A Ruthenium(II) Complex with a Tetradentate C_2-Symmetric Bis(phosphino)-bis(oxazoline) Ligand for Asymmetric Transfer Hydrogenation of Aromatic Ketones

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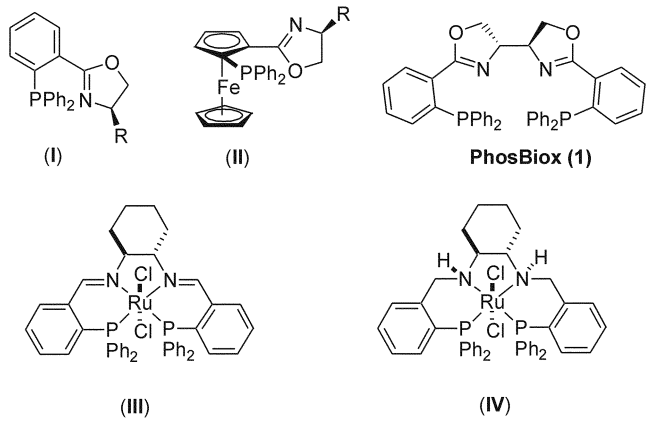
In the past decade, oxazoline-based bidentate ligands have proven very valuable in asymmetric catalysis, mainly as heterotoditopic ligands, such as the phosphino-oxazoline **I**-**II** or as bis(oxazoline) ligands with or without a coordinating connecting group.[1] In contrast to the bidentate or tridentate ligands, chiral tetradentate bis(oxazolinyl)-type ligands have been less extensively developed.[2] A possible difficulty in using chiral tetradentate ligands is that, in comparison to their bidentate analogues, they can often offer a larger diversity of binding modes and this requires the coordination geometry of their metal complexes to be characterized with great care. An exact knowledge of the structure of a catalyst precursor is the most helpful in order to gain a better insight into the overall reaction and allow subsequent fine-tuning of the catalytic system, although it is intrinsically difficult to identify the active species in a catalytic process. We have recently developed a series of new type of C_2-symmetric tetradentate chiral ligands such as (*S*,*S*)-PhosBiox **1**, where the two oxazoline rings connected directly at the stereogenic center.[3] The *P*,*N*,*N*,*P*-tetadentate ligand **1** showed excellent enantioselectivities in Rh-catalyzed hydrosilylation of ketones[3b,3c] and Pd-catalyzed allylic substitution reactions.[4] Ligand **1** can form a chelate in square-planar Pd(II) complexes which is an active catalyst precursor for enantioselective allylic substitution reaction.[4] Here we report on the coordination behavior of **1** toward Ru(II) and its catalytic activity in asymmetric transfer hydrogenation of aryl alkyl ketones.[5]



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Results and Discussion

Studies by Noyori *et al.* with *P*,*N*,*N*,*P*-tetradentate Ru(II) complexes of *N*,*N*′-bis[*o*-(diphenylphosphino)benzylidene]-cyclohexane-1,2-diamine (**III**) and *N*,*N*′-bis[*o*-(diphenyl-phosphino)benzyl] cyclohexane-1,2-diamine (**IV**) suggested that an NH moiety in complex **IV** plays a pivotal role in controlling reaction selectivity during the transfer hydrogenation.[6] Therefore, if the Ru(II) complex of PhosBiox **1** form *P*,*N*,*N*,*P*-tetradentate chelate, which may have resemble structure with complex **III**, it could be expected that it may not induce effectively the product chirality. However, if it form *P*,*N*-bidentate Ru(II) complex, similar catalytic activities could be expected with those of the Ru(II) complexes of phosphino-oxazolines **I** and **II**, which showed moderate to excellent enantioselectivity.[1f,7] To elucidate the coordination behavior toward Ru(II), the (*S*,*S*)-PhosBiox **1** was reacted with either 1 equiv. or 2 equiv. of $[RuCl_2(DMSO)_4]$ in refluxing toluene for 8 h. Under these conditions, only the six-coordinate dichloride complex $[RuCl_2$ (**1**)] (**2**), as indicated by the single signal at δ 49.5 ppm in ^{31}P NMR spectrum, was formed in quantitatively. The *trans* arrangement of the chloride ligands could be supported by the single band at 313 cm^{-1} in the Ru-Cl stretching region.[6] The tetradentate structure of complex **2** was confirmed unambiguously by X-ray crystallographic analysis (Figure 1).

To examine the catalytic efficiency of the complex **2** in transfer hydrogenation, the reduction was carried out with acetophenone as our test substrate using 0.1 mol% of **2** and 2.5 mol% of KOH in 1.0 M solution of ^{i}PrOH at 80 °C for 20 h. Unfortunately, no chiral induction has been observed,

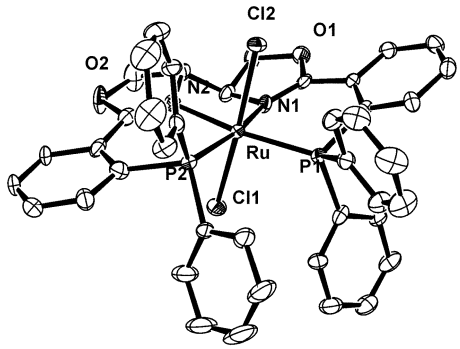
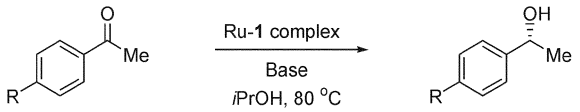


Figure 1. X-Ray structure of **2**.

Table 1. Asymmetric transfer hydrogenation of arylketones using Ru-complexs of (*S,S*)-PhosBiox **1**[a]



Entry	R	Ru(II) (mol%)	Base (mol%)	Conc. (M)	Time (h)	Yield (%)[b]	% ee[c]
1	H	$RuCl_2(DMSO)_2$ (0.1)	KOH (2.5)	1	20	73	racemic
2	H	$RuCl_2(DMSO)_2$ (0.1) + PPh_3 (0.1)	KOH (2.5)	1	20	77	53
3	H	$RuCl_2(DMSO)_2$ (0.1) + PPh_3 (0.3)	KOH (2.5)	1	20	81	56
4	H	$RuCl_2(PPh_3)_3$ (0.1)	KOH (2.5)	1	20	77	68
5	H	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	20	81	65
6	H	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (1.5)	1	20	76	77
7	H	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	0.1	20	36	36
8	H	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	0.5	20	82	61
9	H	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	5	20	76	57
10	H	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	1	77	77
11	H	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	5	76	76
12	H	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	10	83	70
13	OMe	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	1	16	78
14	OMe	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	10	30	58
15	Me	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	1	54	80
16	Me	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	10	69	76
17	Cl	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	1	36	67
18	Cl	$RuCl_2(PPh_3)_3$ (0.1)	^{i}PrOK (2.5)	1	10	59	47

[a]1 M solution of ketone (10 mmol) in ^{i}PrOH. [b]Determined by GC using tetradecane as an internal standard. [c]Determined by GC using a Chrompak Chirasil-Dex CB 25 m × 0.32 μm column and all product alcohols have *R* configuration which determined by the sign of optical rotation or retention time of GC peak.

thus, provided the racemic product in 70% yield (entry 1). An Interesting finding was that an additional PPh_3 was necessary to give enantioenriched product. Thus, addition of 0.1 and 0.3 mol% of PPh_3 increased the enantioselectivity to 53% ee and 56% ee, respectively (entries 2 and 3). To examine whether the added PPh_3 is coordinated to Ru metal or not, we employed $RuCl_2(PPh_3)_3$ having PPh_3 ligand. Interestingly, the complex prepared by reaction of **1** with 1 equiv. of $RuCl_2(PPh_3)_3$ in toluene reflux for 8 h has the same structure with **2** indicating that all of the three PPh_3 ligand in $RuCl_2(PPh_3)_3$ was exchanged with PhosBiox **1**. However, a catalyst prepared *in situ* by reaction of **1** with $RuCl_2(PPh_3)_3$ in ^{i}PrOH for 1 h reflux reduced the ketone stereoselectively. Thus, using the catalyst in this manner, the enantioselectivity reached 68% ee, but the yield was slightly decreased to 77% (entry 4). Although it is difficult to know at this time how the PPh_3 is involved in enantiodiscrimination step, these results clearly indicate that the additional PPh_3 is necessary for asymmetric induction. When the base was changed to ^{i}PrOK, the yield increased slightly to 81% with almost the same enantioselectivity (compare entries 4 and 5). The enantioselectivity increased to 77% ee upon decrease of the amounts of base (entry 6). Since the transfer hydrogenation is reversible reaction, it has been generally known that the reaction proceeded more efficiently at lower concentration. However, when the reaction carried out at 0.1 M solution, both of the yield and enantioselectivity decreased (entry 7) compared to those obtained at 0.5 M, even to those obtained at 5 M solution (compare entries 5, 7, 8 and 9). Furthermore, the enantioselectivity was gradually decreased as the reaction time became longer (see entries 10-12). Similar erosions of enantioselectivities at longer reaction time have been observed in other substrates (entries 13-18). The reversibility of the reaction could cause the erosions of the enantioselectivity at the prolonged reaction time.

In summary, we have been prepared a novel *P,N,N,P*-tetradentate Ru-complex **2** by reaction of bisphosphinobisoxazoline, Phos-Biox **1**, with either $RuCl_2(DMSO)_2$ or $RuCl_2(PPh_3)_3$. This complex acts as a catalyst for transfer hydrogenation of aromatic ketones. However, additional PPh_3 is necessary for asymmetric induction.

Experimental Section

Unless otherwise noted, all reactions were carried out in an inert atmosphere. All solvents were degassed prior to use. NMR spectra were recorded on a Bruker 300 spectrometer. GC analyses were performed using a Hewlett-Packard 5890 Model.

Synthesis of Ru (Phos-Biox)Cl_2 complex 2. A solution of Phos-Biox **1** (132 mg, 0.2 mmol) and *trans*-$RuCl_2(DMSO)_4$ (97 mg, 0.2 mmol) in toluene (15 mL) was refluxed for 8 hr. The resulting dark red solution was concentrated by vacuum, and the solid residue was purified by column chromatography on silica-gel with CH_2Cl_2 : acetone = 20 : 1 eluent to give pure the tetradentate complex **2** (96%). Recrystallization with CH_2Cl_2/hexane afforded a single crystal suitable for X-ray analysis. $[\alpha]_D = -185.95^o$ (*c* 0.89, $CHCl_3$); ^{1}H

NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 7.7 Hz, 2H), 7.44-7.25 (m, 6H), 7.17-7.01 (m, 16H), 6.87 (m, 4H), 4.90 (m, 4H), 4.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.9, 72.3, 127.0, 127.1, 127.2, 127.3, 128.7, 128.9, 129.4, 133.9, 134.0, 134.4, 134.5, 134.6, 136.2, 163.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 49.54 (external standard: H_3PO_4). Crystal data of **2**: $C_{42}H_{34}Cl_2N_2O_2P_2Ru$, orthorhombic, $P2_1P2_1P2_1$, a = 10.474(2), b = 18.352(2), c = 19.382(3) Å, V = 3725.6 Å^3, Z = 4, D_c = 1.484 g/cm^3, F(000) = 1696, 2494 Goodness of fit = 0.844. Independent reflections with $I/\sigma(I) \geq 2.0$ were used on the analysis. Data for crystallographic analysis were measured on an Enraf-Nonius CAD-4 diffractormeter using graphite-monochromate Mo Kα (λ = 0.71073 Å) and ϖ-2 scans in the range of θ; $1.53 < \theta < 25.15$. Structure was solved by direct methods and refined by least squares using the SHEL-X. Selected bond length (Å): N(1)-Ru 2.064, N(2)-Ru 2.071, P(1)-Ru 2.264, P(2)-Ru 2.279, Ru-Cl(1) 2.412, Ru-Cl(2) 2.422. Selected bond angle (degree): N(1)-Ru-N(2) 79.4, N(1)-Ru-P(1) 87.2, N(2)-Ru-P(1) 166.5, N(1)-Ru-P(2) 168.4, N(2)-Ru-P(2) 89.5, P(1)-Ru-P(2) 103.99, N(1)-Ru-Cl(1) 88.1, N(2)-Ru-Cl(1) 85.0, P(1)-Ru-Cl(1) 95.12, P2-Ru-Cl(1) 87.98, N(1)-Ru-Cl(2) 82.5, N(2)-Ru-Cl(2) 88.2, P(1)-Ru-Cl(2) 89.65, P(2)-Ru-Cl(2) 100.24, Cl(1)-Ru-Cl(2) 169.24.

Ru (Phos-Biox)Cl_2 complex 2 catalyzed transfer hydrogenation of acetophenone. To a degassed solution of Ru(**1**)Cl_2 (**2**) (8.35 mg 0.01 mmol) in 2-propanol (5 mL) was added a degassed solution of acetophenone (1.2 mL, 10 mmol) in 2-propanol (3 mL) at room temperature. For PPh_3 effect, 0.01 or 0.03 mmol of PPh_3 was added. The reaction mixture was heated to reflux for 15 min and allowed to cool down to room temperature. After addition of the degassed solution of KOH (14 mg, 0.25 mmol) in 2-propanol (2 mL), the reaction mixture was refluxed for 20 hr. After cooling to room temperature, the reaction mixture was passed through a short silica gel column to remove the catalyst. Without any further purification, the conversion determined with GC using tetradecane as an internal standard. The enantiomeric excess measured with chiral GC using Chrompak Chirasil-Dex CB 25 m × 0.32 μm column.

Asymmetric transfer hydrogenation of arylketones using in situ generated catalyst from Phos-Biox 1 and $RuCl_2(PPh_3)_3$. A degassed solution of PhosBiox **1** (8.6 mg, 0.013 mmol) and [$RuCl_2(PPh_3)_3$] (9.6 mg, 0.01 mmol) in 2-propanol (5 mL) were refluxed for 1hr. After cooled to room temperature, the degassed solution of aryl ketone (10 mmol) in 2-propanol (4.75 mL) was added to the reaction mixture, and refluxed again for 15min. After addition of 1 M solution $(CH_3)_2CHOK$ in 2-propanol (0.25 mL) at room temperature, the reaction mixture was reflux for 20 hr. The conversion and enantiomeric excess determined as above.

1-Phenylethanol: column temperature: 95 °C isothermal, t_1 = 7.9 min (*R*), t_2 = 8.8 min (*S*).

1-Tolylethanol: column temperature: 95 °C isothermal, t_1 = 11.9 min (*R*), t_2 = 14.0 min (*S*).

1-(*p*-Chlorophenyl)ethanol: column temperature: 110 °C isothermal, t_1 = 14.l min (*R*), t_2 = 16.5 min (*S*).

1-(*p*-Methoxyphenyl)ethanol: column temperature: 110 °C isothermal, t_1 = 14.9 min (*R*), t_2 = 16.0 min (*S*).

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