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Dedicated to Full Member of the Russian Academy of Sciences B.A. Trofimov on the 65th Anniversary of His Birth

Catalytic Hydrogenation of Acetophenone with Hydrogen Transfer over Chiral Diamine Rhodium(I) Complexes

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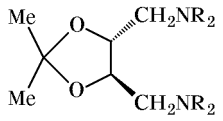
Abstract—The catalytic activity and stereoselectivity of Rh(I) complexes with C_2-symmetric chiral diamines, (4*S*,5*S*)-3,4-isopropylidenedioxy-1,4-butanediamine and (4*S*,5*S*)-*N*,*N*,N′,*N*′-tetramethyl-3,4-isopropylidenedioxy-1,4-butanediamine [skeletal analogs of 2,3-dihydroxy-2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-butane (DIOP)], were studied in hydrogen transfer from 2-propanol to acetophenone in the presence of KOH or *t*-BuOK. The product, (*S*)-(–)-2-phenylethanol, was thus obtained with an optical yield of 67%. Covalent chloride rhodium complexes with the above ligands give rise to the same stereoisomer, whereas the opposite stereoselectivity is observed under catalysis by cationic trifluoromethanesulfonate rhodium(I) complexes. X-Ray phase analysis showed formation of nanosize particles in the precipitate of metallic rhodium.

Despite wide application of organophosphorus ligands in metal complex catalysis, phosphine metal complexes are not free from some disadvatages, among which their high cost, oxidizability, and a tendency to P–C bond cleavage with subsequent decomposition of the ligand. These properties restrict the use of phosphine metal complexes in industry. In the recent years, nitrogen-containing ligands attract interest due to their accessibility, low cost, and greater stability as compared to phosphorus ligands.

The application of optically active secondary alcohols in pharmaceutical chemistry gave an impetus to extensive development of procedures for asymmetric reduction of prochiral aromatic ketones, in particular, for asymmetric hydrogenation of the C=O bond with hydrogen transfer from an appropriate source in the presence of ruthenium(II), rhodium(I), and iridium(I) complexes with chiral ligands, such as bipyridines [1], alkylphenanthrolines [2], diimines [3–5], diamines [5–7], ureas, and thioureas [8].

While continuing our studies on the catalytic activity and asymmetric induction of Rh(I) complexes with C_2-symmetric chiral diamines in hydrogenation processes [9–12], in the present work we examined the reduction of acetophenone via hydrogen transfer from isopropyl alcohol over rhodium(I) complexes with primary diamine **I** and tertiary diamine **II**. Diamines **I** and **II** are skeletal analogs of DIOP, 2,3-dihydroxy-2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)butane. The reactions were performed with the use of a base co-catalyst, potassium hydroxide or potassium *tert*-butoxide.



I, II

I, R = H; **II**, R = Me.

We previously showed by ^{1}H NMR spectroscopy that the reaction of 2 equiv of (4*S*,5*S*)-*N*,*N*,*N*′,*N*′-tetramethyl-3,4-isopropylidenedioxy-1,4-butanediamine (**II**, L^2) with a solution of cationic bis(cyclooctadiene) trifluoromethanesulfonate rhodium (I) complex, $[(1,5\text{-COD})_2Rh]^+ CF_3SO_3^-$ (**III**), results in replacement of both cyclooctadiene molecules from the metal coordination sphere by the diamine. The complex thus

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Table 1. ^{1}H NMR parameters of diamines **I** and **II**, their rhodium complexes **IV** and **V**, and cyclooctadiene trifluoromethanesulfonate complex **III**

Compound no. (solvent)	Chemical shifts δ, ppm, and coupling constants *J*, Hz				
	CH	H_A in CH_2	H_B in CH_2	NCH_3	CCH_3
I ($CDCl_3$)	3.77 m	2.89, J_{AC} = 3.52, J_{AB} = 13.2	2.81, J_{BC} = 5.92	1.4 br.s (NH)	1.40 s
II (acetone-d_6)	3.80 m	2.52, J_{AC} = 3.65, J_{AB} = 12.9	2.37, J_{BC} = 6.20	2.21	1.29 s
II (methanol-d_4)	3.78 m	2.55, J_{AC} = 2.0, J_{AB} = 13.1	2.46, J_{BC} = 7.7	2.29	1.36 s
IV (methanol-d_4)	3.90 m	2.87, J_{AC} = 12.9	2.79, J_{BC} = 6.59, J_{AB} = 13.0	2.47	1.38 s
V ($CDCl_3$)	4.20 m (COD), 3.95 m (**I**)	2.43 m (COD), 3.13 d (I), J_{AB} = 12.2	1.82 m (COD), 2.86 d.d (**I**), J_{BC} = 6.6, J_{AB} = 12.2	2.8 br.s (NH)	1.40 s
III	4.16 (COD)	2.50 (COD)	1.77 (COD)		

formed was isolated and characterized by ^{1}H and ^{13}C NMR spectroscopy. It was assigned the structure of homoligand bisdiamine square–planar complex $[Rh(L^2)_2]^+ CF_3SO_3^-$ (**IV**) [9] (Scheme 1).

Scheme 1.

$$[Rh(COD)_2]^+ CF_3SO_3^- + 2\mathbf{II} \longrightarrow [Rh(L^2)_2]^+ CF_3SO_3^- + 2COD$$

III → **IV**

It should be noted that diamine rhodium complexes (both cationic [13] and neutral chloride [14]) usually tend to form diene–diamine complexes. For example, the complex [(1,5-COD)Rh(TMEDA)]ClO_4 was obtained with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Unlike compound **II**, diamine **I** (L^1) reacts with complex **III** even at a **I**-to-Rh ratio of 2 to give the expected yellow cyclooctadiene–diamine complex **V**, $[Rh(COD)(L^1)]^+ CF_3SO_3^-$ (Scheme 2). Complex **V** was also isolated as individual substance and was characterized by spectral and chemical methods. Table 1 contains the ^{1}H NMR parameters of diamines **I** and **II** and their rhodium complexes **IV** and **V**.

Scheme 2.

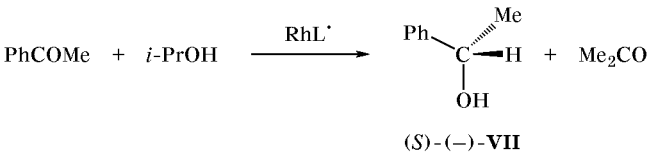
$$[Rh(COD)_2]^+ CF_3SO_3^- + \mathbf{I} \longrightarrow [Rh(L^1)(COD)]^+ CF_3SO_3^- + COD$$

III → **V**

Coordination of the diamine to rhodium is confirmed by the IR spectra: In going from free ligand **I** to complex **V**, absorption bands due to NH stretching vibrations shift from 3365 and 3292 cm^{-1} to 3225 and 3115 cm^{-1}, respectively.

Enantioselective hydrogenation of acetophenone via hydrogen transfer was performed with the use of both individual cationic rhodium complexes **IV** and **V** and those formed *in situ* by reactions of the covalent dimeric complex $[Rh(COD)Cl]_2$ (**VI**) with diamines **I** and **II** at a ligand-to-metal ratio of 2:1. The hydrogenation afforded preferentially (*S*)-(–)-2-phenylethanol (**VII**) (Scheme 3). The results are summarized in Table 2.

Scheme 3.



(*S*)-(–)-**VII**

The turnover number in the hydrogen transfer reaction over $Rh(L^2)_2^+ CF_3SO_3^-$ increased with rise in the substrate-to-Rh ratio, but the optical yield of the product decreased by an order of magnitude (Table 2, run nos. 1, 2). The process is accompanied by liberation of metallic rhodium (as a black precipitate) from the initialy homogeneous reaction mixture. Its amount and precipitation time depend on the conditions. Metallic rhodium began to separate from the solution in 1 h after the reaction started when the concentrations of the substrate and complex **IV** in solution are low (Table 2, run nos. 1, 4). In this case, the turnover

Table 2. Asymmetric reduction of acetophenone via hydrogen transfer from 2-propanol over rhodium(I) complexes (reaction time 3–5 days)

Run no.	Catalyst, $c \times 10^3$, M	Temperature, °C	Ratio KOH/Rh	Ratio substrate/Rh (c_{sub}, M)	Chemical yield, % (time, days)	Optical yield, %, isomer	TON[a]	System
1	$Rh(L^2)_2^+ CF_3SO_3^-$ (2.5)	70	4[b]	80 (0.2)	7.5 (3)	22.8, *S*-(–)	6	Homogeneous
2	$Rh(L^2)_2^+ CF_3SO_3^-$ (1)	60	5	400 (0.4)	6.1 (3)	5.6, *S*-(–)	26	Homogeneous
3	$Rh(L^2)_2^+ CF_3SO_3^-$ (2.5)	82	5	80 (0.4)	8.0 (3)	23.0, *S*-(–)	6.5	Homogeneous
4	$Rh(L^2)_2^+ CF_3SO_3^-$ (1.1)	82	3	98 (0.1)	52.0 (14 h)	5.7, *S*-(–)	51.5	Rh precipitate (in 1 h)
5	$Rh(L^2)_2^+ CF_3SO_3^-$ (0.9) + toluene	82	2.8	100 (0.1)	15.4 (1)	11.2, *S*-(–)	15.4	Rh precipitate (on 2nd day)
6	$Rh(L^2)_2^+ CF_3SO_3^-$ (1.1) + toluene + PPh_3	70	2.6[b]	80 (0.09)	97.5 (1.5 h)	2.1, *S*-(–)	78	Homogeneous
7	$Rh(L^2)_2^+ CF_3SO_3^-$ (2.5) + 2**II**	82	3	80 (0.4)	18.3 (3)	67, *S*-(–)	15	Rh precipitate (on 2nd day)
8	$[Rh(COD)Cl]_2$ (2.5) + 4**II**	70	3	80 (0.2)	5.0 (5)	54.8, *S*-(–)	4	Homogeneous
9	$[Rh(COD)Cl]_2$(1.1) + 4**II** + toluene	78	3[b]	80 (0.1)	5.7 (5)	54.3, *S*-(–)	4	Homogeneous
10	$[Rh(COD)_2]^+ CF_3SO_3^-$ (1.1) + 2**I**	73	3	96 (0.11)	11.0 (5)	1.8, *R*-(+)	11	Homogeneous
11	$[Rh(COD)(L^1)]^+ \cdot CF_3SO_3^-$ (2.5)	73	3	80 (0.4)	7.0 (5)	6.1 *R*-(+)	6	Homogeneous
12	$[Rh(COD)Cl]_2$ (2.5) + 4**I**	82	3	80 (0.2)	23.1 (4)	2.4, *S*-(–)	19	Homogeneous
13	$[Rh(COD)Cl]_2$ + DPEN[c]	20	7	20	100 (7)	67.0, *R*-(+)	20	[7]

[a] Turnover number.

[b] Potassium *tert*-butoxide was used as co-catalyst.

[c] DPEN is (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine.

number increases, and the optical yield of the hydrogenation product decreases. By raising the substrate concentration, the catalyst concentration remaining unchanged, we succeeded in avoiding precipitation of metallic rhodium over a period of up to 3 days (run nos. 2, 4), but the optical yield was as low as before.

The formation of metallic rhodium in the presence of reducing species is explained by the absence of electron-acceptor ligands in the metal coordination sphere, which could take up excess electron density from the central atom. Such ligands may be olefins, arenes, carbonyl compounds, and other π acceptors. Probably, a large excess of acetophenone (substrate-to-rhodium ratio 400) favors stabilization of diamine rhodium complexes by molecules of the substrate which coordinate to the metal through the carbonyl group or π system of the benzene ring. The low optical yield may be due to partial replacement of the chiral ligand from the metal coordination sphere by excess substrate molecules.

In order to prevent precipitation of rhodium, we added to the catalytic system 3 ml of toluene as solvent. This led to decrease in the turnover number, increase in the optical yield, and stabilization of the system: metallic rhodium began to precipitate only after 24 h (Table 2, run nos. 4, 5). Addition of 1 equiv of triphenylphosphine to complex **IV** in the presence of toluene sharply increased the rate of acetophenone reduction (the catalyst turnover frequency was 78 h^{-1}) and reduced the enantioselectivity of the process, presumably as a result of change of the active Rh(I) complex (Table 2, run nos. 5, 6). Approximately the same catalytic activity was observed in the reduction of acetophenone via hydrogen transfer from *i*-PrOH

in the presence of phosphine rhodium(I) complexes and a base [15].

By adding to complex **IV** (which contains two molecules of diamine **II** in the coordination sphere) an additional 2 equiv of diamine **II**, we succeeded in attaining 67% enantiomeric excess of (*S*)-(–)-1-phenylethanol; also, the conversion of initial acetophenone increased, and precipitation of metallic rhodium accelerated (Table 2, run nos. 3, 7).

Cationic rhodium complex **V** with diamine **I** possessing primary amino groups showed the opposite enantioselectivity in the reduction of acetophenone; however, in the systems containing a dimeric chloride rhodium complexes, the reduction products obtained with ligands L^1 and L^2 had the same sign of optical rotation. In both cases, with diamine **I** as ligand, the enantioselectivity was poor, 2.4 to 6.1% (Table 2, run nos. 11, 12). The opposite configurations of the major enantiomer may result from the different substituents on the nitrogen atoms in diamines **I** and **II**, despite the same chiral skeleton. In particular, diamine **I** in the rhodium coordination sphere can be involved in additional interaction with the substrate via formation of hydrogen bonds between the amino hydrogen atoms and carbonyl oxygen. This interaction may affect the mode of substrate coordination to the active complex and hence change the enantioselectivity of the process.

As follows from the data in Table 2, the reduction of acetophenone over complex **IV** and chloride Rh(I) complex formed *in situ* gives excess (*S*)-(–)-1-phenylethanol; the chloride complex ensures higher enantioselectivity, the ligand-to-Rh ratios being equal (Table 2, run nos. 1, 9 and 3, 8). Unlike the catalytic system including the cationic trifluoromethanesulfonate rhodium complex (where metallic rhodium begins to separate from the solution even in 1 h), in the system based on the dimeric dichloride complex the appearance of metallic rhodium becomes appreciable only on the second day (Table 2, run nos. 4, 9).

Thus the stereoselectivity attained with complex **IV** approaches that observed with the catalytic systems reported previously [7], where an ee value of 67% was reached for (*S*)-(–)-1-phenylethanol in the hydrogenation of acetophenone via hydrogen transfer from 2-propanol over $[Rh(COD)Cl]_2$ in the presence of (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine as ligand (substrate-to-Rh ratio 20, reaction time 7 days; Table 2). The authors [7] also observed liberation of metallic rhodium, but its effect on the catalytic process was not taken into account. In our case, precipitation of metallic rhodium was accompanied by increase in the turnover number and reduction in the enantioselectivity; therefore, we made an attempt to examine the composition of the Rh precipitate by X-ray phase analysis.

The obtained diffractogram consisted of a set of diffuse lines; their identification with the use of PDF database [16] showed the presence of elemental rhodium having a cubic crystal system. The apparent crystal size was determined from broadening of the rhodium diffraction line, 2.202 Å; it was about 45 Å [17]. Apart from the interplane *d*/*n* distances corresponding to rhodium, the diffractogram contained a line at 2.207 Å with an intensity of 22%, which was not identified.

Most probably, the main factor responsible for the reduced optical yield in the catalytic system is formation of nanosize amorphous rhodium particles which also exhibit catalytic activity in the process under study. Visual detection of a black precipitate is the result of final stage of aggregation of smaller particles; i.e., after some time, catalytic solutions become arbitrarily homogeneous (or quasihomogeneous). We cannot rule out that some molecules of the chiral diamine or its fragments responsible for asymmetric induction are retained on the metal surface.

Mono- and multimetal colloids with a size of 1–10 nm, which are protected sterically or electrostatically to prevent aggregation, are known to be effective hydrogenation catalysts. The protecting shell may consist of quaternary ammonium or phosphonium cations or (in some cases) solvent molecules, e.g., tetrahydrofuran. Bonemann and Braun recently reported on enantioselective catalytic hydrogenation over metal colloids with chiral stabilizing species [18]. A more detailed study of the nature of nanosize rhodium particles and their role in the reduction of ketones via hydrogen transfer will be the subject of our further work.

EXPERIMENTAL

The IR spectra were recorded on an IKS-29 instrument from samples pelleted with KBr. The ^1H and ^{13}C NMR spectra were measured on a Bruker DPX-400 spectrometer at 400 and 100 MHz, respectively; chloroform-*d* was used as solvent, and HMDS, as internal reference (the chemical shifts are given relative to TMS). GLC analysis was performed on an LKhM-80 chromatograph equipped with a thermal conductivity detector; 2000 × 3-mm column was packed with 5% of SE-30 on Chromaton N-AW-DMCS; carrier gas helium. X-Ray phase analysis of solid precipitates was performed on a DRON-3M X-ray diffractometer (CuK_α radiation). The precipitate

separated from the catalytic system containing complex **IV** and KOH was filtered off, washed with 2-propanol, and dried under argon. The optical rotations of the products were determined on a Polamat A polarimeter at a concentration of 2 to 30 g/100 ml in methanol at λ 546 nm and were recalculated to λ 589 nm using a coefficient of 1.17543. The optical yields were calculated relative to the specific optical rotation of (*S*)-(–)-1-phenylethanol, $[\alpha]_D$ = –45.0° (*c* = 5, MeOH) [2].

Acetophenone and the solvents (2-propanol and toluene) were thoroughly purified, dehydrated, and stored under argon. All syntheses were carried out under argon. Diamines **I** [11] and **II** [19] were synthesized by known procedures.

Complex $[Rh(COD)(I)]^+ CF_3SO_3^-$ (V). A solution of 92.5 mg (0.578 mmol) of diamine **I** in 3 ml of chloroform was added with stirring under argon to a solution of 135 mg (0.289 mmol) of complex **III** in 30 ml of chloroform. After 1 h, the light brown solution was concentrated under reduced pressure to a volume of 3 ml, 3 ml of hexane was added, and the light yellow precipitate was washed with hexane (3 × 5 ml) and dried for 2 h at 30°C (1 mm). IR spectrum, ν, cm^{-1}: 3225 br (NH), 3115 br (NH), 1600 (δNH). Found, %: C 37.11; H 5.62; F 10.20; N 6.08; S 6.08. $C_{16}H_{28}F_3N_2O_5RhS$. Calculated, %: C 36.93; H 5.42; F 10.95; N 5.38; S 6.16.

Hydrogenation of acetophenone. A reactor was purged with argon and charged with 0.05 mmol of complex **III**–**V** or 0.025 mmol of complex **VI** in 10–25 ml of 2-propanol, 2–4 equiv of diamine **I** or **II** (with complexes **III** and **VI**) was added, the mixture was stirred for 30 min in a stream of argon, 3 equiv of KOH or *t*-BuOK in 10–20 ml of 2-propanol was added, the mixture was stirred for 3 h, and 0.5 ml of acetophenone was added. The mixture was heated to 70–82°C (Table 2) and was vigorously stirred for 3–5 days. The progress of the reaction was monitored by GLC (samples were withdrawn intermittently). The hydrogenation product was isolated as follows. The mixture was evaporated under reduced pressure, 20 ml of chloroform was added to the residue, and the organic phase was washed with three 10-ml portions of 0.1 M hydrochloric acid and with distilled water and dried over calcined sodium sulfate for 12 h. The solvent was removed, and the residue was distilled under reduced pressure.

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