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Ruthenium(II)-catalyzed asymmetric transfer hydrogenation of ketones using chiral oxazolinylferrocenylphosphines and one of their Ru(II) complex

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Abstract

Chiral oxazolinylferrocenylphosphines act as efficient ligands for Ru(II)-catalyzed asymmetric transfer hydrogenation of a variety of alkyl aryl ketones and alkyl methyl ketones to give the corresponding alcohols in moderate yield with moderate-to-good enantiomeric excess. A new ruthenium(II) complex containing a chiral oxazolinylferrocenylphosphine has been prepared and fully characterized by X-ray crystallography, the complex being revealed to work as a catalyst for this hydrogenation as well.

Keywords: Transfer hydrogenation; Oxazolinylferrocenylphosphine; Ruthenium(II) complex; Crystal structure

1. Introduction

A large number of studies have recently appeared in the field of a transition metal-catalyzed enantioselective hydrogenation of ketones using 2-propanol or formic acid under basic conditions [1,2], because the method has advantages such as the low cost, ease of handling and high solubility of 2-propanol or formic acid as a hydrogen donor reagent. Among a variety of chiral ligands investigated for this reaction, tetradentate diphosphine/diamine ligands or 1,2-diamine monosulfonamides developed by Noyori et al. seem to be the best in Ru(II)-catalyzed reaction of alkyl aryl ketones in respect to catalytic activity, enantioselectivity and product yield [3]. Helmchen and co-workers applied chiral phosphinooxazolines to this reaction as ligands and found that the reaction proceeds with a high turnover and enantioselectivity, but the selectivity is modest for alkyl methyl ketones, such as cyclohexyl methyl ketone [4]. These reports prompted the authors to examine their oxazolinylferrocenylphosphines, which act very efficiently as chiral ligands for the Rh(I)- and Ir(I)-catalyzed asymmetric hydrosilylation of unfunctionalized simple ketones [5,6], for transfer hydrogenation of ketones using 2-propanol/NaOH system [7]. Independently, Sammakia and co-workers reported a quite highly enantioselective Ru(II)-catalyzed transfer hydrogenation of alkyl aryl ketones with oxazolinylferrocenylphosphines using 2-propanol/potassium isopropoxide system [8,9]. They discussed the structure of the ruthenium complex containing an oxazolinylferrocenylphosphine in view of ^{1}H- and ^{31}P-NMR spectroscopic studies, but the isolation of the

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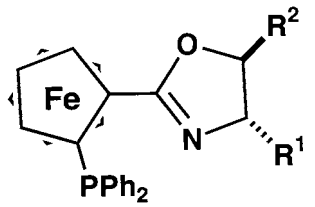


1: R^1 = Ph; R^2 = Ph
2: R^1 = *t*-butyl; R^2 = H
3: R^1 = *i*-propyl; R^2 = H
4: R^1 = *s*-butyl; R^2 = H
5: R^1 = benzyl; R^2 = H

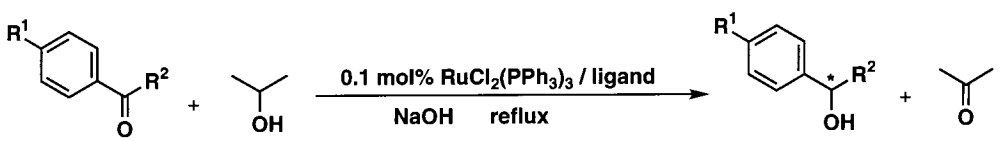
Scheme 1.

complex and its full characterization were not carried out. In this paper, the authors report results of Ru(II)-catalyzed asymmetric transfer hydrogenation of not only alkyl aryl ketones but also alkyl methyl ketones using several chiral oxazolinylferrocenylphosphines and one of their ruthenium complex as well as the unambiguous characterization of the complex by X-ray crystallography.

2. Results and discussion

2.1. Ruthenium(II)-catalyzed asymmetric transfer hydrogenation of alkyl aryl ketones

The chiral oxazolinylferrocenylphosphines **1**–**5** (Scheme 1) were prepared by the reported methods [5,6,10,11]. These chiral compounds were first employed as ligands for the Ru(II)-catalyzed transfer hydrogenation of acetophenone using 2-propanol and NaOH (Scheme 2, Table 1, runs 1–9). The procedure of the reaction was as follows. A 2-propanol solution of $RuCl_2(PPh_3)_3$ (0.10 mol%) and a chiral oxazolinylferrocenylphosphine (0.11 mol%) was stirred at reflux temperature for 30 min under nitrogen and then acetophenone in 2-propanol was added to this solution and the mixture was stirred for another 30 min at this temperature. A 2-propanol solution of NaOH was then added and the resulting mixture was stirred for an appropriate time. The chiral 1-phenylethanol was obtained in moderate yield with moderate-to-good enantiomeric excess. The ee values and the configuration of 1-phenylethanol were determined by HPLC and GLC. The reaction scarcely proceeded at lower temperature, such as 50°C. Best enatioselectivity (83% ee) was obtained by use of ligand **2** among the five oxazolinylferrocenylphosphines (runs 1, 2, 5, 8 and 9), while the use of ligand **1**, the best ligand in Rh(I)- and Ir(I)-catalyzed

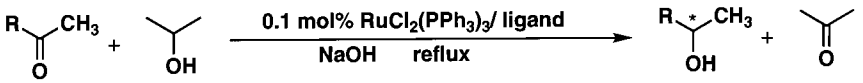


Scheme 2.

Table 1
Ruthenium(II)-catalyzed asymmetric transfer hydrogenation of alkyl aryl ketones

Run	R^1	R^2	Ligand	Time (min)	Yield (%)[a]	ee (%) (configuration)
1	H	Me	**1**	5	57	47 (*R*)
2	H	Me	**2**	5	27	82 (*R*)
3	H	Me	**2**	60	56[b]	83 (*R*)
4	H	Me	**3**	1	66	66 (*R*)
5	H	Me	**3**	5	77	48 (*R*)
6[c]	H	Me	**3**	5	75[b]	49 (*R*)
7	H	Me	**3**	30	89	16 (*R*)
8	H	Me	**4**	5	43	50 (*R*)
9	H	Me	**5**	5	64	54 (*R*)
10	Me	Me	**2**	60	48[b]	60 (*R*)
11	Cl	Me	**2**	60	15[b]	–
12	OMe	Me	**2**	60	6[b]	–
13	H	Et	**2**	60	30	85 (*R*)
14	H	*i*-Pr	**2**	60	23[b]	73 (*R*)

[a] GLC yield.
[b] Isolated yield.
[c] The ruthenium complex **6** was used.



Scheme 3.

Table 2
Ruthenium(II)-catalyzed asymmetric transfer hydrogenation of alkyl methyl ketones

Run	R (alkyl)	Ligand	Time (h)	Yield (%)[a]	ee (%) (configuration)
1	Cyclohexyl	**1**	1	54	59 (*S*)
2		**2**	1	47	52 (*S*)
3		**3**	1	46	14 (*S*)
4		**4**	1	59	12 (*S*)
5		**5**	1	46	17 (*S*)
6	*n*-Hexyl	**1**	1	39	20 (*S*)
7		**2**	1	40	36 (*S*)
8	*t*-Butyl	**1**	2	57[b]	93 (*S*)
9		**2**	2	Trace[b]	–

[a] Isolated yield.
[b] GLC yield.

hydrosilylation of acetophenone [5,6], resulted in lower enantioselectivity (47% ee). In the case of ligand **2**, 1-phenylethanol was obtained in higher yield by prolonging the reaction time without any decrease of ee (runs 2 and 3). In the case of ligand **3**, however, the longer reaction time improved the yield of the alcohol with a decrease of ee, probably because of reverse transfer hydrogenation (runs 4, 5 and 7). In fact, it was confirmed separately that the racemization of enantiomerically pure (*R*)- or (*S*)-1-phenylethanol occurred within 1 h under the same reaction conditions using chiral ligand **3**. The introduction of *p*-Me (48%), *p*-Cl (15%) and *p*-MeO (6%) to aromatic ring of ketones decreased the product yield (runs 10, 11 and 12). The product yield of transfer hydrogenation of propiophenone ($R^2 = Et$) and isobutyrophenone ($R^2 = i$-Pr) decreased because of the bulkiness of the alkyl group as expected [Me (56%) > Et (30%) > *i*-Pr (23%)], while enantioselectivity was not much affected (runs 3, 13 and 14). 2-Acetonaphthalene afforded 33% of the reduced compound with 40% ee (*R*) under these conditions.

2.2. Ruthenium(II)-catalyzed asymmetric transfer hydrogenation of alkyl methyl ketones

The authors next applied this Ru(II)-catalyzed transfer hydrogenation to alkyl methyl ketones, which have been known to be more difficult to achieve high enantioselectivity than alkyl aryl ketones (Scheme 3, Table 2). The ee values and the configuration of the produced chiral alcohols were determined by GLC of the corresponding acetate or trifluoroacetate using Chiraldex GT-A (30 m). Using cyclohexyl methyl ketone as a substrate, the efficiency of the chiral ligands **1**–**5** was investigated. As a result, higher enantioselectivity was observed in the reactions using ligands **1** and **2**, but the use of the ligands **3**, **4** and **5** resulted in a poor selectivity (runs 1–5). When *n*-hexyl methyl ketone was employed as a substrate, higher enantioselectivity was obtained in the case of ligand **2** than in that of ligand **1** (runs 6 and 7). On the contrary, and interestingly, in the reaction of *t*-butyl methyl ketone, a very high selectivity (93% ee) was attained in the combination with ligand **1**, but not with ligand **2** (runs 8 and 9), and the results were reproducible. From the results in Table 2 it is clear that the bulkiness of alkyl group affects the enantioselectivity; the bulkier the group is, the higher the selectivity is (*t*-butyl > cyclohexyl > *n*-hexyl). It is to be noted that the ruthenium-catalyzed highly enantioselective transfer hydrogenation of dialkyl ketones has not yet been reported in contrast to the case of alkyl aryl ketones.

2.3. Preparation, catalytic activity and structural analysis of the Ru(II)complex of chiral oxazolinylferrocenylphosphine

As described above, these chiral phosphines worked as effective ligands for Ru(II)-catalyzed asymmetric transfer hydrogenation of ketones. In order to obtain some information for this catalytic reaction, the authors attempted to prepare the complex between $RuCl_2(PPh_3)_3$ and the ligand to check its catalytic activity in this reaction.

By treatment of chiral phosphine **3** with $RuCl_2(PPh_3)_3$ in toluene at r.t. for 20 h, the corresponding Ru(II) complex **6** [$RuCl_2 \cdot \mathbf{3} \cdot (PPh_3)$] was obtained in 81% yield as red crystals. Recrystallization from dichloromethane–diethyl ether afforded a single crystal of **6**, the molecular structure of which being unambiguously clarified by X-ray analysis. An ORTEP drawing of one of the two independent molecules of **6** in each

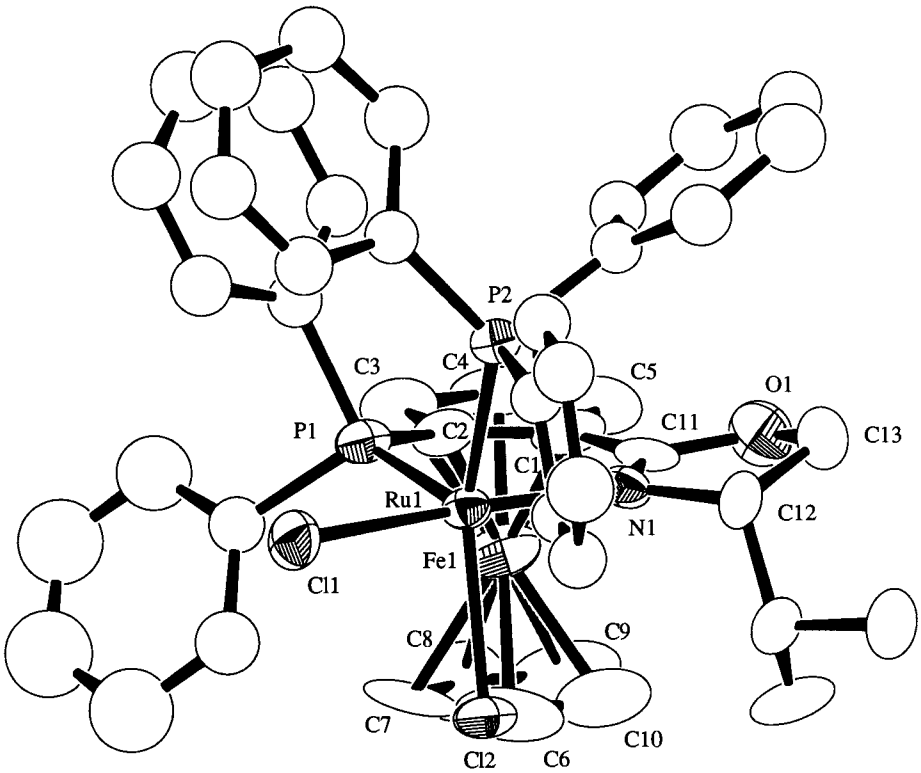


Fig. 1. Crystal structure of **6**, showing 50% probability thermal ellipsoids. The hydrogen atoms are omitted for clarity.

unit cell is shown in Fig. 1 and the selected bond lengths and angles are summarized in Table 3. The bond lengths of Ru(1)–N(1) (Ru(2)–N(2)) and Ru(1)–P(1) (Ru(2)–P(3)) are 2.11(1) Å (2.09(1) Å) and 2.197(5) Å (2.196(4) Å), respectively, which are reasonable compared with the reported values of some ruthenium-oxazoline complexes [12,13] and ruthenium–ferrocenylphosphine [14,15] complexes. The ruthenium atom has a distorted trigonal bipyramidal geometry with *cis*-co-ordination of the nitrogen and the phosphorous atom of **3**. The P(1)–Ru(1)–N(1) and P(3)–Ru(2)–N(2) angles are 95.4(4)° and 96.8(4)°, respectively. The torsion angle of Ru(1)–P(1)–C(2)–C(1) is −18(1)°, and the ruthenium atom of **6** exists almost on the plane of the substituted cyclopentadienyl ring of ferrocene.

Table 3
Selected bond lengths (Å) and angles (°) for **6**

Bond lengths (Å)			
Ru(1)–P(1)	2.197(5)	C(1)–C(2)	1.46(3)
Ru(1)–P(2)	2.262(5)	C(1)–C(11)	1.42(3)
Ru(1)–N(1)	2.11(1)	Fe(1)–C(1)	2.05(2)
Ru(1)–Cl(1)	2.406(5)	Fe(1)–C(2)	2.05(2)
Ru(1)–Cl(2)	2.428(5)	Fe(1)–C(3)	2.08(2)
P(1)–C(2)	1.79(2)	Fe(1)–C(4)	2.02(3)
P(1)–C(17)	1.82(2)	Fe(1)–C(5)	2.05(2)
P(1)–C(23)	1.84(2)	Fe(1)–C(6)	2.02(3)
N(1)–C(11)	1.28(2)	Fe(1)–C(7)	2.01(2)
N(1)–C(12)	1.52(2)	Fe(1)–C(8)	2.10(3)
O(1)–C(11)	1.37(2)	Fe(1)–C(9)	2.03(3)
O(1)–C(13)	1.41(2)	Fe(1)–C(10)	2.06(3)
Bond angles (°)			
Cl(1)–Ru(1)–Cl(2)	88.0(2)	Ru(1)–N(1)–C(11)	129(1)
Cl(1)–Ru(1)–P(1)	89.6(2)	Ru(1)–N(1)–C(12)	123(1)
Cl(1)–Ru(1)–P(2)	89.9(2)	Ru(1)–P(1)–C(2)	112.2(6)
Cl(1)–Ru(1)–N(1)	174.9(4)	Ru(1)–P(1)–C(17)	121.6(6)
Cl(2)–Ru(1)–P(1)	109.9(2)	C(2)–P(1)–C(17)	102.4(9)
Cl(2)–Ru(1)–P(2)	150.8(2)	C(2)–P(1)–C(23)	102.5(9)
Cl(2)–Ru(1)–N(1)	90.1(4)	N(1)–C(11)–C(1)	128(1)
P(1)–Ru(1)–P(2)	99.2(2)	O(1)–C(11)–N(1)	115(1)
P(1)–Ru(1)–N(1)	95.4(4)	O(1)–C(11)–C(1)	115(1)
P(2)–Ru(1)–N(1)	89.5(4)	C(11)–O(1)–C(13)	107(1)

When complex **6** was employed as a catalyst of the transfer hydrogenation of acetophenone, almost the same and reproducible result was obtained as in the case of the reaction using a ligand and $RuCl_2(PPh_3)_3$ (compare Table 1, runs 5 and 6).Thus, it is clear that the chiral oxazolinylferrocenylphosphine is co-ordinated with the ruthenium(II) complex in place of two triphenylphosphine to produce the Ru–phosphine complex in situ during the reaction. Although Sammakia et al. observed two diastereomers of ruthenium (II) complex prepared in situ from $RuCl_2(PPh_3)_3$ and oxazolinylferrocenylphosphine [8], this result indicates that the existence of the minor diastereomer of the ruthenium complex has no influence on the enantioselectivity of the transfer hydrogenation of acetophenone under the above reaction conditions.

3. Experimental

^{1}H- (270 MHz) and ^{31}P-NMR spectra (109 MHz) were recorded on a JEOL JNM-EX-270 or JEOL GSX-270 spectrometer as solutions in $CDCl_3$. GLC analyses were performed on a Hitachi 163 instrument (1 m × 3 mm stainless steel column packed with 20% EGSS on Shimalite) and a Shimadzu GC-14A instrument (25 m HiCap-CBP-10-S25 capillary column) with flame-ionization detectors and N_2 as carrier gas. Column chromatographies on SiO_2 were performed with Wakogel C-300 (hexane and hexane/ethyl acetate as eluents). All the solvents were distilled from CaH_2 or $LiAlH_4$ and stored over molecular sieves 4 Å under nitrogen. All the starting ketones and the resultant alcohols are known compounds and commercially available.

3.1. Typical procedure for asymmetric transfer hydrogenation of ketones with a ruthenium(II) complex and a chiral ligand or a ruthenium(II)–chiral ligand complex

In a 10-ml round-bottomed flask equipped with a reflux condenser $RuCl_2(PPh_3)_3$ (4.79 mg, 5.0×10^{-3} mmol) and oxazolinylferrocenylphosphine **2** (2.72 mg, 5.5×10^{-3} mmol) or the isolated complex [$RuCl_2 \cdot$ **3** $\cdot (PPh_3)$] (4.58 mg, 5.0×10^{-3} mmol) were placed under nitrogen. 2-Propanol (2.5 ml) was added and then the mixture was magnetically stirred and heated to reflux for 30 min. A solution of acetophenone (600.6 mg, 5.0 mmol) in 2-propanol (1.5 ml) was added and the mixture was refluxed for 30 min. The reaction was started by the addition of 0.125 N NaOH/2-propanol solution (1.0 ml) and the solution was kept at reflux for an appropriate time and then quenched with HCl (1 N, 5.0 ml). The mixture was taken up in diethyl ether, washed with H_2O, $NaHCO_3$, and then brine. For GLC analyses, dibenzyl was added as an internal standard. For isolation, the extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure by an aspirator. The residue was purified by column chromatography to provide the corresponding alcohol. The ee value and the configuration of the alcohols were determined by HPLC on a Daicel Chiralcel OJ, OD, OB and OF columns (2-propanol/hexane as eluent). The ee values of 2-octanol, 1-cyclohexylethanol and 3,3-dimethyl-2-butanol were determined by GLC of the corresponding acetate or trifluoroacetate using Chiraldex GT-A (30 m).

3.2. Preparation of ruthenium complex [$RuCl_2 \cdot$ **3** $\cdot (PPh_3)$] (**6**)

In a 20-ml round-bottomed flask, the $RuCl_2(PPh_3)_3$ (480 mg, 0.50 mmol) and **3** (240 mg, 0.50 mmol) were placed under nitrogen. Anhydrous toluene (15 ml) was added, and then the resulting solution was magnetically stirred at r.t. for 20 h. The original purple solution changed to a red suspension. After addition of hexane (20 ml), the reaction mixture was filtered. Recrystallization of the resultant solid from dichloromethane/*n*-hexane gave **6** (375 mg, 0.41 mmol, 81%) as red crystals. ^{1}H-NMR δ 0.57 (d, 3H, $J = 7$ Hz), 0.97 (d, 3H, $J = 7$ Hz), 2.12 (dd, 1H, $J = 8$ and 8 Hz), 3.21 (m, 1H), 3.28 (m, 1H), 3.80 (dd, 1H, $J = 3$ and 8 Hz), 4.02 (s, 5H), 4.59 (m, 1H), 4.68 (m, 1H), 4.84 (m, 1H), 6.5–8.4 (m, 25H). ^{31}P-NMR δ 40.1 (d, $J = 45$ Hz), 77.0 (d, $J = 45$ Hz). Anal Calc. for $C_{46}H_{43}Cl_2FeNOP_2Ru$: C, 60.34; H, 4.73; N, 1.53. Found: C, 60.30; H, 4.89; N, 1.52.

3.3. X-ray structural determination of **6**

Data for **6** (a red crystal, grown by slow diffusion of diethyl ether into a dichloromethane solution of **6** at r.t.) of $C_{46}H_{43}Cl_2FeNOP_2Ru$ was collected on a Rigaku AFC7R diffractometer with graphite monochromated Mo–K_α radiation ($\lambda = 0.71069$ Å) and a 12 kW rotating anode generator at 25°C using the ω–2θ scan technique. No significant decay was observed for three standard reflections that were monitored every 150 reflections. The two independent molecules of **6** each occupy a unit cell. The structures of these two independent molecules are almost the same. The selected bond lengths and angles are summarized in Table 3. Crystal data [16] for **6** are as follows: triclinic, space group $P\bar{1}$ (No. 1); $a = 12.032(4)$, $b = 19.461(6)$, $c = 10.570(3)$ Å; $\alpha = 98.41(3)°$, $\beta = 113.62(2)°$, $\gamma = 73.40(3)°$; $V = 2171(1)$ Å^3; $Z = 2$; $D_{calc.} = 1.400$ g cm^{-3}; μ(Mo–K_α) = 9.13 cm^{-1}. For structure analysis and refinement, computations were performed using TEXSAN [17] crystallographic software package of molecular structure. The final R value was 0.063 ($R_w = 0.079$) for 5906 unique reflections with $I > 3\sigma(I)$. The structure was solved by Patterson method (DIRDIF92 PATTY). The carbon atoms of phenyl rings were refined isotropically. All other non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined.

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