Ruthenium-Catalyzed Asymmetric Hydrosilylation of Ketones and Imine

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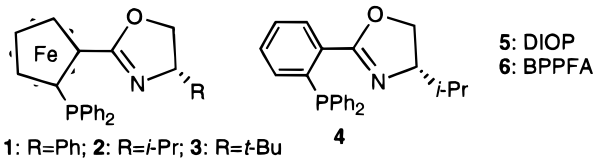
Summary: Ruthenium complexes with (oxazolinylferrocenyl)phosphines, $RuCl_2(PPh_3)$((oxazolinylferrocenyl)phosphine), have been prepared and characterized by spectroscopy. These ruthenium complexes are very effective catalysts for asymmetric hydrosilylation of not only ketones but also an imine to give the corresponding sec-alcohols (up to 97% ee) and a sec-amine (88% ee) after acid hydrolysis, respectively.

Intensive studies have recently been focused on the asymmetric hydrosilylation of ketones to obtain chiral alcohols, owing to the exceedingly mild reaction conditions and technical simplicity as compared to the asymmetric hydrogenation of ketones.[1−3] A variety of transition-metal complexes are now known to show catalytic activity in the hydrosilylation of ketones, but effective catalysts for asymmetric hydrosilylation are strictly limited to rhodium complexes with various kinds of chiral ligands.[1−4] In contrast, asymmetric hydrosilylation of imines remains undeveloped. Only a few examples of rhodium−chiral diphosphine catalysts have been reported, but none of these reactions afforded amines with high enantioselectivity.[5] Quite recently, the highly enantioselective titanocene-catalyzed hydrosilylation of ketones and imines has been reported by Buchwald *et al.*[6,7] These findings prompted us to develop an alternative transition-metal-catalyzed asymmetric hydrosilylation of ketones and imines, although the highly efficient asymmetric hydrogenation and transfer hydrogenation of alkyl aryl ketones and imines have been realized by using ruthenium complexes.[8] We wish here to describe a quite efficient ruthenium-catalyzed asymmetric hydrosilylation of ketones and an imine by employing chiral (oxazolinylferrocenyl)phosphines.[9]

Scheme 1

$$RuCl_2(PPh_3)_3 + \mathbf{L} \longrightarrow RuCl_2(PPh_3)(\mathbf{L})$$

Various ruthenium complexes having chiral ligands were prepared from $RuCl_2(PPh_3)_3$ and the chiral chelate compound **L** (Scheme 1; **L** = **1**−**6**). When an equimolar



mixture of $RuCl_2(PPh_3)_3$ and **1** was reacted in toluene at room temperature for 20 h, the ruthenium complex [$RuCl_2(PPh_3)$(**1**)] was obtained in 86% yield. Recrystallization from dichloromethane−diethyl ether afforded single crystals of [$RuCl_2(PPh_3)$(**1**)], and the formation of its diastereoisomer was not observed by NMR in $CDCl_3$. The molecular structure of [$RuCl_2(PPh_3)$(**1**)] was unambiguously clarified by X-ray analysis, and an ORTEP drawing is shown in Figure 1.[10] The ruthenium atom has a distorted-trigonal-bipyramidal geometry

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(10) Crystal data for [$RuCl_2(PPh_3)$(**1**)]·CH_2Cl_2 are as follows: monoclinic, space group $P2_1$ (No. 4); a = 11.370(8) Å, b = 17.914(8) Å, c = 12.210(4) Å, β = 114.63(3)°; V = 2260(1) Å^3; Z = 2; D_{calcd} = 1.520 g cm^{-3}; μ(Mo Kα) = 10.01 cm^{-1}. The final R value was 0.040 (R_w = 0.043) for 4264 unique reflections with $I > 3\sigma(I)$.

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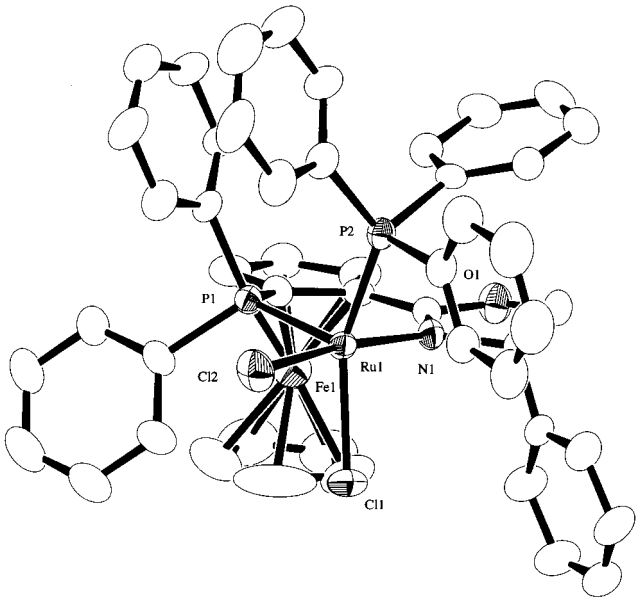


Figure 1. Crystal structure of $[RuCl_2(PPh_3)(\mathbf{1})]\cdot CH_2Cl_2$, showing 50% probability thermal ellipsoids. The hydrogen atoms and CH_2Cl_2 are omitted for clarity. Selected distances (Å) and angles (deg): Ru(1)−Cl(1), 2.396(3); Ru(2)−Cl(2), 2.392(2); Ru(1)−P(1), 2.199(2); Ru(1)−P(2), 2.283(2); Ru(1)−N(1), 2.110(7); Cl(1)−Ru(1)−Cl(2), 87.97(9); Cl(1)−Ru(1)−P(1), 107.07(7); Cl(1)−Ru(1)−P(2), 154.16(7); Cl(1)−Ru(1)−N(1), 87.5(2); Cl(2)−Ru(1)−P(1), 93.06(9); Cl(2)−Ru(1)−P(2), 90.19(9); Cl(2)−Ru(1)−N(1), 171.3(2); P(1)−Ru(1)−P(2), 98.77(7); P(1)−Ru(1)−N(1), 95.3(2); P(2)−Ru(1)−N(1), 90.7(2).

Scheme 2

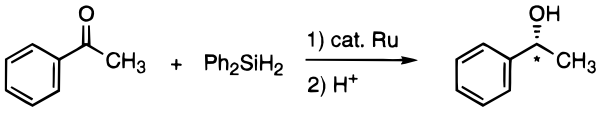


Table 1. Ruthenium-Catalyzed Asymmetric Hydrosilylation of Acetophenone[a]

run no.	ligand (**L**)	additive	reacn time (h)	1-phenylethanol (*R*) yield (%)[b]	ee (%)[c]
1	**1**	AgOTf	24	56	93
2	**1**	$Cu(OTf)_2$	24	59	95
3	**1**	−	24	46	67
4	**2**	AgOTf	5	42	90
5	**2**	$Cu(OTf)_2$	36	38	92
6	**3**	AgOTf	24	52	45
7	**4**	AgOTf	70	34	84

[a] All reactions were carried out in the presence of $[RuCl_2(PPh_3)(\mathbf{L})]$ (1 mol %) and AgOTf or $Cu(OTf)_2$ (1 mol %) with diphenylsilane (2.0 mmol) and acetophenone (1.0 mmol) in Et_2O at 0 °C. [b] GLC yield. [c] Determined by GLC.

with *cis* coordination of the nitrogen and phosphorus atoms of **1** on the basal plane. The apical positions are occupied by PPh_3 and one Cl anion. Other ruthenium complexes $[RuCl_2(PPh_3)(\mathbf{L})]$ (L = **2**−**6**) were also obtained by a similar procedure in 60−90% yields.

These new ruthenium complexes were used as catalysts for asymmetric hydrosilylation of acetophenone (Scheme 2). Typical results are shown in Table 1. Interestingly, the addition of AgOTf or $Cu(OTf)_2$ to the reaction system dramatically improved the enantioselectivity and also slightly the catalytic activity (Table 1, runs 1−3). The ligand **1** with a phenyl-substituted oxazoline was the most effective for the ruthenium-catalyzed asymmetric hydrosilylation of acetophenone to give the corresponding alcohol with 95% enantiomeric excess (ee).[11] The ruthenium complex having the (oxazolinylphenyl)phosphine **4**, without the planar chirality of ferrocene, showed lower catalytic activity, compared with that having the (oxazolinylferrocenyl)phosphine **2** (Table 1, runs 4 and 7). It is noteworthy that (oxazolinylferrocenyl)phosphines, **1** and **2** did not work effectively as chiral ligands for the rhodium- and iridium-catalyzed asymmetric hydrosilylation of unfunctionalized simple ketones, whereas introduction of a phenyl group at the 5-position of the oxazolinyl ring gave rise to the formation of the corresponding alcohols with high enantioselectivity.[3] For example, the ee values of 1-phenylethanol obtained by rhodium or iridium catalysts with **2** were only 46% (*R*) and 38% (*S*), respectively.[3] Furthermore, no reaction occurred when ruthenium complexes with chiral diphosphines such as 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) (**5**) and [1-(1,2-bis(diphenylphosphino)ferrocenyl)ethyl]-dimethylamine (BPPFA) (**6**) were used under the same conditions. This is in contrast with the *rhodium*/DIOP-catalyzed asymmetric hydrosilylation of acetophenone, which gave 1-phenylethanol with moderate enantioselectivity.[1]

Table 2. Ruthenium-Catalyzed Asymmetric Hydrosilylation of Various Ketones[a]

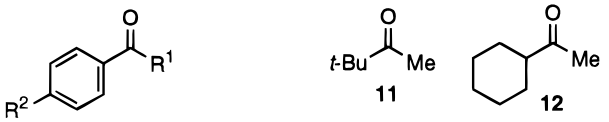
run no.	ketone	additive	reacn time (h)	alcohol (*R*) yield (%)[b]	ee (%)[c]
1	**7**	$Cu(OTf)_2$	40	76	97
2	**7**	AgOTf	70	80	91
3	**8**	$Cu(OTf)_2$	24	45	95
4	**8**	AgOTf	70	36	85
5	**9**	$Cu(OTf)_2$	20	55	85
6	**9**	AgOTf	40	28	77
7	**10**	$Cu(OTf)_2$	20	60	86
8	**10**	AgOTf	20	48	77
9	**11**	AgOTf	48	42	67
10	**12**	AgOTf	70	52	43

[a] All reactions were carried out in the presence of $[RuCl_2(PPh_3)(\mathbf{1})]$ (1 mol %) and AgOTf or $Cu(OTf)_2$ (1 mol %) with diphenylsilane (2.0 mmol) and ketone (1.0 mmol) in Et_2O at 0 °C. [b] GLC yield. [c] Determined by GLC.

Asymmetric hydrosilylation of several other simple ketones with diphenylsilane also proceeded highly stereoselectively in the presence of a catalytic amount of $[RuCl_2(PPh_3)(\mathbf{1})]$. Typical results are shown in Table 2. In the case of propiophenone, the best enantioselectivity of 97% ee was achieved with a high yield of the

(11) **General Procedure for Ruthenium-Catalyzed Asymmetric Hydrosilylation of Ketones.** In a 20-mL flask were placed $[RuCl_2(PPh_3)(\mathbf{1})]$ (0.01 mmol; 1.0 mol %) and AgOTf or $Cu(OTf)_2$ (0.01 mmol; 1.0 mol %) under N_2. Anhydrous diethyl ether (10 mL) was added, and then the mixture was magnetically stirred at room temperature for 1 h. After addition of a ketone (1.0 mmol), the reaction flask was dipped in a thermoregulated bath at 0 °C. Diphenylsilane (2.0 mmol) was slowly added by a syringe. The reaction was run by keeping the temperature at 0 °C. For the workup, methanol (1 mL) was slowly added at 0 °C to the reaction mixture, which was stirred for 0.5 h. After gas evolution ceased, 1 N aqueous HCl (5 mL) was added to the reaction mixture, which was stirred for 1 h at room temperature. The reaction mixture was extracted with brine (50 mL) and diethyl ether (50 mL × 3) and then dried over anhydrous $MgSO_4$. For the GLC analyses, naphthalene was added as an internal standard. For isolation, the extract was concentrated under reduced pressure by an aspirator and then distilled under vacuum by Kugelrohr to give the corresponding alcohol together with the unreacted starting ketone. Dimethoxydiphenylsilane was left in the residue. The ee value and the configuration of the alcohol were determined by GLC on a cyclodextrin phase (Chiraldex GT-A, 30 m).

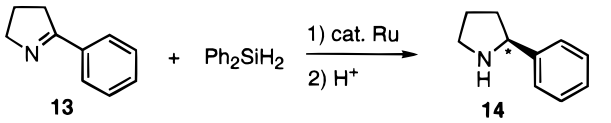
product (Table 2, run 1). Introduction of a *p*-Me or *p*-Cl substituent to the aromatic ring of acetophenone slightly decreased the stereoselectivity (Table 2, runs 5−8). Dialkyl ketones such as **11** and **12**, which are difficult



7: R^1=Et, R^2=H; **8**: R^1=*n*-Pr, R^2=H
9: R^1=Me, R^2=Cl; **10**: R^1=Me, R^2=Me

to transform into the corresponding alcohols with high enantioselectivity even by hydrogenation and transfer hydrogenation, were also converted into the corresponding dialkyl alcohols with moderate enantioselectivity (Table 2, runs 9 and 10).

Scheme 3



Complex $[RuCl_2(PPh_3)(\mathbf{1})]$ was also found to be an effective catalyst for asymmetric hydrosilylation of an imine. Hydrosilylation of the imine **13** with diphenylsilane in the presence of a catalytic amount of $[RuCl_2(PPh_3)(\mathbf{1})]$ in toluene at 0 °C for 48 h afforded the amine **14** in moderate yield with high enantioselectivity (Scheme 3). As described above, in the case of ketones, higher selectivities were attained by addition of AgOTf or $Cu(OTf)_2$. In contrast, the addition of AgOTf to the present system completely inhibited the hydrosilylation of the imine. It is to be noted that the analogous *rhodium*−(oxazolinylferrocenyl)phosphine system offered low enantioselectivity in the hydrosilylation of imines.[3c] Actually, the rhodium-catalyzed hydrosilylation of **13** using **1** at 0 °C for 20 h gave **14** in 75% yield with 34% ee. Since the structures of 2-aryl-1-pyrrolines are often found in natural products or drugs including alkaloid nicotines,[12] we are making efforts to apply this system to other prochiral imines, the results of which will be reported in due course.

In conclusion, we have developed the first highly enantioselective *ruthenium*-catalyzed hydrosilylation of both *ketones* and *an imine*.[13] In this ruthenium-catalyzed asymmetric hydrosilylation, it has been found that employment of *phosphine*−*nitrogen hybrid ligands* is necessary to achieve high catalytic activity with high stereoselectivity. Further work is currently in progress aiming at the elucidation of the reaction mechanism and broadening the scope of this asymmetric hydrosilylation.

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Supporting Information Available: Text giving experimental procedures and physical data for all compounds and tables giving crystallographic data for $[RuCl_2(PPh_3)(\mathbf{1})]\cdot CH_2Cl_2$ (26 pages). Ordering information is given on any current masthead page.

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(12) Several studies have demonstrated that substituted 2-aryl-1-pyrrolines may have benefical effects in the treatment of Parkinson's disease, Alzheimer's disease, attention deficit hyperactivity disorder, Tourette's syndrome, and schizophrenia. For a recent example, see: Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; McCallum, J. S.; McDonald, I. A. *J. Org. Chem.* **1998**, *63*, 1109−1118 and references therein.

(13) During the preparation of this manuscript, the ruthenium-catalyzed asymmetric hydrosilylation of alkyl aryl ketones using tridentate ligands was reported. However, the enantioselectivities were moderate (up to 66% ee); Zhu, G.; Terry M.; Zhang, X. *J. Organomet. Chem.* **1997**, *547*, 97−101.