A Ruthenium(II) Complex with a C_2-Symmetric Diphosphine/Diamine Tetradentate Ligand for Asymmetric Transfer Hydrogenation of Aromatic Ketones†

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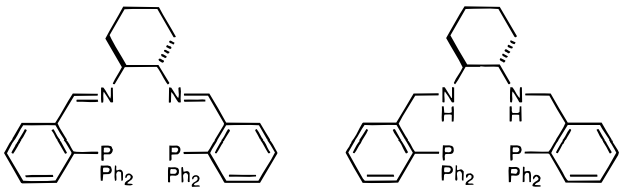
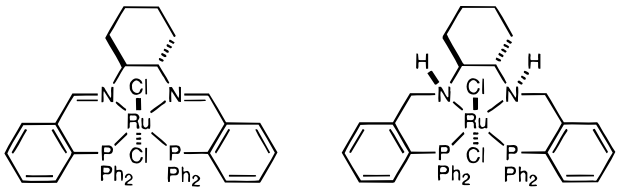
Summary: The trans-$Ru^{II}Cl_2$ *complexes with structurally similar N,N′-bis[o-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine and N,N′-bis[o-(diphenylphosphino)-benzyl]cyclohexane-1,2-diamine ligands have been synthesized, and their molecular structures have been determined. The* C_2*-symmetric diphosphine/diamine-based Ru complex acts as an excellent catalyst precursor in asymmetric transfer hydrogenation of acetophenone in a 0.1 M 2-propanol solution, leading to 2-phenylethanol in 97% ee and in 93% yield after 7 h at 45 °C. This transfer hydrogenation is characterized by low reversibility under these conditions.*

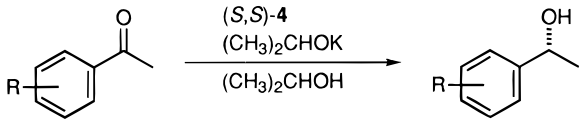
Although transfer hydrogenation of ketones using 2-propanol as a hydrogen donor is a long-known synthetic operation, it has only been during recent years that some selective methods for the asymmetric reaction have been reported.[1−4] An inherent problem of this potentially useful catalysis is the reversibility of the reaction, which prevents complete conversion and also causes the deterioration of enantiomeric purity of the chiral product.[4,5] In order to achieve a synthetically meaningful asymmetric reaction, the unfavorable reverse process must be minimized. As a part of our research program on this subject, we have been interested in the synthesis of Ru(II) complexes possessing the chiral tetradentate ligands *N,N′*-bis[*o*-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine (**1**) and *N,N′*-bis[*o*-(diphenylphosphino)benzyl]cyclohexane-1,2-diamine (**2**). This paper describes the molecular structures of the chiral Ru(II) complexes **3** and **4** and the characteristics of the transfer hydrogenation catalyzed by them.



(*S,S*)-**1**, P_2N_2 ligand (*S,S*)-**2**, $P_2(NH)_2$ ligand



(*S,S*)-**3** (*S,S*)-**4**



5 (*R*)-**6**

a: R = H **d**: R = F
b: R = Cl **e**: R = OCH_3
c: R = CN

The chiral compounds **1** (P_2N_2 ligand) and **2** ($P_2(NH)_2$ ligand) commonly have two soft phosphorus atoms and two hard nitrogen atoms.[6] When an equimolar mixture of *trans*-$RuCl_2(DMSO)_4$ and (*S,S*)-**1** or (*S,S*)-**2** was refluxed in toluene, the Ru(II) complex (*S,S*)-**3** or (*S,S*)-**4** was obtained in high yield.[7] The *R,R* complexes were also prepared in a similar manner. These products are soluble in many common organic solvents and stable to air and moisture at room temperature. Single-crystal X-ray analysis of the red P_2N_2 complex **3** indicates a distorted-octahedral geometry that approximates C_2 symmetry, as visualized in Figure 1a. The four equatorial positions around the Ru center are occupied by the tetradentate ligand **1** and the axial positions by two chloro ligands. The N,N-ligated five-membered ring has

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Table 1. Asymmetric Transfer Hydrogenation of Aromatic Ketones Catalyzed by the P_2N_2− and $P_2(NH)_2$−Ru^{II} Complexes 3 and 4[a]

ketone substrate	catalyst	conditions: temp, °C	conditions: time, h	alcohol product: yield, %[b]	alcohol product: % ee[c]	alcohol product: config[d]
5a	(*S*,*S*)-**3**	23	48	3	18	*R*
5a	(*S*,*S*)-**3**	82	4	7	5	*R*
5a	(*R*,*R*)-**4**	23	25	91	97	*S*
5a	(*S*,*S*)-**4**	45	7	93	97	*R*
o-**5b**	(*S*,*S*)-**4**	45	5	15	91	*R*
m-**5b**	(*S*,*S*)-**4**	45	6	99	95	*R*
p-**5b**	(*S*,*S*)-**4**	45	5	95	94	*R*
p-**5c**	(*S*,*S*)-**4**	45	6	99	89[e]	*R*[f]
p-**5d**	(*S*,*S*)-**4**	45	6	97	80[g]	*R*[f]
m-**5e**	(*S*,*S*)-**4**	45	6	74	95[h]	*R*
p-**5e**	(*S*,*S*)-**4**	45	6	67	58[h]	*R*
$C_6H_5COC_2H_5$	(*S*,*S*)-**4**	45	7	78	96[i]	*R*

[a] Reaction was carried out using a 0.1 M solution of substrate (2.0 mmol) in 2-propanol; substrate:Ru:$(CH_3)_2CHOK$ = 200:1:0.5. [b] GLC analysis. [c] Capillary GLC analysis using a chiral Chrompack CP-cyclodextrin-β-236-M-19 column unless otherwise specified. [d] Determined by comparison of the retention times of the enantiomers on the GLC traces with literature values[1] unless otherwise specified. [e] HPLC analysis using a Daicel Chiralcel OJ column (eluent, 10:90 2-propanol−hexane; flow rate, 0.5 mL/min). [f] Determined by sign of rotation. See Supporting Information. [g] Chiralcel OB column (5:95 2-propanol−hexane). [h] Chiralcel OB column (10:90 2-propanol−hexane). [i] Chiralpak AS column (20:80 2-propanol−hexane).

a δ conformation. The yellow $P_2(NH)_2$ complex **4** has a similar near-C_2 geometry, where the ligand **2** occupies the four equatorial coordination sites (Figure 1b).[8,9] The stereogenic nitrogen atoms have an *R*,*R* configuration.

The catalytic reduction of acetophenone (**5a**) was conducted with a substrate/catalyst molar ratio (S/C) of 200 using a 0.1 M solution in 2-propanol containing a small amount of potassium 2-propoxide ($^1/_2$ equiv with respect to Ru) as cocatalyst. The reaction with the diimine complex (*S*,*S*)-**3** proceeded very slowly, producing (*R*)-1-phenylethanol ((*R*)-**6a**) in only 3% yield and in 18% ee (23 °C, 48 h) or in 7% yield and in 5% ee (reflux, 4 h) (Table 1). On the other hand, the diamine complex (*S*,*S*)-**4** has proved to be an excellent catalyst, giving (*R*)-**6a** in 97% ee and in 91% yield after reaction for 25 h at 23 °C. The reaction under more forcing conditions, at 45 °C for 7 h, gave a similar result, 97% ee and 93% yield. An ee value as high as 95% is obtainable even after 72% conversion in the reaction using a 1.0 M (not 0.1 M) solution of **5a** in 2-propanol at 23 °C for 44 h.[10]

Examples of the asymmetric reaction of acetophenone derivatives with the $P_2(NH)_2$-based Ru catalyst **4** are listed in Table 1. The rate and stereoselectivity are

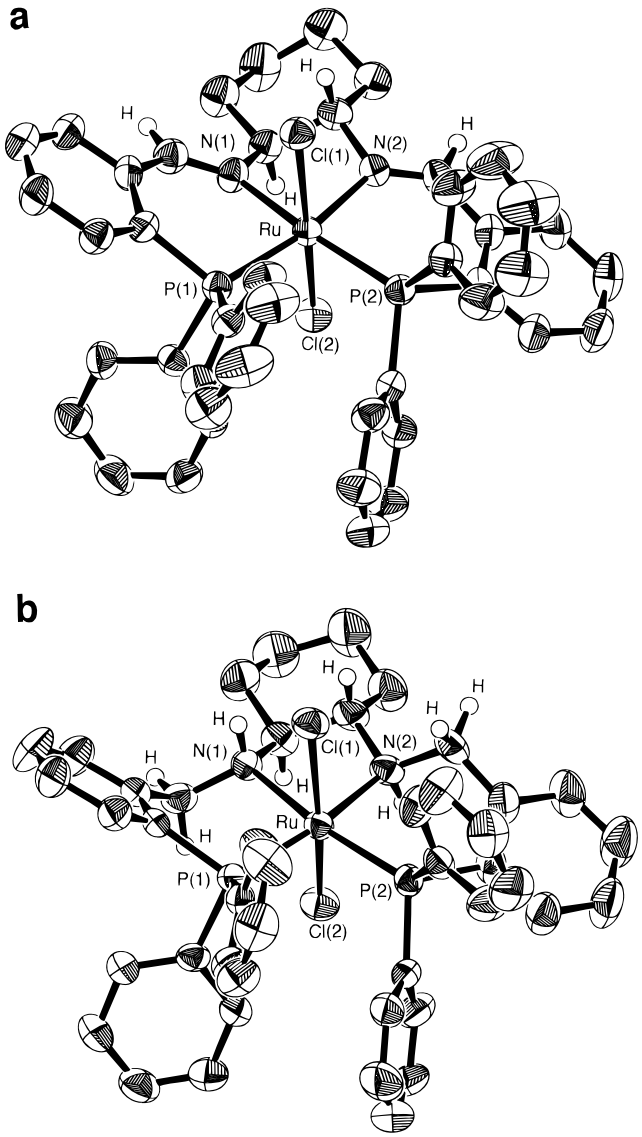

Figure 1. ORTEP plot (50% probability ellipsoids) of the molecular structures of the diphosphine/diimine and diphosphine/diamine complexes (*S*,*S*)-**3** (a) and (*S*,*S*)-**4**[8] (b). Most hydrogen atoms are omitted for clarity. The solvent molecules are not given. Selected bond distances (Å) and angles (deg) are as follows. **3**: Ru−Cl(1), 2.439(2); Ru−Cl(2), 2.403(2); Ru−P(1), 2.295(2); Ru−P(2), 2.288(2); Ru−N(1), 2.100(5); Ru−N(2), 2.091(5); Cl(1)−Ru−Cl(2), 171.67(6); N(1)−Ru−N(2), 80.9(2); P(1)−Ru−P(2), 99.52(6). **4**: Ru−Cl(1), 2.409(2); Ru−Cl(2), 2.430(2); Ru−P(1), 2.296(2); Ru−P(2), 2.290(2); Ru−N(1), 2.141(4); Ru−N(2), 2.164(5); Cl(1)−Ru−Cl(2), 164.22(5); N(1)−Ru−N(2), 80.4(2); P(1)−Ru−P(2), 98.55(6).

(7) A solution of (*S*,*S*)-**1** (0.13 g, 0.2 mmol) and *trans*-$RuCl_2(DMSO)_4$ (0.10 g, 0.2 mmol) in toluene (15 mL) was refluxed with stirring for 16 h. The resulting dark red solution was concentrated to ca. 5 mL under reduced pressure. Addition of 15 mL of hexane gave crude (*S*,*S*)-**3** as a red crystalline precipitate. Elution of the crude product through a silica gel column (2 × 12 cm) with CH_2Cl_2 gave pure (*S*,*S*)-**3** as red crystals in 83% yield (0.14 g). Mp: 251−254 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (m, 2H, CH_2), 2.07 (m, 4H, CH_2), 2.69 (d, 2H, CH_2), 4.16 (d, 2H, CH), 6.87−7.61 (m, 28H, C_6H_5), 8.88 (d, 2H, C_6H_5CH=N). ^{31}P NMR ($CDCl_3$, 85% H_3PO_4 standard, downfield positive): δ 48.04. Anal. Calcd for $C_{56}H_{52}Cl_2N_2P_2Ru$ (986.96): C, 68.08; H, 5.27; N, 2.84. Found: C, 67.42; H, 5.32; N, 2.92. Similarly, (*S*,*S*)-**4** was prepared by the reaction of (*S*,*S*)-**2** (0.26 g, 0.4 mmol) and *trans*-$RuCl_2(DMSO)_4$ (0.20 g, 0.4 mmol) in toluene (15 mL) at 110 °C for 18 h. Silica gel chromatography of the crude product with CH_2Cl_2 and acetone afforded pure (*S*,*S*)-**4** as yellow crystals in 87% yield (0.29 g). Mp: 304−310 °C dec. ^{1}H NMR ($CDCl_3$): δ 1.17 (m, 4H, CH_2), 1.78 (d, 2H, CH_2), 2.71 (d, 2H, CH_2), 2.94 (m, 2H, NH), 3.88 (d, 2H, CH), 4.03 (m, 2H, $C_6H_5CH_2$), 4.66 (m, 2H, $C_6H_5CH_2$), 6.88−7.25 (m, 28H, C_6H_5). ^{31}P NMR ($CDCl_3$, 85% H_3PO_4 standard, downfield positive): δ 43.28. Anal. Calcd for $C_{44}H_{44}Cl_2N_2P_2Ru$ (833.91): C, 63.32; H, 5.28; N, 3.36. Found: C, 63.07; H, 5.45; N, 3.30.

(8) Actual crystallographic analysis was done for (*R*,*R*)-**4** (Supporting Information). For convenience in the structural comparison, the geometry of the *S*,*S* isomer is given.

(9) Crystal data for (*S*,*S*)-**3**: $C_{56}H_{52}Cl_2N_2P_2Ru$, M_r = 986.96, monoclinic, space group $P2_1$, a = 11.637(5) Å, b = 14.668(4) Å, c = 14.725(4) Å, β = 108.48(3)°, V = 2383(1) Å^3, Z = 2, D_c = 1.374 g cm^{-3}, μ = 5.48 cm^{-1}, R (R_w) = 0.040 (0.038) for 4541 observed reflections ($I > 3.00\sigma(I)$). Crystal data for (*R*,*R*)-**4**: $C_{51}H_{52}Cl_2N_2P_2Ru$, M_r = 926.91, orthorhombic, space group $P2_12_12_1$, a = 12.946(3) Å, b = 34.800(2) Å, c = 9.994(3) Å, V = 4502(1) Å^3, Z = 4, D_c = 1.367 g cm^{-3}, μ = 48.64 cm^{-1}, R (R_w) = 0.033 (0.027) for 3419 observed reflections ($I > 3.00\sigma(I)$).

(10) 1-Phenylethyl alcohol/acetophenone equilibrium ratios are ca. 80:20 in a 1 M 2-propanol solution and 97:3 in a 0.1 M solution.[5]

delicately influenced by reaction conditions as well as steric and electronic properties of the substituents of the ketones. Increase of the base:Ru ratio from 0.5:1 to 2:1 slightly accelerates the reaction with a slight loss of enantiomeric purity of the product. The ketones having an electron-withdrawing substituent are reduced smoothly with a high enantioselectivity, while the introduction of an electron-donating substituent such as methoxyl to the para position tends to lower the rate and stereoselectivity. *o*-Chloroacetophenone reacted very slowly with moderate stereoselectivity. Propiophenone was reduced satisfactorily, while the more congested isobutyrophenone and pivalophenone were inert to reduction even at 55 °C. Overall, the chiral efficiency attains a very high level in the asymmetric reduction of aromatic ketones and compares well with the recently discovered catalyst systems.[1,2]

Normally, asymmetric transfer hydrogenation of ketones is accomplished by kinetic discrimination of the enantiofaces, but the rate of ketone + 2-propanol ⇌ alcohol + acetone equilibration is not negligible.[5] Therefore, the product ee tends to decrease with the increase of substrate concentration and the progress of the reaction.[1,2,4] The high enantioselectivity attained with **4** relies on the low reversibility of the reaction in addition to the excellent enantioface-differentiating ability of the catalyst ($k_{Si}/k_{Re} = 99/1$). Control experiments using racemic alcohol **6a** and acetone (1:1 molar ratio) in 2-propanol revealed that (*S*,*S*)-**4** catalyzes dehydrogenation of the *R* alcohol ca. 100 times faster than the reaction of the *S* enantiomer. Although this effect deteriorates the enantiomeric purity of the product, such a reverse process is much slower than the forward reaction and does not participate in the actual catalytic reaction to any great extent.[11]

The most notable result is the difference in reactivities of the diimino complex **3** and the diamino complex **4**, which have similar geometrical parameters, except for the higher planarity of the P,N-ligated six-membered rings in **3** (Figure 1). The chiral tetradentate $P_2(NH)_2$ ligand in fact exerts marked beneficial effects. The difference between the sp^2- and sp^3-hybridized nitrogens does not cause any significant electronic influence on the Ru center.[12] For example, as one goes from **3** to **4**, the ^{31}P signal in the NMR spectrum ($CDCl_3$, 85% H_3PO_4 standard) is shifted only slightly upfield from 48.0 to 43.3 ppm (free ligands **1** and **2**, −13.0 and −15.2 ppm, respectively). Furthermore, the Ru−P bond lengths of **3** and **4** are almost identical, 2.288−2.295 *vs* 2.290−2.296 Å, while the Ru−N distance of **3** is slightly shorter than in **4**, 2.091−2.100 *vs* 2.141−2.164 Å.[6a,c] These results indicate that the NH functions are responsible for the high reactivity of the $P_2(NH)_2$-based catalyst **4**, whatever the exact reaction mechanism.

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Supporting Information Available: Text giving the experimental procedure for the transfer hydrogenation of acetophenone derivatives (**5**) catalyzed by [$RuCl_2$\{(1*S*,2*S*)-*N*,*N*′-bis[*o*-(diphenylphosphino)benzyl]cyclohexane-1,2-diamine\}] ((*S*,*S*)-**4**) and text, tables, and figures giving data for the single-crystal X-ray analyses of [$RuCl_2$\{(1*S*,2*S*)-*N*,*N*′-bis[*o*-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine\}] ((*S*,*S*)-**3**) and [$RuCl_2$\{(1*R*,2*R*)-*N*,*N*′-bis[*o*-(diphenylphosphino)benzyl]cyclohexane-1,2-diamine\}] ((*R*,*R*)-**4**) (49 pages). Ordering information is given on any current masthead page.

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(11) The (*S*,*S*)-**4**-catalyzed reaction of **5a** in a 1 M 2-propanol solution at 23 °C gave (*R*)-**6a** in 95% ee and in 87% yield after 24 h and in 95% ee and 93% yield after 44 h. The reaction of the *p*-chloro compound *p*-**5b** (0.1 M, 45 °C) afforded (*R*)-*p*-**6b** in 94% ee and in 95% yield after 5 h, and these values did not change even after 29 h.

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