also affected the enantioselectivity of the reduction reaction. The *ortho*-methyl acetophenone was reduced with higher enantioselectivity but lower activity compared to the aromatic ketones with chloride substituent in the *meta* or *para* position (Table 2, Entries 8—10). An analogous trend was found for the chloro-substituted acetophenone(Table 2, Entries 11—13). The ketones having an electron-withdrawing substituent, *meta*- or *para*-chloroacetophenone showed higher activity compared to the methoxyl acetophenone containing electron-donating substituent(Table 2, Entries 12—14).

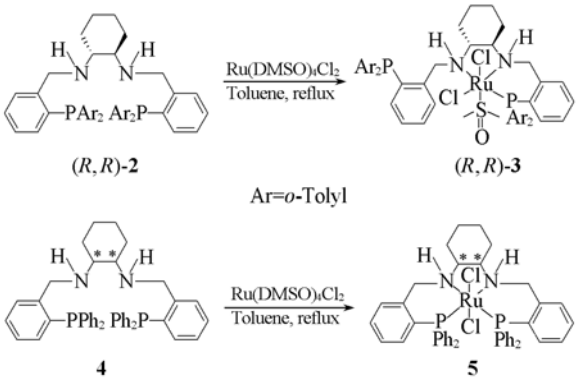
Table 2 ATH of various ketones catalyzed by $RuCl_2(PPh_3)_3$/ligand(*R*,*R*)-2[a]

Entry	Substrate	Time/h	Conv.[b](%)	*e.e.*[b](%)	Config.[c]
1		0.5	90	90	*S*
2		1	95	95	*S*
3[d]		1	94	93	*R*
4		2	95	93[e]	*S*
5[d]		2	96	91	*R*
6[e]		4	95	96[f]	*S*
7[e]		4	99	87[f]	*S*
8		2	98	95	*S*
9		1	95	84	*S*
10		1	91	84	*S*
11		1	99	90	*S*
12		0.2	96	84	*S*
13		0.3	96	87	*S*
14		1	97	82	*S*

a. Reaction conditions: ketone, 1 mmol; ^{i}PrOH, 10 mL; ketone:[M]:ligand:KOH=200:1:1.2:8, molar ratio; temp.: 45 °C; *b*. yield and *e.e.* were determined by GC analysis on a chiral CP-Chirasil-Dex CB column; *c*. the configurations were determined by comparison of the retention time of the enantiomer on the GC traces with literature values; *d*. ligand (*S*,*S*)-**2**; *e*. temp.: 60 °C; *f*. the *e.e.* values were determined on a chiralcel OD column (eluent, ^{i}PrOH: hexane=1:99, volume ratio).

3.3 Synthesis of Chiral Ruthenium Complex 3

The interaction of *trans*-$Ru(DMSO)_4Cl_2$ with (*R*,*R*)-**2** in refluxing toluene gave chiral ruthenium(II) complex (*R*,*R*)-**3** in good yield(73%) as an orange-yellow solid(Scheme 1). The ^{31}P NMR spectrum of (*R*,*R*)-**3** exhibits two signals at δ 49.65 and –29.03, indicating that only one phosphorous atom coordinated to the ruthenium center.



Scheme 1 Synthesis of complex (*R*,*R*)-3

The structure of (*R*,*R*)-**3** was established by an X-ray diffraction study, which revealed a non-C_2-symmetric configuration for the complex(Fig.2). The selected bond lengths and bond angles are listed in Table 3.

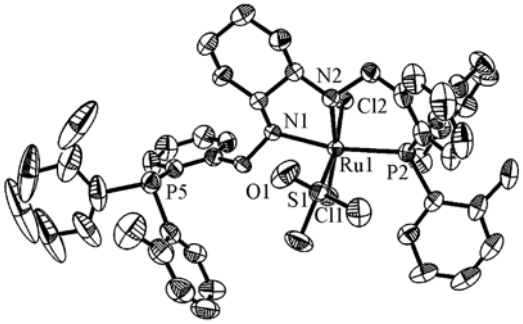


Fig.2 Structure of complex (*R*,*R*)-3

All hydrogen atoms are omitted for clarity. The solvent molecules are not given.

Table 3 Selected bond lengths(nm) and bond angles(°)

Ru1—N1	0.2185(3)	Ru1—N2	0.2140(3)
Ru1—P2	0.23389(11)	Ru1—Cl1	0.24329(11)
Ru1—Cl2	0.24389(11)	Ru1—S1	0.22162(11)
N2—Ru1—N1	80.63(12)	N2—Ru1—S1	88.07
N1—Ru1—S1	91.54(10)	N2—Ru1—P2	92.46(9)
N1—Ru1—P2	168.33(9)	S1—Ru1—P2	97.65(4)
N2—Ru1—Cl1	167.58(9)	N1—Ru1—Cl1	87.41(9)
S1—Ru1—Cl1	95.63(5)	P2—Ru1—Cl1	98.77(4)
N2—Ru1—Cl2	87.81(10)	N1—Ru1—Cl2	80.08(10)
S1—Ru1—Cl2	171.17(4)	P2—Ru1—Cl2	90.33(4)
Cl1—Ru1—Cl2	86.84(4)		

Complex (*S*,*S*)-**3** was synthesized by the similar procedure. In our previous study[14], the interaction of *trans*-$RuCl_2(DMSO)_4$ with chiral PNNP ligand **4** gave a C_2-symmetric ruthenium(II) complex **5**, in which two phosphino groups are coordinated and equivalent. The possible explanation is that in the complex (*R*,*R*)-**3** the four tolyl groups create an unfavorable

steric clash, which lead to one of the P-pendants distorting away from the metal center and no coordinate to Ru atom.

3.4 ATH of Ketones Catalyzed by Chiral Ruthenium Complex (*R*,*R*)-3

The chiral ruthenium(II) complex (*R*,*R*)-**3** was applied to the ATH of prochiral ketones. The catalytic performance exhibited high activity and lower enantioselectivity: acetophenone (70% *e.e.*, 74% conversion), propiophenone(82% *e.e.*, 98% conversion), *n*-butyrophenone(75% *e.e.*, 97% conversion), phenyl cyclohexyl ketone(75% *e.e.*, 96% conversion) and 1,1-diphenylacetone(72% *e.e.*, 99% conversion). The reason might be that the steric hindrance of the complex prevented the formation of an efficient chiral environment around the metal in the catalytic reaction, which is responsible for the chiral efficiency of chiral catalyst.

4 Conclusions

In summary, we have synthesized the new chiral PNNP ligands (*R*,*R*)-**1** and (*R*,*R*)-**2** and investigated their application in the asymmetric transfer hydrogenation of ketones. The catalytic system generated from (*R*,*R*)-**2** and $RuCl_2(PPh_3)_3$ was employed to efficiently catalyze the asymmetric reduction of a variety of aromatic ketones with high activity(99% conversion) and excellent enantioselectivity(up to 96% *e.e.*) under mild conditions. The turnover frequency reached 960 h^{-1} at 45 °C. The PNNP-Ru complex (*R*,*R*)-**3** bearing a non C_2-symmetric structure was also synthesized and characterized. In order to reveal the exact reaction mechanism, isolation and characterization of the catalytic active species is under further investigation.

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