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New chiral phosphinite ligands with C₂-symmetric axis and their possible applications in Ru-catalyzed asymmetric transfer hydrogenation

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The new chiral ligands *N*,*N'*-bis-[(1*R*)-1-ethyl-2-O-(diphenylphosphinite)ethyl]ethanediamide, 1, and *N*,*N'*-bis-[(1*S*)-1-isobutyl-2-O-(diphenylphosphinite)ethyl]ethanediamide, 2, and the corresponding ruthenium complexes 3 and 4 were prepared and their structures were elucidated by a combination of multinuclear NMR spectroscopy, IR spectroscopy and elemental analysis. Following activation by NaOH, these chiral ruthenium complexes serve as catalyst precursors for the asymmetric transfer hydrogenation of acetophenone derivatives in *i*PrOH. The complexes 3 and 4 showed high catalytic activity but low selectivity in asymmetric transfer hydrogenation reactions. Copyright © 2009 John Wiley & Sons, Ltd.

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Introduction

The chemistry of transition-metal complexes containing hemilabile ligands has been the subject of many studies in recent years.^[1-3] The term was first introduced by Jeffrey and Rauchfuss;^[4] hemilabile ligands contain both a strong donor group, fixing the ligand to the metal, and a weaker donor group, which can be easily replaced by another ligand. Ligands possessing both 'soft' and 'hard' donors atoms coordinated to the same metal centre have been found suitable for catalytic purposes since the stability of intermediate species is favored.^[5,6] Recently, many efforts have been made to improve the catalytic activity of some complexes by using hemilabile ligands.^[7,8] Among 'soft' donor atoms, phosphorus is the most common in homogeneous catalysis and, for this reason, it is found in many ligands combined with a variety of 'hard' labile donor groups (i.e. N- or O-donors). Although hemilabile P-Odonor ligands have been widely studied, [9-11] increased attention has recently been given to hemilabile P-N donor ligands.^[12,13]

Phosphine and phosphite ligands have found widespread applications in transition metal-catalyzed asymmetric transformations.^[14,15] Phosphinites provide different chemical, electronic and structural properties compared with phosphines. Thus, they open many opportunities to design new improved ligands for asymmetric catalysis. The metal–phosphorus bond is often stronger for phosphinites compared with the related phosphine due to the presence of electron-withdrawing P–OR group. In addition, the empty σ^* -orbital of the phosphinite P(OR)R₂ is stabilized and it makes the phosphinite a better acceptor.^[16]

Chiral alcohols are very important building blocks and synthetic intermediates in organic synthesis and the pharmaceutical industry.^[17,18] Reduction of prochiral ketones to give chiral alcohols is among the most fundamental subjects in modern synthetic chemistry. Catalytic reduction is preferred to stochiometric reduction for large-scale industrial processes of ketones hydrogenation and they are well known.^[19-21] Hydrogen gas presents considerable safety hazards, especially for large-scale reactions.^[22,23] The use of a solvent that can donate hydrogen overcomes these difficulties. 2-Propanol is a popular reactive solvent for transfer hydrogenation reactions since it is easy to handle (b.p. 82°C) and is relatively nontoxic, environmentally benign and inexpensive. The volatile acetone by-product can also be easily removed to shift unfavourable equilibria. Noyori and co-workers provided an elegant solution for the asymmetric catalytic H₂-hydrogenation of simple aryl ketones.^[24,25] Complexes of the type trans-RuCl₂(diamine)(diphosphine) with matching configurations of chiral diphosphine and diamine, e.g. (S)-BINAP/(S,S)-DPEN, show high reactivity and enantioselectivity.^[26] The use of organometallic complexes as catalysts for asymmetric transfer hydrogenation from a suitable donor (usually *iso*-propanol or formic acid) has been the subject of ongoing research for some decades. Efficient catalysts for the asymmetric transfer hydrogenation of ketones include Evans' samarium complexes with chiral amino alcohols ligand^[27] and Noyori's ruthenium complexes containing arene and N-(p-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) ligands.^[28,29] Chiral diphosphinite ligands derived from the reaction of 1,1'-bi-2-naphthol (BINOL) with chlorodiarylphosphine were easily synthesized and modified and they were widely used as chiral auxiliaries in rhodium, iridium and palladium asymmetric catalytic reactions.[30,31]

The most important advantage of chiral phosphinite ligands over the corresponding phosphine ligands is the ease of

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preparation. The synthesis of phosphinites by reacting the corresponding alcohols with chlorophosphines in the presence of an organic base is very convenient, and the yields are usually quantitative. From a practical standpoint, it is of substantial interest to develop highly effective chiral phosphinite ligands for asymmetric catalysis. The excellent catalytic performance of phosphinite-based transition metal complexes^[32,33] prompted us to develop new Ru(II) complexes with well-shaped ligands. Thus, following our continuous interest in the chemistry of phosphinite ligands and the applications of ruthenium complexes^[34] herein, we report the convenient, modular synthesis and characterization of new chiral phosphinite ligands N,N'-bis-[(1R)-1-ethyl-2-O-(diphenylphosphinite)ethyl]ethanediamide,

1, and N,N'-bis-[(15)-1-isobutyl-2-O-(diphenylphosphinite) ethyl]ethanediamide, **2**, and corresponding ruthenium complexes **3** and **4** and their application in the asymmetric transfer hydrogenation reactions of acetophenone derivatives with *iso*-propanol as the hydrogen source. This approach allows the opportunity for rapid tuning of the catalyst structure due to the modular nature of the ligands and precatalysts. These compounds were also fully characterized using elemental analysis, FT-IR and multi-nuclear NMR spectroscopies.

Experimental

Materials and Methods

Unless otherwise stated, all reactions were carried out under an atmosphere of argon using conventional Schlenk glassware. Solvents were dried using established procedures and distilled under argon immediately prior to use. Analytical grade and deuterated solvents were purchased from Merck. The starting materials [Ru(η^6 -*p*-cymene)(μ -Cl)Cl]₂ and PPh₂Cl were purchased from Fluka and were used as received. *N*,*N*'-bis[(1*R*)-1ethyl-2-hydroxyethyl]ethanediamide and *N*,*N*'-bis[(1*S*)-1-isobutyl-2-hydroxyethyl]ethanediamide were prepared according to the literature procedure.^[35]

Spectroscopic Analyses

The IR spectra were recorded on a Mattson 1000 ATI Unicam FT-IR spectrometer as KBr pellets. ¹H (400.1 MHz), ¹³C NMR (100.6 MHz) and ³¹P – {¹H} NMR (162.0 MHz) spectra were recorded on a Bruker Avance 400 spectrometer, with δ referenced to external TMS and 85% H₃PO₄, respectively. Elemental analysis was carried out on a Fisons EA 1108 CHNS-O instrument. Melting points were recorded by Gallenkamp Model apparatus with open capillaries.

GC Analyses

GC analyses were performed on a HP 6890N Gas Chromatograph equipped with cyclodex B (Agilent) capillary column (30 m \times 0.32 mm i.d. \times 0.25 µm film thickness). The GC parameters were for asymmetric transfer hydrogenation of ketones as follows: initial temperature, 110 °C; initial time, 1 min; solvent delay, 4.48 min; temperature ramp 80 °C/min; final temperature, 200 °C; final time, 21.13 min; injector port temperature, 200 °C; detector temperature, 200 °C, injection volume, 2.0 µL.

Procedure for the Preparation of the Chiral Ligands and Ruthenium Complexes

$\label{eq:synthesis} Synthesis of N,N'-bis-[(1R)-1-ethyl-2-O-(diphenylphosphinite) ethyl]ethane-diamide, \textbf{1}$

PPh₂Cl (0.20 g, 0.86 mmol) was slowly added to a solution of N,N'-bis[(1R)-1-ethyl-2-hydroxyethyl]ethanediamide (0.10 g, 0.43 mmol) and triethylamine (0.09 g, 0.86 mmol) in 25 ml of toluene at room temperature. The mixture was stirred for 4 h and triethylammonium chloride was filtered off. Evaporation of the solvent in vacuo gave N,N'-bis-[(15)-1-ethyl-2-O-(diphenylphosphinite)ethyl]ethanediamide, 1 as a white solid (yield: 0.24 g, 92.0%); m.p.: 86–88 °C. $[\alpha]_D^{25} = +32.6$ (c 1.0, DMSO). C₃₄H₃₈N₂O₄P₂: calcd C, 67.99; H 6.38; N 4.66; anal. found: C, 67.85; H 6.34; N 4.62%. Selected IR, v (cm⁻¹): 3405 (N-H), 3028, 3075 (Ar-H), 1658 (C=O, first amide band), 1516 (C=O, second amide band), 1035 (C-O), 962 (P-O). ¹H NMR $(CDCl_3) \delta$ (ppm): 0.94 (t, 6H, $J = 7.4 \text{ Hz}, -CH_2CH_3$), 1.59 (m, 2H, -C \underline{H}_2 CH₃) (a), 1.70 (m, 2H, -C \underline{H}_2 CH₃) (b), 3.86 (m, 4H, -CH2O-P), 4.00 (m, 2H, -CH-N), 7.20-7.56 (m, 20H, o-, m- and *p*-protons of phenyls), 7.71 (d, 2H, J = 8.4 Hz, <u>NH</u>). ¹³C-{¹H} NMR (CDCl₃) δ (ppm): 10.38 (-CH₂CH₃), 24.36 (-CH₂CH₃), 52.35 (-CH-N), 70.15 $(-CH_2O-P)$, 129.53 $(d, {}^{3}J_{31P-13C} = 7.0 \text{ Hz}, m\text{-carbons})$ of phenyls), 129.53 (d, ${}^{4}J_{31P-13C} = 2.0$ Hz, *p*-carbons of phenyls), 130.50 (d, ${}^{2}J_{31P-13C} = 20.1$ Hz, o-carbons of phenyls), 141.30 (d, ${}^{1}J_{31P-13C} = 18.1 \text{ Hz}$, *i*-carbons of phenyls), 159.41 (s, C=O), assignment was based on the ¹H-¹³C HETCOR and ¹H-¹H COSY spectra. ${}^{31}P - {}^{1}H$ NMR (CDCl₃) δ (ppm): 117.20 (s, O-**P**-(C₆H₅)₂).

Synthesis of N,N'-bis-[(1S)-1-isobutyl-2-O-(diphenylphosphinite) ethyl]ethane-diamide, ${\bf 2}$

PPh₂Cl (0.16 g, 0.70 mmol) was slowly added to a solution of *N*,*N*'-bis[(1*S*)-1-isobutyl-2-hydroxyethyl]ethanediamide (0.10 g, 0.35 mmol) and triethylamine (0.07 g, 0.70 mmol) in 25 ml of toluene at room temperature. The mixture was stirred for 4 h and triethylammonium chloride was filtered off. Evaporation of the solvent in vacuo gave N,N'-bis-[(1S)-1-isobutyl-2-O-(diphenylphosphinite)ethyl]ethanediamide,2 as a colorless oil (yield: 0.22 g, 95.0%); $[\alpha]_D^{25} = -35.2$ (c 1.0, DMSO). $C_{38}H_{46}N_2O_4P_2$: calcd C, 69.50; H 7.06; N 4.27; anal. found: C, 69.43; H 7.01; N 4.24%. Selected IR, υ (cm⁻¹): 3295 (N–H), 3056, 3112 (Ar–H), 1655 (C=O, first amide band), 1512 (C=O, second amide band), 1035 (C–O), 951 (P–O). ¹H NMR (CDCl₃) δ (ppm): 0.89 [d, 6H, $J = 6.4 \text{ Hz}, -\text{CH}(\text{C}\underline{H}_3)_2$ (a)], 0.93 [d, 6H, $J = 6.0 \text{ Hz}, -\text{CH}(\text{C}\underline{H}_3)_2$ (b)], 1.50 [m, 4H, -CH₂-CH(CH₃)₂], 1.60 [m, 2H, -CH(CH₃)₂], 3.70 (m, 4H, -CH2O-P), 4.05 (m, 2H, -CH-N), 7.28-7.53 (m, 20H, om- and p-protons of phenyls), 7.73 (d, 2H, J = 8.8 Hz, NH). ¹³C-{¹H} NMR (CDCl₃) δ (ppm): 22.14 [-CH(\underline{C} H₃)₂ (a)], 22.97 [-CH(<u>C</u>H₃)₂ (b)], 24.72 [-<u>C</u>H(CH₃)₂], 40.43 [-<u>C</u>H₂-CH(CH₃)₂], 50.63 $(-\underline{C}H-N)$, 65.29 $(-\underline{C}H_2O-P)$, 128.41 (d, ${}^{3}J_{31P-13C} = 8.0$ Hz, *m*-carbons of phenyls), 129.56 (d, ${}^{4}J_{31P-13C} = 3.0$ Hz, *p*-carbons of phenyls), 130.75 (d, ${}^{2}J_{31P-13C} = 12.0$ Hz, o-carbons of phenyls), 141.30 (d, ${}^{1}J_{31P-13C} = 18.0$ Hz, *i*-carbons of phenyls), assignment was based on the ¹H-¹³C HETCOR and ¹H-¹H COSY spectra. ³¹P-{¹H} NMR $(CDCl_3) \delta$ (ppm): 117.50 [s, O-**P**- $(C_6H_5)_2$].

Synthesis of [*Ru*{*chloro*(*p*-*cymene*)(*N*,*N*'-*bis*[(1*R*)-1-*ethy*]-2-O-(*dipheny*]*phosp-hinite*)*ethy*]*ethanediamide*)}]*chloride*, **3**

 $[Ru(\eta^6-p-cymene)(\mu-Cl)Cl]_2$ (0.05 g, 0.085 mmol) and *N*,*N*'-bis-[(1*R*)-1-ethyl-2-*O*-(diphenylphosphinite)ethyl]ethanediamide, **1** (0.10 g, 0.170 mmol) were dissolved in 20 ml of toluene and stirred for 3 h at room temperature. The volume was concentrated to ca 1-2 ml under reduced pressure and addition of diethyl ether (20 ml) gave 3 a clear red solid. The product was collected by filtration and dried in vacuo (yield: 0.13 g, 86.1%); m.p.: 204–206 °C. $[\alpha]_D^{25} = +36.0$ (c 1.0, DMSO). [(C₃₄H₃₈N₂O₄P₂)RuCl₂(CH₃C₆H₄CH(CH₃)₂]: calcd C, 58.28; H 5.78; N 3.09; anal. found: C, 58.13; H 5.73; N 3.06%. Selected IR, υ (cm⁻¹): 3396 (N–H), 3032, 3055 (Ar–H), 1674 (C=O, first amide band), 1507 (C=O, second amide band), 1038 (C-O), 997 (P-O). ¹H NMR (CDCl₃) δ (ppm): 0.85 (t, 6H, J = 7.2 Hz, -CH₂C**H**₃), 1.05 [d, 6H, J = 7.2 Hz, (CH₃)₂CHPh of *p*-cymene], 1.60 (m, 4H, -CH2CH3), 1.86 (s, 3H, CH3-Ph of p-cymene), 2.66 (m, 1H, -CH- of *p*-cymene), 3.82 (d, 4H, J = 3.6 Hz, -C<u>H</u>₂O-P), 3.91 (m, 2H, -C<u>H</u>-N), 5.21 (d, 2H, J = 6.0 Hz, aromatic protons of p-cymene), 5.30 (d, 2H, J = 6.0 Hz, aromatic protons of p-cymene), 7.32–7.48 (m, 12H, m- and p-protons of phenyls), 7.54 (d, 2H, J = 8.8 Hz, NH), 7.86 (dd, 8H, J = 7.2 and 10.6 Hz, o-protons of phenyls). $^{13}C - \{^{1}H\}$ NMR (CDCl₃) δ (ppm): 10.30 (-CH₂CH₃), 17.58 (CH₃Ph of p-cymene), 21.69 [(CH₃)₂CHPh of p-cymene], 24.37 (-CH₂CH₃), 30.09 (-CH- of p-cymene), 51.93 (-CH-N), 68.06 (-CH₂O-P), 87.44, 88.13 (aromatic carbons of p-cymene), 97.41, 111.98 (quaternary carbons of *p*-cymene), 128.16 (d, ${}^{3}J_{31P-13C} = 11.1$ Hz, *m*-carbons of phenyls), 131.25 (d, ${}^{4}J_{31P-13C} = 2.0$ Hz, *p*-carbons of phenyls), 132.81 (d, ${}^{2}J_{31P-13C} = 11.1$ Hz, o-carbons of phenyls), 136.45 (d, ${}^{1}J_{31P-13C} = 42.4$ Hz, *i*-carbons of phenyls), 159.37 (s, C=O), assignment was based on the ¹H-¹³C HETCOR and ¹H-¹H COSY spectra. ${}^{31}P - {}^{1}H NMR (CDCl_3) \delta (ppm): 115.12 [s, O-P-(C_6H_5)_2].$

Synthesis of [Ru{chloro(p-cymene)(N,N'-bis[(1S)-1-isobutyl-2-O-(diphenyl-phosphinite)ethyl]ethanediamide)}]chloride, 4

 $[Ru(\eta^6-p-cymene)(\mu-CI)CI]_2$ (0.05 g, 0.076 mmol) and N,N'-bis-[(15)-1-isobutyl-2-O-(diphenylphosphinite)ethyl]ethanediamide, 2 (0.10 g, 0.152 mmol) were dissolved in 20 ml of toluene and stirred for 3 h at room temperature. The volume was concentrated to ca 1-2 ml under reduced pressure and addition of diethyl ether (20 ml) gave 4 a clear red solid. The product was collected by filtration and dried in vacuo (yield: 0.12 g, 81.8%); m.p.: 119–121 °C. $[\alpha]_D^{25} = -38.2$ (c 1.0, DMSO) [(C₃₈H₄₆N₂O₄P₂)RuCl₂(CH₃C₆H₄CH(CH₃)₂]: calcd C, 59.87; H 6.28; N 2.91; anal. found: C, 59.74; H 6.23; N 2.86%. Selected IR, υ (cm⁻¹): 3210 (N–H), 3050, 3063 (Ar–H), 1671 (C=O, first amide band), 1508 (C=O, second amide band), 1032 (C-O), 896 (P-O). ¹H NMR (CDCl₃) δ (ppm):^[1]H NMR (CDCl₃) δ (ppm): 0.86 [d, 6H, J = 6.0 Hz, -CH(C<u>H</u>₃)₂ (a)], 0.88 [d, 6H, J = 6.0 Hz, -CH(C<u>H</u>₃)₂ (b)], 1.08 [d, 6H, J = 6.8 Hz, $(C\underline{H}_3)_2$ CHPh of *p*-cymene], 1.36 [m, 4H, -CH2-CH(CH3)2], 1.48 [m, 2H, -CH(CH3)2], 1.85 (s, 3H, CH3-Ph of *p*-cymene), 2.65 (m, 1H, -C<u>H</u>- of *p*-cymene), 3.76 [m, 2H, -C<u>H</u>₂O-P (a)], 3.82 [m, 2H, -CH₂O-P (b)], 4.08 (m, 2H, -CH-N), 7.28-7.84 (m, 20H, o-, m- and p-protons of phenyls), 8.56 (d, 2H, J = 8.4 Hz, N**H**). ${}^{13}C-{}^{1}H$ NMR (CDCl₃) δ (ppm): 17.55 (**C**H₃Ph of *p*-cymene), 21.70 [(CH₃)₂CHPh of *p*-cymene], 21.91 [-CH(CH₃)₂ (a)], 22.80 [-CH(CH₃)₂ (b)], 24.56 [-CH(CH₃)₂], 30.10 (-CH- of *p*-cymene), 40.37 [-CH₂-CH(CH₃)₂], 48.67 (-CH-N), 68.89 (-CH₂O-P), 87.44, 88.02 (aromatics carbons of p-cymene), 97.34, 112.03 (guaternary carbons of *p*-cymene), 128.17 (d, ${}^{3}J_{31P-13C} = 10.1$ Hz, *m*-carbons of phenyls), 131.23 (d, ${}^{4}J_{31P-13C} = 2.5$ Hz, *p*-carbons of phenyls), 132.88 (d, ${}^{2}J_{31P-13C} = 11.1$ Hz, o-carbons of phenyls), 136.48 (d, ${}^{1}J_{31P-13C} = 50.3$ Hz, *i*-carbons of phenyls), assignment was based on the ¹H-¹³C HETCOR and ¹H-¹H COSY spectra. ³¹P-{¹H} NMR $(CDCI_3) \delta$ (ppm): 114.96 [s, O-**P**- $(C_6H_5)_2$].

General procedure for the transfer hydrogenation of ketones

Typical procedure for the catalytic hydrogen-transfer reaction: a solution of the ruthenium complexes [Ru{chloro (*p*-cymene)(*N*,*N*[′]-bis[(1*S*)-1-ethyl-2-*O*-(diphenylphosphinite) ethyl]-ethanediamide)}]chloride, 3, or [Ru{chloro(p-cymene) (*N*,*N*′-bis[(1*S*)-1-isobutyl-2-*O*-(diphenyl-phosphinite)ethyl] ethanediamide)}]chloride, 4 (0.005 mmol), NaOH (0.025 mmol) and the corresponding ketone (0.5 mmol) in degassed isopropanol (5 ml) was refluxed for 1 h. After this time a sample of the reaction mixture is taken off, diluted with acetone and analyzed immediately by GC, yields obtained are related to the residual unreacted ketone.

Results and Discussion

Synthesis of chiral ligands, 1 and 2

Compounds 1 and 2 were prepared from the reaction of N,N'bis[(1R)-1-ethyl-2-hydroxyethyl]ethanediamide or N,N'-bis[(1S)-1isobutyl-2-hydroxyethyl]ethanediamide and two equivalents of chlorodiphenylphosphine in the presence of Et₃N at room temperature under argon atmosphere in high yield, respectively (Scheme 1).

The ${}^{31}P - {}^{1}H$ NMR spectra of compounds **1** and **2** show single resonances due to phosphinite at 117.20 and 117.50 ppm, respectively, indicating that two phosphorus atoms in the molecules are equivalent.^[36-38] The ³¹P-{¹H} NMR spectra also display formation of PPh₂PPh₂ and P(O)Ph₂PPh₂, as indicated by signals at about δ -15.0 ppm as singlet and δ 37.2 ppm and δ -21.6 ppm as doublets with ¹J_(PP) 224 Hz, respectively.^[39] These by-products were easily eliminated by washing the residue with copious amounts of dry diethyl ether. Solutions of 1 and 2 in CDCl₃, prepared under anaerobic conditions, are unstable and decompose gradually to give oxide and bis(diphenylphosphino)monoxide [P(O)Ph₂PPh₂] derivatives. Compounds 1 and 2 are also not stable in air and decompose rapidly on exposure to air or moisture. Characteristic $J_{(31P-13C)}$ coupling constants of the carbons of the phenyl rings were observed in the ¹³C NMR spectra (including *i-, o-, m-, p*carbons of phenyl rings, for details see Experimental section), which are consistent with the literature values.^[40-44] Furthermore, ¹H NMR spectral data **1** and **2** are consistent with the structures proposed. The FT-IR spectra of 1 and 2 give characteristic bands at 3405, 1655, 1516, 1035 cm⁻¹ and 3295, 1655, 1512, 1035 cm⁻¹ due to v(N-H), v(C=O, first amide band), v(C=O, second amide band) and v(P-O) stretching, respectively, and v(O-H) stretching bands were not observed. The compounds 1 and 2 were isolated as analytically pure materials and fully characterized by microanalysis as well, and found to be in good agreement with the theoretical values.

Synthesis of the Ruthenium Complexes 3 and 4

The whole reactions with $[Ru(\eta^6-p-cymene)(\mu-Cl)Cl]_2$ with ligands **1** and **2** are depicted in Scheme 2. The reactions of $[Ru(n^6-p$ cymene)(μ -Cl)Cl]₂ with 2 equivalents of **1** and **2** in toluene at room temperature gave the red compounds 3 and 4 in high yields (86.1% **3** and 81.8% **4**).

The reactions between Ru(II) precursor and bis(phosphinite) ligands, 1 and 2 are not affected by the molar ratio of $[Ru(\eta^6-p-cymene)(\mu-Cl)Cl]_2$ as well as the steric and electronic properties of the donor phosphorus atoms. The initial color



Scheme 1. Synthesis of the N,N'-bis-[(1R)-1-ethyl-2-O-(diphenylphosphinite)ethyl]ethanediamide, 1 and N,N'-bis-[(1S)-1-isobutyl-2-O-(diphenylphosphinite)ethyl]ethanediamide, 2.



Scheme 2. Synthesis of the Ru{chloro(p-cymene)(N,N'-bis[(1R)-1-ethyl-2-O-(diphenylphosphinite)ethyl]ethanediamide)}]chloride, 3 and [Ru{chloro(pcymene)(N,N'-bis[(1S)-1-isobutyl-2-O-(diphenylphosphinite)ethyl]ethanediamide)}]chloride, 4.

change, i.e. from clear orange to deep red, was attributed to the dimer cleavage most probably by the bis(phosphinite) ligand.^[45] Ru{chloro(p-cymene)(N,N'-bis[(1R)-1-ethyl-2-O-(diphenylphosphinite)ethyl]ethanediamide)}]chloride, **3**, and [Ru{chloro(p-cymene)(N,N'-bis[(1S)-1-isobutyl-2-O-(diphenylphosphinite)ethyl]ethanediamide)}]chloride, 4, were isolated as indicated by singlets in the ${}^{31}P-{}^{1}H$ NMR spectra at (δ) 115.12 and 114.96 ppm, respectively in line with the values previously observed for similar compounds.^[46,47] It is significant to remark that ${}^{31}P-{}^{1}H$ NMR signals of ligands and complexes do not differ significantly.^[48] Elemental analyses of products **3** and **4** are consistent with the suggested molecular formulas. The absorption bands corresponding to compounds in the infrared spectra do not show significant differences with respect to those of free ligands except disappearance of OH bands. ¹H and ¹³C NMR spectra of compounds 3 and 4 display all the signals of coordinated ligands. In the ${}^{13}C-{}^{1}H$ NMR spectra of compounds **3** and **4**, $J({}^{31}P-{}^{13}C)$ coupling constants of the carbons of the phenyl rings were observed, which are consistent with the literature values.^[49,50] In the compounds **3** and **4**, the coupling between *i*-carbons and the phosphorus is relatively large, ¹J(PC) 42.4 and 50.3 Hz, while the coupling between o-carbon and the phosphorus relatively small ²J(PC) 11.1 and 11.0 Hz, respectively. The most relevant signals of ${}^{13}C-{}^{1}H$ NMR spectra of complexes **3** and **4** are those corresponding to arene ligands (p-cymene). Carbon atoms of the arene rings in p-cymene ligands are observed as two singlets 87.44 and 88.13 ppm in complex 3 and 87.44 and 88.02 ppm in complex **4.** Furthermore, ¹H NMR spectral data of complexes are consistent with the structures proposed. In the ¹H NMR spectra, **3** and **4** are characterized by isopropyl methyl doublets of *p*-cymene groups, at δ 1.05 and 1.08 ppm, respectively (for details see Experimental section).

Table 1. Transfer hydrogenation of acetophenone with *iso*-propanolcatalyzed by Ru{chloro(p-cymene)(N, N'-bis[1R)-1-ethyl-2-O-(diphenyl-phosphinite)ethyl]ethanediamide)}]chloride,**3** and [Ru{chloro(p-cymene)(N, N'-bis[(1S)-1-isobutyl-2-O-(diphenylphosphinite)ethyl]ethanediamide)}] chloride,**4**



Entry	Catalyst	s/c	Time	Conversion(%) ⁱ	TOF(h ⁻¹) ^k
1	3 ^a	100:1	30 min	<1	-
2	4 ^a	100:1	30 min	<1	-
3	3 b	100:1	24 h	35	-
4	4 ^b	100:1	24 h	34	-
5	3 ^c	100:1	30 min	87	174
6	4 ^c	100:1	30 min	88	176
7	3 ^d	100:1	60 min	-	-
8	4 ^d	100:1	60 min	-	-
9	3 ^e	500:1	4 h	94	118
10	4 ^e	500:1	4 h	95	119
11	3 ^f	1000:1	2 h (7 h)	29 (100)	145
12	4 ^f	1000:1	2 h (7 h)	28 (100)	140
13	3 ^g	100:1	60 min (4 h)	62 (100)	62
14	4 ^g	100:1	60 min (4 h)	64 (100)	64
15	3 ^h	100:1	6 h	93.	16
16	4 ^h	100:1	6 h	93	16
			2		

Reaction conditions: ^a at room temperature; acetophenone–Ru–NaOH, 100:1:5. ^b At 50 °C; acetophenone–Ru–NaOH, 100:1:5. ^c Refluxing in *i*PrOH; acetophenone–Ru–NaOH, 100:1:5. ^d In the absence of base. ^e Refluxing in *i*PrOH; acetophenone–Ru–NaOH, 100:1:5. ^g Added 0.1 ml H₂O. ^h Carried out (refluxing) the reaction in air. ⁱ Determined by GC (three independent catalytic experiments). ^k Referred at the reaction time indicated in column; TOF = (mol product/mol Ru(II) Cat.) $\times h^{-1}$. No significant ee was observed.

Asymmetric Transfer Hydrogenation of Prochiral Ketones

In a preliminary study, complexes **3** and **4** were evaluated as precursors for the catalytic transfer hydrogenation of acetophenone by *i*PrOH. A comparison of complexes **3** and **4** as precatalysts for the asymmetric transfer hydrogenation of acetophenone by *i*PrOH in the presence of NaOH is summarized in Table 1.

Based on our results, these complexes catalyzed the reduction of acetophenone to corresponding alcohol [(*R*), (*S*)-1-phenylethanol] via hydrogen transfer from *i*PrOH with NaOH as a promoter. At room temperature, transfer hydrogenation of acetophenone occurred very slowly with low conversion (1–2% after 1 h, entries 1 and 2) and enantioselectivity (3–5% ee) in all the reactions. At 50 °C, the rates remained low (5% after 24 h, entries 3 and 4) and the enantiomeric excess was still low. In addition, the catalytic activity of [Ru(η^6 -*p*-cymene)(μ -Cl)Cl]₂ under the applied experimental conditions is negligible.^[51,52] However, when the temperature was increased to 82 °C, smooth reduction of acetophenone into

1-phenylethanol occurred with conversion ranging from 87 to 88% after 30 min for 3 and 4. The catalytic activities of 3 and 4 are comparable, with the TOF values referred to 30 min of 174 and 176 h⁻¹, respectively (Table 1, entries 5 and 6). In addition, the ees do not vary with the time, as indicated by the catalytic results collected with 3 and 4 after 10 min of the reaction. In these cases conversions higher than 20% have always been obtained (TOFs up to 120 h⁻¹), indicating that the reactions start immediately after the addition of NaOH without any induction time. Furthermore, as can be inferred from the Table 1 (entries 7 and 8), the precatalysts and the presence of NaOH are necessary to observe appreciable conversions and the absence of base leads to the deactivation of the catalysts.^[53] The base facilitates the formation of ruthenium alkoxide by abstracting proton of the alcohol and subsequently alkoxide undergoes β -elimination to give ruthenium hydride, which is an active species in this reaction. This is the mechanism proposed by several workers on the studies of ruthenium-catalyzed transfer hydrogenation reaction by metal hydride intermediates.[54-57] The results show that conversions are significantly affected by the substrate concentration. A lower concentration of substrate gives a higher conversion of the alcohol. Furthermore, the ratio of the substrate to catalyst has less effect on the enantioselectivity. Performing the reaction in air slowed down the reaction but did not affect enantioselectivity (Table 1, entries 15 and 16). For the asymmetric transfer hydrogenation of acetophenone, the catalyst systems showed high activity even in the presence of small amount of water. When we increased the amount of water in the reaction system, the high conversion remained intact (Table 1, entries 13 and 14).

These complexes were extensively investigated with variety of substrates. After optimizing the reaction conditions, the excellent yields were achieved in the reduction of acetophenone to 1-phenylethanol when $[Ru\{chloro(p-cymene)(N,N'-bis[(1R)-1-ethyl-2-O-(diphenylphosphinite)ethyl]ethanediamide)\}]chloride,$

and [Ru{chloro(p-cymene)(N,N'-bis[(1S)-1-isobutyl-2-O-3, (diphenylphosphinite)ethyl]ethanediamide)}]chloride, 4, were used as the catalytic precursors in 60 min and it is noteworthy that 3 and 4 complexes display the same catalytic activities and selectivities in the transfer hydrogenation of acetophenone derivatives (Table 2). That is to say, replacing an ethyl moiety by isobutyl group induced no increase in the conversion and enantioselectivity. The highest ee (14%) was obtained in the case of the reduction of acetophenone to $(S)_{R}$ -1-phenylethanol catalyzed by 3 or 4, respectively. The catalytic reduction of acetophenone derivatives was tested with the conditions optimized for acetophenone. Complexes 3 and 4 showed very high activity for most of the ketones. The rate was also affected by the electronic properties of the substituent on the phenyl rings. The introduction of electron withdrawing substituents, such as F, Cl and Br, to the para position of the aryl ring of the ketone decreased the electron density of the C=O bond so that the activity was improved, giving rise to easier hydrogenation.[58-60]

Conclusions

In conclusion, we have synthesized the two new ruthenium complexes from chiral bidendate ligands and investigated their use in the asymmetric transfer hydrogenation of aromatic ketones. Disappointingly, in no case was a significant ee observed, even

$[Ru(\eta^6-p-cymene)(\mu-Cl)Cl]_2$ and $N, N'-bis-[(1R)-1-ethyl-2-O-(diphenylphosphinite)ethyl]ethanediamide, 3, and N, N'-bis-[(1S)-1-isobutyl-2-O-(diphenylphosphinite)ethyl]ethanediamide, 4a$									
		О Н							
	L.	OH OH	Cat / NaOH						
	R	+	→ R — []	+					
Entry	Catalyst	Substrate	Product	Conversion(%) ^b	TOF (h ⁻¹) ^c				
1	3	O	OH	98	98				
2	4			99	99				
3	3	Ö	он	100	100				
4	4	F' V	F 🔶	100	100				
5	3	0	OH	100	100				
			E Contraction of the second se						
		CI CI	CI						
6	4			100	100				
7	3	O II	OH S	99	99				
0	4	Br	Br	00	00				
9	3	OMe O	ОМе он	98	99				
			L S						
10	4	·	~	98	98				
11	3	O II	OH S	97	97				
12	4	H ₃ CO ² ↔	H ₃ CO ~	96	96				
	-			20	20				

Table 2 Asymmetric transfer hydrogenation results for substituted acetophenones with the catalyst systems propared from

^a Catalyst (0.005 mmol), substrate (0.5 mmol), iPrOH (5 ml), NaOH (0.025 mmol%), 82 °C, 1.0 h for 3 and 4; concentration of acetophenone, 0.1 M. ^b Purity of compounds checked by NMR and GC (three independent catalytic experiments), yields are based on methyl aryl ketone.

^c TOF = (mol product/mol cat.) \times h⁻¹.

No significant ee was observed.

though the activities of the two catalysts were good. In a certain case, optically active alcohols with up 14% ee in high yield were obtained. This can be attributed to: (i) the oxygen atoms in complexes 3 and 4 increase the distance between the chiral bis(amino alcohol)oxalamide moiety and the PPh₂ groups and therefore decrease the influence of the bis(amino alcohol)oxalamidyl functionality on the stereopositions of the phenyl rings of the PPh2 group-consequently there is no less control of stereoselectivity in the catalyst-substrate interactions; (ii) the presence of the C-O-P bond in ligand moiety substantially increases the flexibility of the backbone and consequently decreases the enantioselectivity of the catalyst.^[61-63] Therefore, the modular construction of these catalysts and their flexibility toward transfer hydrogenation make these promising systems to pursue.

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