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Asymmetric transfer hydrogenation of prochiral ketones catalyzed by chiral ruthenium complexes with aminophosphine ligands

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Abstract

The condensation of (*S*)-propane-1,2-diamine with two equivalents of *o*-(diphenylphosphino)benzaldehyde gives (*S*)-*N*,*N*′-bis[*o*-(diphenylphosphino)benzylidene]propane-1,2-diamine [(*S*)-**1**] ligand. The reduction of (*S*)-**1** with excess $NaBH_4$ is carried out in refluxing ethanol to afford corresponding (*S*)-*N*,*N*′-bis[*o*-(diphenylphosphino)benzyl]propane-1,2-diamine [(*S*)-**2**]. The interaction of *trans*-$RuCl_2(DMSO)_4$ with one equivalent of (*S*)-**1** or (*S*)-**2** in refluxing toluene gives (*S*)-**3** or (*S*)-**4** in good yield, respectively. (*S*)-**1**, (*S*)-**2**, (*S*)-**3** and (*S*)-**4** have been fully characterized by analytical and spectroscopic methods. The structure of (*R*)-**3** has been also established by an X-ray diffraction study. Catalytic studies showed that (*S*)-**4** as an excellent catalyst precursor for the asymmetric transfer hydrogenation of acetophenone with 90% yield and up to 91% enantiomeric excess.

Keywords: Chiral ligand; Ruthenium complex; Asymmetric transfer hydrogenation; Ketones

1. Introduction

Optically active secondary alcohols are versatile building blocks for synthesis of natural and unnatural biological active compounds as well as functional materials. Chiral biphosphine ligands provide a useful tool for preparing optically active secondary alcohols and have attracted considerable attention as chiral ligands for metal-catalyzed asymmetric reactions [1,2]. It should be noted, however, that in the field of enantioselective transfer hydrogenation the most used chiral auxiliary ligands contain nitrogen as the donor atom [3]. Recently, importance of nitrogen donor has been reviewed [4] and some chiral ruthenium complexes bearing nitrogen donors have been developed with great successes for asymmetric transfer hydrogenation of aromatic ketones [5,6]. For the past several

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years, we have been interested in the synthesis of well-designed ligands possessing two 'soft' phosphorus atoms and two 'hard' nitrogen atoms for preparation of polydentate–metal complexes. These ligands can serve as bi-, tri- and tetradentate ligands depending on the reaction conditions and display some interesting structural [7–11], chemical and catalytic properties [12,13]. In this paper we would like to describe the synthesis and characterization of new chiral ruthenium complexes with structurally similar (*S*)-**1**, (*S*)-**2**, (*R*)-**1** and (*R*)-**2** ligands, as well as their application to enantioselective transfer hydrogenation of aromatic ketones.

2. Experimental

2.1. General

All experiments were carried out under a nitrogen atmosphere using a vacuum line and standard Schlenk-tube techniques. IR spectra were recorded on a PE-Spectroy 2000 spectrophotometer. NMR spectra were recorded on a Varian Unity-500 spectrometer. ^{31}P NMR spectra were measured with 85% phosphoric acid as an external standard. Elemental analyses were performed by the Fujian Institute of structure on the matter, Chinese Academy of Sciences. All the solvent were purified according to standard methods before use. *trans*-$RuCl_2(DMSO)_4$ was prepared as previously described [14].

The asymmetric hydrogen transfer reactions of ketones were performed according to the following procedure: The ruthenium complex (*S*)-**3** or (*S*)-**4** was dissolved in 20 ml of 2-propanol in a schlenk-tube under nitrogen atmosphere at room temperature and to the resulting solution appropriate amounts of ketone and *iso*-PrOK/*iso*-PrOH solution were added, respectively. The solution was stirred and heated to the desired temperature. The reaction mixture was measured by capillary GLC analysis using a chiral Chrompack CP-cyclodextrin-β-236-M-19 column.

2.2. Procedure for the preparation of the chiral ligands and the ruthenium complexes

2.2.1. (S)-N,N′-bis[o-(diphenylphosphino)benzylidene]propane-1,2-diamine, (S)-1

To a mixture of *o*-(diphenylphosphino)benzaldehyde (1.45 g, 5.0 mmol) and anhydrous Na_2SO_4 (3.55 g, 25.0 mmol) in CH_2Cl_2 (15 ml) was added a solution of (*S*)-propane-1,2-diamine (0.24 g, 2.5 mmol). The mixture was stirred at room temperature for 24 h. The resulting solution was filtrated and the solvent was removed under vacuum to leave a pale yellow solid (*S*)-**1** (1.45 g, 88% yield). m.p. 60–63°C. Anal. calcd. for $C_{41}H_{36}N_2P_2$: C, 79.63; H, 5.82; N, 4.53%. Found C, 79.78; H, 6.02; N, 4.57%. IR (cm^{-1}): 3057m, 2838m, 1635s, 1582w, 1478w, 1431vs, 1347w, 1184w, 1089m, 1023m, 744vs, 696vs, 545m, 497s. ^{1}H NMR, δ: 8.75 (m, 2H, *Ph*CH=), 6.82–7.90 (m, 28H, C_6H_5–), 3.51 (*S*, 1H, –CH<), 3.37 (*S*, 2H, $-CH_2-$), 0.89 (m, 3H, $-CH_3$). ^{31}P NMR, δ: −11.81, 12.44.

2.2.2. (S)-N,N′-bis[o-(diphenylphosphino)benzyl]propane-1,2-diamine, (S)-2

A mixture of (*S*)-**1** (1.24 g, 2.0 mmol) and $NaBH_4$ (0.46 g, 12.0 mmol) in 40 ml of absolute C_2H_5OH was heated at reflux with stirring for 36 h. Then, 20 ml of H_2O was added and the solvent was removed under reduced pressure. The white residue was extracted repeatedly with CH_2Cl_2 (20 ml × 3) and the combined extracts was neutralized by saturated NH_4Cl solution. The solution was washed with H_2O and organic layer was dried on anhydrous $MgSO_4$. Removal of the solvent afforded a white solid (*S*)-**2** (0.86 g, 70% yield). m.p. 59–62°C. Anal. calcd. for $C_{41}H_{40}N_2P_2$: C, 79.12; H, 6.42; N, 4.50%; Found C, 78.62; H, 6.50; N, 4.20%. IR (cm^{-1}): 3411m, 3057m, 1478m, 1431vs, 1347m, 1156m, 1089m, 1024w, 744vs, 696vs, 545m, 497s. ^{1}H NMR, δ: 6.87–7.62 (m, 28H, C_6H_5–), 4.14 (m, 2H, PhCH–), 3.99 (m, 2H, PhCH–), 2.85 (*S*, 2H, –NH–), 2.67 (*S*, 1H,

–CH <), 2.63 (m, 2H, $-CH_2-$), 1.07 (m, 3H, $-CH_3$). ^{31}P NMR, δ: −15.41, −15.51.

Ligands (*R*)-**1** and (*R*)-**2** are also prepared according to the above procedure.

2.2.3. (R)-$RuCl_2(P_2N_2$ Me), (R)-3

A mixture of (*R*)-**1** (0.309 g, 0.5 mmol) and *trans*-$RuCl_2(DMSO)_4$ (0.242 g, 0.5 mmol) in 15 ml of toluene was heated under reflux for 16 h. The resulting red solution was cooled to room temperature and the solvent was removed under vacuum to leave a red-brown residue. The solid was dissolved in a minimum amount of CH_2Cl_2 and chromatographed on a silica gel column (2×15 cm) using CH_2Cl_2/acetone (1:1) solution as an eluant. The solvent was removed to give a red solid (*R*)-**3** (0.32 g, 81% yield). m.p. 280–283°C. Anal. calcd. for $C_{41}H_{36}N_2P_2Cl_2$. $1.25CH_2Cl_2$: C, 56.60; H, 4.87; N, 3.12%; Found: C, 56.99; H, 4.55; N, 3.39%. IR (cm^{-1}): 3048m, 2914s, 1725w, 1626m, 1474m, 1426s, 1261s, 1090s, 1024w, 749s, 692vs, 526vs, 474s. ^{1}H NMR, δ: 8.76 (m, 2H, PhCH=), 6.86–7.64 (m, 28H, C_6H_5-), 4.70 (*S*, 1H, –CH <), 4.29 (m, 2H, $-CH_2-$), 1.72 (m, 3H, $-CH_3$). ^{31}P NMR, δ: 48.12, 48.51.

A suitable crystal of (*R*)-**3** for X-ray diffraction measurements was obtained from CH_2Cl_2/*n*-hexane. A dark-red crystal of dimensions $0.15 \times 0.18 \times 0.20$ mm^3 was mounted on a CAD4 diffractometer. Reflection data were collected with graphitemonchromated Cu Kα ($\lambda = 1.5418$ Å) radiation by $\omega/2\theta$ scan mode. A total of 3679 independent reflections within $4° < 2\theta < 65°$ were collected of which 2692 reflections with $I > 3\sigma(I)$ were used in the refinements. The structure analysis was completed on a PC computer with MOLEN program package. The intensity data were corrected by Lorentz-polarization factor and PSI empirical absorption. The structure was solved by Patterson method and ΔF syntheses. Full-matrix least-squares refinements were used with anisotropic temperature factors for all non-hydrogen atoms. All hydrogen atoms were not refined and extreme in the final difference map was 1.139 eÅ^{-3}. Final value is $R = 0.063$, $R_w = 0.067$, $\Delta/\delta < 0.01$. A perspective drawing of (*R*)-**3** is showing in Fig. 1. Crystal data for (*R*)-**3**: $C_{41}H_{36}N_2P_2Cl_2Ru$, $M = 790.67$, monoclinic, space group $P2_1$, $a = 11.569(1)$ 2 Å, $b = 15.079(1)$ Å, $c = 11.972(1)$ Å, $\beta = 97.42(1)°$, $V = 2071.13(1)$ Å^3, $Z = 2$, $D_c = 1.540$ g/cm^3, $\mu = 78.1$ cm^{-1}, $F(000) = 976$, $T = 23 \pm 1°$.

2.2.4. (S)-$RuCl_2(P_2N_2H_4$Me), (S)-4

The procedure was similar to that of (*R*)-**3**, except (*S*)-**2** (0.311 g, 0.5 mmol) and *trans*-$RuCl_2(DMSO)_4$ (0.242 g, 0.5 mmol) were used. The resulting solid was recrystallized from CH_2Cl_2/hexane to afford pale-yellow crystals (*S*)-**4** (0.25 g, 65% yield). m.p. 226–228°C. Anal. calcd. for $C_{41}H_{40}N_2P_2Cl_2Ru \cdot 0.5C_6H_{14}$:

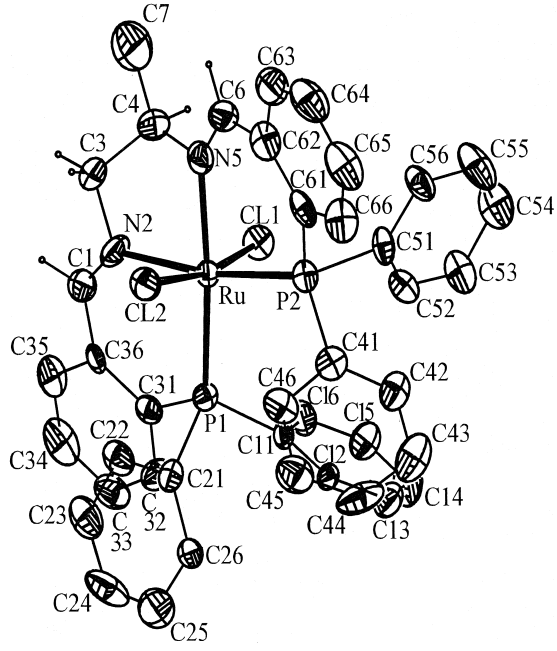


Fig. 1. A perspective view of the structure of *trans*-$RuCl_2(C_{41}H_{36}N_2P_2)$. Selected bond lengths (Å) and angles (°): Ru–CL(**1**) 2.399(**4**); Ru–CL(**2**), 2.440(4); Ru–P(**1**), 2.297(**4**); Ru–P(**2**), 2.277(**4**); Ru–N(**2**), 2.08(**1**); Ru–N(**5**), 2.07(**1**); N(**2**)–C(**1**), 1.30(**2**); N(**2**)–C(**3**), 1.51(**2**); N(**5**)–C(**4**), 1.45(**2**); N(**5**)–C(**6**), 1.35(**2**); CL(**1**)–Ru–CL(**2**), 170.2(**1**); P(**1**)–Ru–P(**2**), 99.8(**1**); P(**1**)–Ru–N(**2**), 91.0(**4**); P(**1**)–Ru–N(**5**); 170.0(**5**); P(**2**)–Ru–N(**2**), 169.1(**4**); P(**2**)–Ru–N(**5**), 95.2(**1**); N(**2**)–Ru–N(**5**), 80.3(**6**); CL(**1**)–Ru–P(**2**), 95.2(**1**).

C, 63.11; H, 5.61; N, 3.34%. Found C, 63.04; H, 5.46; N, 3.35%. IR (cm^{-1}): 3450m, 3057m, 2867m, 1474s, 1431vs, 1227w, 1089s, 950s, 744s, 692vs. ^{1}H NMR, δ: 6.82–7.34 (m, 28H, C_6H_5–), 4.03 (m, 2H, $PhCH_2$–), 3.98 (m, 2H, $PhCH_2$–), 3.73 (d, 1H, –CH <), 3.60 (*S*, 2H, –NH–), 3.04 (d, 2H, $-CH_2$–), 0.91 (m, 3H, $-CH_3$). ^{31}P NMR, δ: 45.18, 43.88.

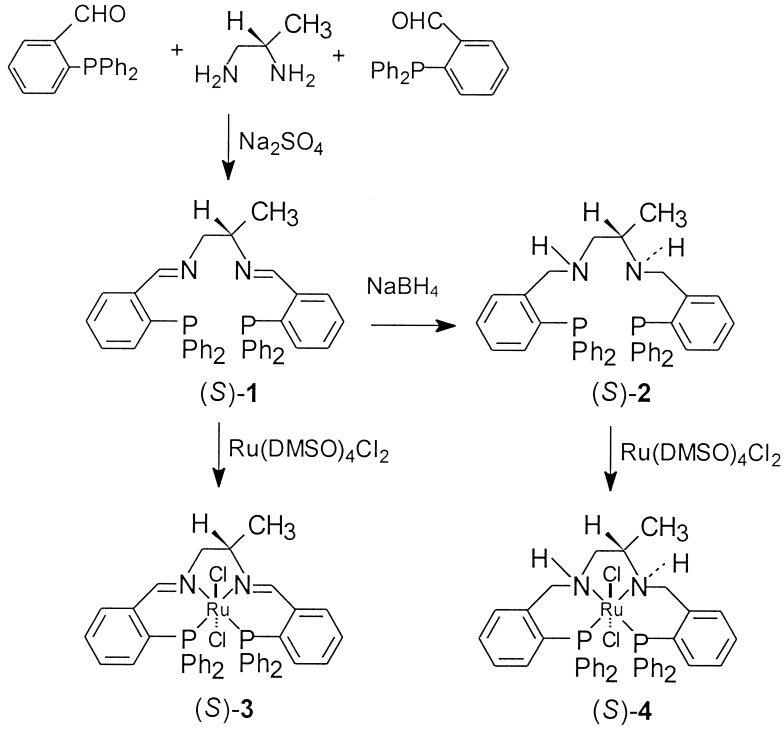
3. Results and discussion

3.1. Synthesis of chiral ligands (S)-1 and (S)-2

When a mixture of *o*-(diphenylphosphino) benzylaldehyde and (*S*)-propane-1,2-diamine in molar ratio of 2:1 was stirring in dichloromethane with excess of Na_2SO_4 as dehydrating agent, a pale-yellow solid (*R*)-*N*,*N*′-bis[*o*-(diphenylphosphino)benzylidene]propane-1,2-diamine [(*S*)-**1**] was produced in 83–88% yield (Scheme 1). The IR spectrum of (*S*)-**1** exhibits a strong C=N stretch at 1635 cm^{-1}. The ^{1}H NMR spectrum exhibits a doublet ($J_{(P-H)}$ = 4.5 Hz) at δ 8.75 for imino protons. The ^{31}P NMR spectrum exhibits two singlets of equal intensities at δ −11.81 and −12.44, respectively. Elemental analysis and spectroscopic data indicate that (*S*)-**1** contains diimino and diphosphino groups.

The reduction of (*S*)-**1** with excess $NaBH_4$ was carried out in refluxing ethanol to afford corresponding (*S*)-*N*,*N*′-bis[*o*-(diphenylphosphino)benzyl]propane-1,2-diamine [(*S*)-**2**] in 68–73% yield. After reduction of (*S*)-**1**, disappearance of infrared band at 1635 cm^{-1} (for –C = N–) and its ^{1}H NMR spectrum at 2.85 for the –NH– protons suggest that the two imino groups were reduced to corresponding diamino groups. ^{31}P NMR spectrum exhibits two singlets of equal intensities at δ −15.14 and −15.51. Based on these spectroscopic data, the structure of (*S*)-**2** is similar to (*S*)-**1**.

Ligands (*R*)-**1** and (*R*)-**2** can be prepared by means of the above similar procedures.



Scheme 1.

3.2. Synthesis of ruthenium complexes (R)-3 and (R)-4

The interaction of *trans*-$RuCl_2(DMSO)_4$ with one equivalent of ligand (*R*)-**1** in refluxing toluene gave (*R*)-$RuCl_2(P_2N_2Me)$ [(*R*)-**3**] in good yield (81%). ^{31}P NMR spectrum of (*R*)-**3** exhibits two singlets of relative intensities 1/1 at δ 48.12 and 48.51, indicating that the two phosphino groups of (*R*)-**1** are coordinated to the ruthenium center. The structure of (*R*)-**3** was established by an X-ray diffraction study, which revealed a distorted octahedral *trans*-configuration for the complex (Fig. 1). The two chloro ligands in the axial position are mutually *trans* to each other and (*R*)-**1** ligand behaves as a tetradentate ligand around the Ru center with the two phosphino group *cis* to each other.

Similar to that of (*R*)-**3**, yellow crystals of (*R*)-**4** were obtained in moderate yield (65%). The ^{31}P NMR spectrum exhibits two singlets of equal intensities at 45.18 and 43.88, indicating the two phosphino groups are coordinated to the Ru center. Attempt to get suitable crystals of complex (*R*)-**4** for structure analysis was unsuccessful. However, based on the spectroscopic data and the molecular structures of *trans*-$RuCl_2(P_2N_2H_4)$ [9,12] and *trans*-$RuCl_2(cyclo\text{-}C_6P_2N_2H_4)$ [13], the structure of ruthenium complex (*R*)-**4** is assignable to analogy with complex (*R*)-**3**. According to the above procedure ruthenium complexes (*S*)-**3** and (*S*)-**4** have been also prepared.

3.3. Asymmetric transfer hydrogenation of prochiral ketones

Complexes (*S*)-**3**, (*R*)-**3**, (*S*)-**4** and (*R*)-**4** have been tested as catalysts in enantioselective transfer hydrogenation of aromatic ketones in a *iso*-PrOH solution. The catalytic hydrogenation of acetophenone (**1a**) was conducted using some potassium 2-propoxide (1–3 equiv. with respect to Ru) as a promoter (Table 1 and Scheme 2).

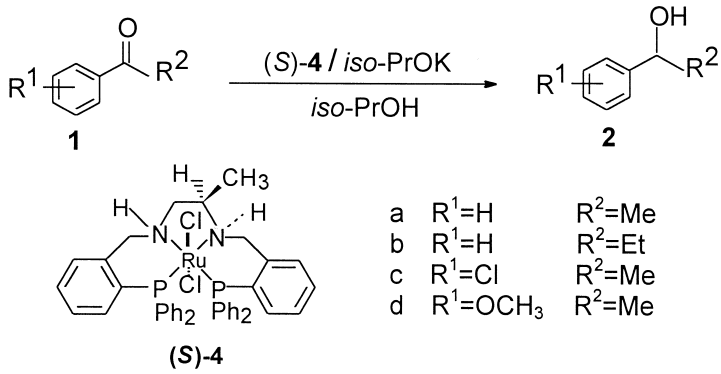
The concentration of *iso*-PrOK is an important factor for catalytic activity and the catalytic system is inactive without a basic co-catalalyst. Increase of reaction temperature accelerates the reaction rate with a slight loss of enantiomeric purity of the product. The ketones possessing an electron-donating substituent such as methoxyl at the para position tend to lower the rate, but still show high stereoselectivity.

It is noteworthy that the diimino complexes (*S*)-**3** and the diamino complex (*S*)-**4** display the differences in reactivities and enantioselec-

Table 1
Asymmetric transfer hydrogenation of ketones catalyzed by chiral $RuCl_2(P_2N_2Me)$ and $RuCl_2(P_2N_2H_4Me)$ complexes[a]

Ketone substrate	Catalyst	S/C/*iso*-PrOK[b] (molar ratio)	Conditions		Alcohol product		
			Temperature/°C	Time/h	Yield/%[c]	ee/%[d]	Configuration[e]
1a	(*R*)-**3**	100:1:3	40	22	63	26	*S*
1a	(*S*)-**3**	100:1:3	40	22	65	14	*R*
1a	(*S*)-**4**	100:1:3	30	46	90	91	*S*
1b	(*S*)-**4**	100:1:2	45	48	55	88	*S*
1b	(*R*)-**4**	100:1:3	30	46	73	91	*R*
m-**1c**	(*S*)-**4**	100:1:2	30	24	99	87	*S*
p-**1c**	(*S*)-**4**	100:1:2	30	24	82	89	*S*
m-**1d**	(*S*)-**4**	100:1:2	30	24	72	85[f]	*S*
p-**1d**	(*S*)-**4**	100:1:2	30	24	49	87[f]	*S*

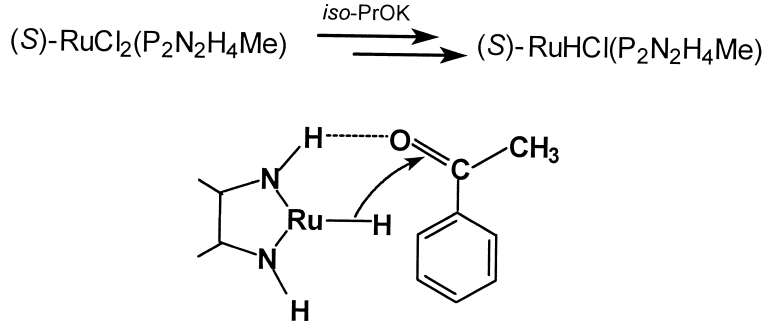
[a] Conditions: catalyst, 0.01 mmol; solvent, *iso*-PrOH, 20 ml.
[b] S/C/*iso*-PrOK = Ketone/Ru/*iso*-PrOK.
[c] GLC analysis.
[d] Capillary GLC analysis using a chiral Chrompack CD-cyclodextrin-β-236 M-19 column unless otherwise specified.
[e] Determined by comparison of the retention times of the enantiomers on the GLC traces with literature values.
[f] Determined by HPLC analysis using a Daicel Chiralcel OB column (10:90 2-propanol–hexane).



Scheme 2.

tivities. The reaction with the diimine complexes (*R*)-**3** or (*S*)-**3** proceeded in moderate yield with very low ee (14–26%). However, the diamine complexes (*R*)-**4** and (*S*)-**4** have proved to be an excellent catalyst precursor in asymmetric transfer hydrogenation of acetonphenone, leading to 2-phenylethanol in 90% yield with 91% ee. Complex (*R*)-**4** or (*S*)-**4** with sp^3-hybridized nitrogens containing N–H bonds displayed higher reaction rate and enantioselectivity.

The reaction mechanism of hydrogen transfer hydrogenation can be envisaged by a 'hydridic route' or a 'direct hydrogen transfer' [15]. The later involves the process in which both the hydrogen donor and the substrate are bound on the catalytic active center. For the catalyst precursor (*S*)-**3** or (*S*)-**4**, a 'direct hydrogen transfer' pathway is difficult to be realized since the catalysts possess the configuration with saturated coordination. Therefore, a reaction mechanism by 'hydridic route' may be performed in hydrogen transfer hydrogenation of acetophenone in this work. Based on the fact that the catalyst precursor, (*S*)-**3** or (*S*)-**4**, has inactive in the absence of *iso*-PrOK and the conversion increases with the increase of *iso*-PrOK concentration, *iso*-PrOK may play a role for promoting the formation of catalytic active ruthenium hydride (Scheme 3) [15–19]. On the other hand, the presence of an NH groups in the ligands is possible to stabilize a six membered cyclic transition state by forming a hydrogen bond with oxygen atom of ketones [20,21]. The study on isolation and characterization of the catalytic active intermediate is now under investigating.



Scheme 3.

Acknowledgements

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