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Hydrogenation of imines catalyzed by ruthenium(II) complexes containing phosphorus-nitrogen ligands via hydrogen transfer reaction

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ABSTRACT

This work describes the synthesis and characterization of Ru(II) compounds with general formula cis-Cl- cis-P cis-N- $RuCl_2(PN)_2$ (where PN represents a heterobidentate PN-donor chelated ligand) and their application as catalysts in the reduction of acetophenone and imines hydrogenation via hydrogen transfer reaction using 2-propanol as the hydrogen source. Single crystal diffraction analysis for all synthesized ruthenium complexes shows non-regular octahedral coordination around the metal. All the synthesized Ru(II) complexes achieved high conversions and turnover frequencies in hydrogen transfer reaction to acetophenone (830 h^{-1}) and imine hydrogenation (760 h^{-1} for N-benzylideneaniline). The complex (dichloro bis-(8-(diphenylphosphino)quinoline) ruthenium(II)) (RuL2) achieved high conversion in imine hydrogenation, while the complex(dichloro bis-(N-(diphenylphosphino)pyridin-2-amine)ruthenium(II)) (RuL3) showed high conversion in acetophenone reduction. It was found that the electronic, structural, and steric properties of the ligands could influence catalytic performance.

1. Introduction

Catalytic imine hydrogenation is an essential synthetic method for the preparation of chiral amines, as the synthesis of enantiopure compounds is important for many subsequent applications, such as building blocks in the fine chemical or pharmaceutical industries, among others. The role of amines in the pharmaceutical industry is immense and the science of using amines as pharmaceutical actives goes back at least a century; amines have a wide range of functionality that includes stimulants, vasoconstrictors, decongestants, antihistamines, and antidepressants [1]. For these reasons, the reduction of C = N bonds are of interest in the pharmaceutical industry, traditionally conduced with reagents such as sodium borohydride or lithium aluminum hydride in stoichiometric amounts, reducing both ketones and imines [2]. Catalytic reduction is preferred over stoichiometric reduction in large-scale industrial use, using molecular (gas) hydrogen for both ketones [3] and imines [4–6]; however, these catalytic processes present considerable safety hazards, especially in large scale reactions [7]. As an alternative, the hydrogen transfer reaction from polar functional groups has significantly contributed to the recent growth in organic synthesis [8]. This reaction is recommended for its safety and simplicity since hydrogen gas is not used. When 2-propanol is used as a hydrogen donor, the only by-product formed is acetone, which is easily removed by distillation during workup. On the other hand, metal complexes containing polypyridine and phosphine ligands are being considered for catalytic imine hydrogenation [9–11]. Aguirre et al. in their studies reported catalytic application of ruthenium complexes with polypyridine ligands in the hydrogenation of N-benzylideneaniline, achieving high conversions under mild catalytic reaction conditions [9–11]. Another type of ligands, used in transition metal chemistry and homogeneous catalysis, are the denominated PN (or phosphorous-nitrogen) ligands (Scheme 1), which combine the soft donor properties of phosphorus (usually phosphine) moiety and a harder nitrogen atom, confering them potentially hemilabile and bifunctional characteristics. A variety of catalytic reactions has been successfully studied using Ru, Pd, and Rh complexes containing phosphorus-nitrogen ligands in different catalytic applications [12–15]. In this study, we report the synthesis and characterization of ruthenium complexes

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dichloro bis-(2-((diphenylphosphino)methyl)pyridine)ruthenium(II) (RuL1), dichloro bis-(8-(diphenylphosphino)quinoline)ruthenium(II) (RuL2), and dichloro bis-(N-(diphenylphosphino)pyridin-2-amine) ruthenium(II) (RuL3). Of all synthesized complexes, it was found that the preferred isomer was with cis-Cl, cis-P- cis-N configuration. These complexes were studied as catalysts for the hydrogen transfer reaction of ketones (acetophenone) and the hydrogenation of imines such as N-benzylideneaniline, benzophenoneimine, N-benzylidenemethyl--amine, and N-benzilidene-tert-buthylamine, using 2-propanol as both solvent and hydrogen source. The complexes studied reported high activities in the hydrogenation reaction while using a high substrate/catalyst ratio.

2. Experimental

All manipulations were carried out under nitrogen using standard Schlenk techniques. Organic solvents and substrates were purified by distillation over desiccant agents and deoxygenated prior to use. PN ligands were synthesized by reported procedures [15]. Commercial products were used without further purification. NMR data were obtained on Bruker 400, 360, or 250 MHz spectrometers. The ^{31}P-NMR experiments were performed uncoupled with ^{1}H. GC analysis was performed on a Hewlett-Packard 5890 series II chromatograph with a flame ionization detector and equipped with an Equity-1 capillary column. Catalytic products were characterized via GC–MS.

2.1. Syntheses of $RuCl_2(PN)_2$ complexes

RuL1 (dichloro bis-(2-((diphenylphosphino)methyl)pyridine)ruthenium(II)): A mixture of precursor $RuCl_2(PPh_3)_3$ (200 mg, 0.208 mmol) and ligand 2-(diphenyl phosphine)methylpyridine (121.6 mg, 0.416 mmol) were dissolved in toluene (30 mL) and refluxed for 1 h, forming a yellow precipitate. The product was washed with diethyl ether (2 × 5 mL), yielding 205 mg (95% yield) of a yellow product. Anal. (%) calcd. for $C_{36}H_{32}Cl_2N_2P_2Ru$: C 59.51, H 4.44, N 3.86. Found: C, 59.42; H, 4.50 N, 3.91. ^{1}H NMR ($CDCl_3$; δ, ppm): 9.85 (H1 pyridine, dd, J_{H-H} = 5.3 Hz, 1H); 8.40 (o-Ph, m, 2H); 7.82 (H1' pyridine, dd, $J_{H\text{-}H}$ = 6.2 Hz, 1H); 7.68 (m-p-Ph, m, 3H); 7.35 (Ph, m, 5H); 7.20 (H4, dd, J_{H-HH} = 6.1 Hz, 1H); 7.14 (H3′, dd, J_{H-H} = 6.3 Hz, 1H); 7.10 (H2, dd, J_{H-H} = 5.2 Hz, 1H); 7.13 (H2′, dd, J_{H-HH} = 5.2 Hz, 1H); 6.97 (Ph, m, 5H); 6.77 (Ph, m, 5H); 6.33 (H4′, dd; J_{H-H} = 5.1 Hz, 1H); 5.93 (H3, dd, J_{H-HH} = 6.3 Hz, 1H); 4.8 (–CH_2, m) 4,07 (-CH_2, m). ^{31}P-NMR ($CDCl_3$; δ, ppm): 62.6 (d, $J_{P\text{-}PP}$= 25.2 Hz); 58.1 (d, $J_{P\text{-}P}$ = 25.2 Hz). ESI-MS (*m/z*): $[M–Cl]^+$ = 691.0769 (calcd. for $[C_{36}H_{32}ClN_2P_2Ru]^+$= 691.0774.

RuL2 (dichloro bis-(8-(diphenylphosphino)quinoline)ruthenium (II)): A mixture of precursor $RuCl_2(PPh_3)_3$ (200 mg, 0.208 mmol) and ligand 8-(diphenyl phosphine)quinoline (130 mg, 0.416 mmol) were dissolved in toluene (30 mL) and refluxed for 1 h, forming a yellow precipitate. The product was washed with diethyl ether (2 × 5 mL), yielding 205 mg (89% yield) of a yellow product. Anal. (%) calcd. for $C_{42}H_{32}Cl_2N_2P_2Ru$: C, 63.16; H, 4.04; N, 3.51. Found: C, 64.22; H, 4.12; N, 3.65. ^{1}H NMR ($CDCl_3$; δ, ppm): 10.83 (H1 quinoline, dd, J_{H-H} = 5 Hz, 1H); 8.39 (Ph, m, 3H); 8.08 (H1' quinoline, dd, J_{H-H} = 8 Hz, 1H); 7.85 (H3, H3', H4, H4', H5, H5', Ph, m, 18H); 6.99 (H2 quinoline, J_{H-H} = 5 Hz, 1H); 6.85 (Phl, m, 3H); 6.57 (Ph, t, 7.5 Hz, 2H); 6.39 (H2', dd, J_{H-H} = 8 Hz, 1H); 6.19 (Ph, m, 2H). ^{31}P-NMR ($CDCl_3$; δ, ppm): 51.1 (d, $J_{P\text{-}P}$ = 28.8 Hz); 40.0 (d, $J_{P\text{-}P}$ = 28.8 Hz). ESI-MS (*m/z*): $[M–Cl]^+$ = 763.0808 (calcd. for $[C_{42}H_{32}ClN_2P_2Ru]^+$ 763.0775).

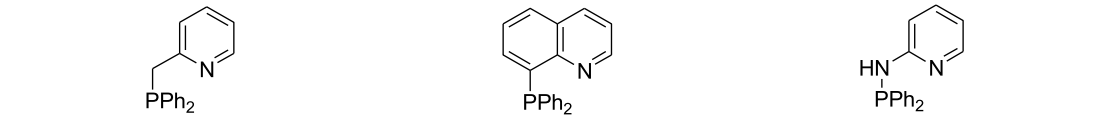
RuL3 (dichloro bis-(N-(diphenylphosphino)pyridin-2-amine)ruthenium(II)): A mixture of precursor $RuCl_2(PPh_3)_3$ (200 mg, 0.208 mmol) and ligand 2-amino-N-(diphenyl phosphine)pyridine (121,9 mg, 0.208 mmol) were dissolved in dichloromethane (30 mL) and refluxed for 1 h, forming a yellow precipitate. The product was washed with diethyl ether (2 × 5 mL) and precipitated in an ethanol/diethyl ether mixture, yielding 205 mg (92% yield) of a yellow product. Anal. (%) calcd. for $C_{34}H_{30}Cl_2N_4P_2Ru$: C, 56.05; H, 4.15; N, 7.69. Found: C, 57.20; H, 3.90 N, 7.73. ^{1}H NMR (CD_3OD; δ, ppm): 8.50 (H1 pyridine, dd, J_{H-} = 7.4 Hz, 1H); 8.20 (H1' pyridine, dd, J_{H-H} = 7.3 Hz, 1H); 7.83 (Phenyl, m, 5H); 7.53 (Ph, m, 5.H); 7.25 (Ph, H3, H3`, m, 12H); 6.77 (H4, dd, $J_{H-H}$ = 7.4 Hz, 1H); 6.68 (H2, t,7.5 Hz, 1H); 6.35 (H2',H4`, m, 2H). ^{31}P-NMR ($CDCl_3$; δ, ppm): 100.1 (d, $J_{P\text{-}P}$ = 29.5 Hz); 90.2 (d, $J_{P\text{-}P}$ = 29.5 Hz). ESI-MS (*m/z*): $[M–Cl]^+$= 592.0201 (calcd. for $[C_{34}H_{30}ClN_4P_2Ru]^+$=592.0422).

1.%2 2.2. Catalytic hydrogenation

Synthesized ruthenium(II) complexes (RuL1 – RuL3, 0.01 mmol) were dissolved in 2-propanol (8 mL) under nitrogen atmosphere in a two-necked round bottom flask equipped with a condenser and refluxed for 10 min; substrates (acetophenone: 10 mmol; N-benzylidene imine: 2 to 10 mmol dissolved in 2-propanol) were added and the mixture was allowed to reflux for an additional 10 min The reaction is initiated with the addition of cocatalyst (sodium hydroxide, 0.24 mmol) previously dissolved in 2-propanol. Reaction progress was monitored via gas chromatography with samples every 30 min. Benzylidenemethylamine, benzophenoneimine, and N-benzylidene-tert-butylamine were studied in imine hydrogenation by hydrogen transfer reaction using a 200/1 substrate/catalyst ratio due to low solubility in the reaction solvent.

2.3. Structural determination

The crystal structures of RuL1, RuL2, and RuL3 were determined via X-ray diffraction. Data collection was done on a SMART-APEX II CCD diffractometer system at room temperature. Data were reduced using SAINT [16], while the structures were solved by direct methods and subsequently completed by Difference Fourier Synthesis and refined by least-squares using SHELXL [17,18]. Multi-scan absorption corrections were applied using SADABS [16]. The hydrogen atom positions were calculated after each cycle of refinement with SHELXL using a riding model for each structure, with a C—H distance of 0.93 Å for aromatic hydrogen atoms and 0.97 Å for the aliphatic ones. U_{iso}(H) values were set equal to 1.2 U_{eq} of the parent carbon atom. Amine nitrogen atoms H12 and H22 on RuL3 and solvating ethanol hydroxyl atom H1a on RuL1 were found on the difference Fourier map and subsequently refined by restricting the distance to their respective parent atoms N12, N22, and O1 to be 0.82 Å. For compound RuL1, the carbon to oxygen (C35-O1) and the carbon to carbon (C35-C36) distances in the solvating ethanol molecule were refined and restricted to be 1.54 Å and 1.47 Å, respectively. During the last stages of the structure completion of RuL3, it was evident in the Fourier map that three methanol molecules occupied the inter complex molecules space. Although their carbon and



2-((diphenylphosphino)methyl)pyridine (L1) 8-(diphenylphosphino)quinoline (L2) *N*-(diphenylphosphino)pyridin-2-amine (L3)

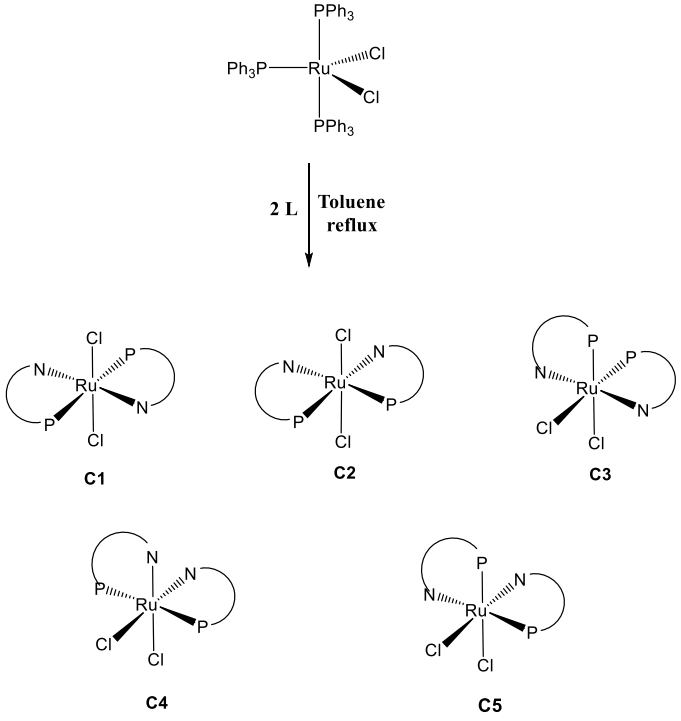
Scheme 1. Phosphorus-nitrogen (PN) ligands studied in this work.

oxygen atoms can be confidently located, efforts to find or place in an ideal geometry the hydrogen atoms failed. After careful consideration, we decided to model the interstitial methanol molecules by using SQUEEZE [19–21]. Comparison of the molecular parameters of RuL3 molecule before and after the use of SQUEEZE shows that almost does not affect any of its geometrical values. Table S1 shows the main data collection and refinement details for each of the compounds and was prepared with the valuable help of publCIF [22]. Tables S2 and S3 (supplementary material) presents selected bond lengths and angles for each complex and non-covalent bond, respectively.

3. Results

3.1. Syntheses and characterization of $RuCl_2(PN)_2$ complexes

The syntheses of proposed ruthenium complexes were carried out by reacting a ruthenium(II) precursor $RuCl_2(PPh_3)_3$ with two equivalents of phosphorus-nitrogen ligand (L1 to L3, scheme 2), and characterized via ^{1}H NMR and ^{31}P-NMR (nuclear magnetic resonance). The reaction between the ruthenium(II) precursor and each ligand can yield five possible isomers (C1 – C5, scheme 2). It was found that the isomer production depends on the solvent choice (toluene, dichloromethane, and methanol were used in this study) and the temperature used for the synthesis; when toluene was used for the synthesis of the complexes, it was observed that it was easy to precipitate and isolate the synthesized complexes. These isomers can be identified by their ^{31}P-NMR spectra. For example, ^{31}P-NMR spectra for isomers C1 – C4 show a single signal, while isomer C5 exhibits two duplets between 56.9 ppm ($J_{P\text{-}P}$= 34.0) and 61.8 ppm ($J_{P\text{-}P}$= 34.0), which allows for following the reaction in-situ using NMR (Figs. 1, 1S-8S supplementary material). When the reaction was carried out in toluene, it was found that complexes RuL1 and RuL2 precipitated in a preferred C5 isometry (or a non-equivalent cis-Cl, cis-P, cis-N arrangement) according to ^{31}P-NMR and ^{1}H NMR spectra (Fig. 1 and 3S, supplementary material), while using ligand L1 yielded two different isomers, C4 (equivalent cis-Cl, cis-P, cis-N arrangement) and C5, in a 30/70 ratio according to ^{31}P-NMR signal integration (figure 6S, supplementary material).



Scheme 2. Possible isomers for $RuCl_2(PN)_2$ complexes.

To obtain only one isomer for RuL3 (and avoid the separation process), we conducted its synthesis using methanol and dichloromethane as solvents (Figure. 7S and 8S, supplementary material); the use of methanol as refluxing solvent leads to a complex mixture of isomeric forms, which is hard to separate with traditional techniques. Finally, when dichloromethane was used, the reaction yielded a C5 isomer almost exclusively, with the formation of C4 isomeric form in low quantity (near 3%), detected and quantified via ^{31}P-NMR signal integration. Additionally, it was found that the C5 isomer precipitates in its pure form in ethanol/diethyl ether (3/1). The high yield of a preferred isomer made it possible to obtain single crystals for all three synthesized complexes, which were analyzed via single-crystal diffraction (supplementary material). The analysis shows that the coordination sphere acquires a non-regular octahedron geometry around the ruthenium(II) center, with two PN ligands arranged in a non-equivalent cis- configuration (Fig. 2), confirming what was proposed by the NMR data. The distortion from the ideal octahedron is reflected in the observed coordination angles differing from the usual angle, 90°, being N1-Ru1-P1, 82.21(11)° and N3-Ru1-P2, 79.95(11)° for RuL1, N1-Ru1-P1, 83.36 (14)° and N2-Ru1-P2, 80.01(15)° for RuL2, and N11-Ru1-P1, 81.08(18)° and N21-Ru1-P2, 80.8(2)° for RuL3, respectively (Table 1S and 2S, supplementary material).

3.2. Catalytic essays

The fully characterized ruthenium(II) complexes were studied in the hydrogen transfer reaction of ketones and imines. For this purpose, acetophenone, N-benzylideneaniline, N-benzylidenemethylamine, and benzophenoneimine were selected as substrates, using 2-propanol in basic medium (NaOH) as solvent and hydrogen source; acetophenone was selected as a benchmark to study the catalytic potential of the synthesized complexes before its study with imine substrates.

Table 1 shows catalytic activities in the hydrogen transfer reaction to acetophenone (Scheme 3) in a 1000:1 substrate/catalyst ratio and using ruthenium complexes RuL1 – RuL3.

All complexes studied reported high conversion and selectivities after 3 h of reaction. RuL3 shows the highest catalytic activity (entry 3), achieving a conversion of 83% towards the corresponding alcohol in only one hour of reaction, while complexes RuL1 and RuL2 achieved lower conversions (48% and 20% respectively) at the same reaction time, steadily increasing up to 73% and 56% after 3 h; in comparison, our group previously studied this reaction catalyzed by ruthenium (II) complexes bearing naphthyridine-derived ligands [11], achieving similar conversions (up to 92% after 3 h of reaction with the most active catalyst).

Once the catalytic capabilities of the ruthenium complexes were confirmed, we proceeded to optimize the catalytic performance using a different base/catalyst ratio (48/1) and sodium tert-butoxide (in 24/1 and 48/1 ratios, Table 2). When the base (NaOH) load was increased, the catalytic performances of RuL1 and RuL2 were similar to those found when a 24/1 base ratio was used. However, when the base concentration is increased, the complex RuL3 shows a significant decrease in its activity. On the other hand, the use of sodium tert-butoxide does not make any noticeable difference (47% versus 48%), while increasing the tert-butoxide load decreases the catalytic performance for RuL1 and RuL3.

Table 3 shows the catalytic activities of RuL1 – RuL3 complexes in the hydrogen transfer reaction of N-benzylideneaniline in a 200/1 ratio, using 2-propanol as a hydrogen source (Scheme 4). All the studied ruthenium complexes were active catalysts, achieving up to 92% conversion after 3 h of reaction; however, unlike acetophenone reduction, the most active catalyst was RuL2, achieving conversions up to 86% within 30 min of reaction, with a near-complete conversion to the corresponding amine after one hour (Table 3, entry 2).

Following these results, RuL2 being the most active of the three complexes, it was used as a catalyst with a higher substrate/catalyst

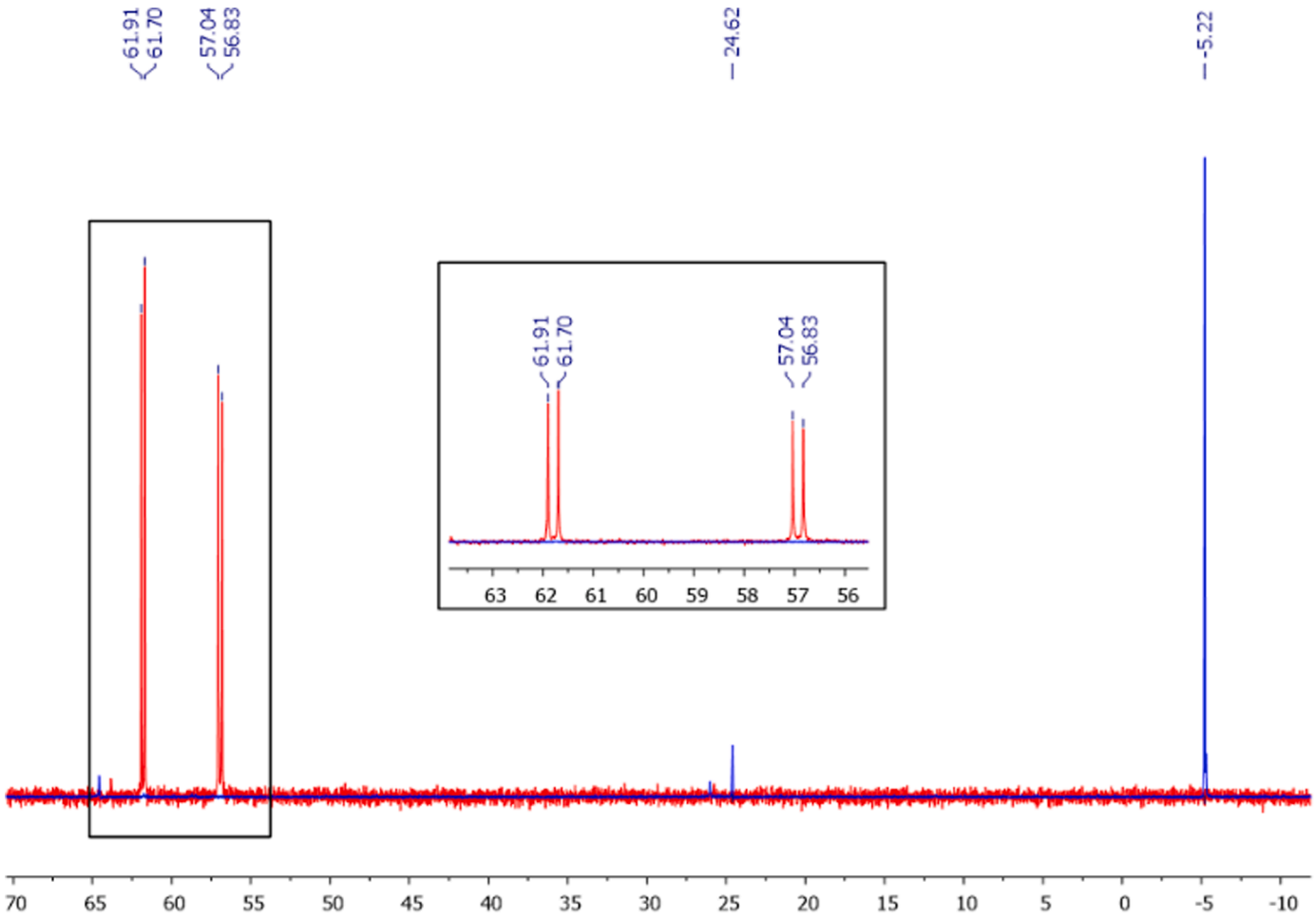


Fig. 1. ^{31}P-NMR spectra (uncoupled with ^{1}H) for RuL1 complex, precipitated in toluene (Red) and remaining toluene solution (Blue), after 2 h of reaction.

ratio (up to 1000/1, Fig. 3) to study its stability and to observe if a higher substrate load could lead to imine hydrolysis. At all ratios, RuL2 achieved high activities with a near-complete conversion with 400/1 and 600/1 ratios (calculated TOF 396 h^{-1} and 594 h^{-1} respectively, compared with the initial 200/1 ratio), while slightly decreasing its activity with a 1000/1 ratio (TOF 760 h^{-1}), with a near-complete conversion at 2 h of reaction.

Based on the results in the hydrogenation of N-benzylideneaniline, other imines were studied seeking to explore new applications of the ruthenium complexes studied as catalysts in this reaction and to study how the substrate might interact with the catalysts (Table 4). When substrate B was used (Table 4, entries 4–6), RuL2 emerges as the most active catalyst, while the other two ruthenium complexes exhibit lower activities. Substrate basicity might be a factor in this case, like what was observed with higher base concentration before.

4. Discussion

4.1. Synthesis of $RuCl_2(PN)_2$ complexes

The three PN ligands studied in this work coordinated mostly in a chelating cis-Cl, cis-P cis-N arrangement to the ruthenium(II) center as expected, according to the obtained NMR and XRD data. These *cis* isomers are favored by intramolecular π-π stabilizing interaction provided by the conjugated ligands, in which the phenyl group belonging to the phosphine moiety interacts with the conjugated moiety of the pyridine (or quinoline) group belonging to the other PN ligand [23]. However, RuL3 yielded both C4 (equivalent cis-Cl, trans-P cis-N) and C5 (cis-Cl, cis-P, cis-N) isomers. To solve this problem, and avoid further separation, methanol and dichloromethane were selected as solvents, as having lower boiling point than toluene would kinetically favor one of the isomers. Finally, when dichloromethane was used, C5 isomer was obtained almost entirely (near 97%, according to ^{31}P-NMR integration), which precipitates in its pure form in an ethanol/diethyl ether mixture.

The purity of the three ruthenium(II) complexes allowed the obtention of single crystals, which were analyzed by XRD. The analysis confirms the formation of distorted, non-equivalent cis-Cl cis-P cis-N octahedral arrangement for all ruthenium(II) complexes. This *cis* arrangement was preferred over trans isomers because it might facilitate the interaction between the complex and the substrate and/or the hydrogen donor molecule [24].

4.2. Catalytic essays

The three ruthenium(II) complexes RuL1 – RuL3 were active catalysts in the hydrogen transfer reaction of acetophenone to 1-phenylethanol; however, complex RuL3 is more active than the other two. These results suggest that this reaction could be influenced by the steric and electronic effects of the ligands around the metal, enhancing its catalytic properties; in particular, the presence of a -NH moiety in the ligand L3 structure, bridging the pyridine and phosphine groups, might assist in the formation of the metal-hydride molecule and/or the hydride transfer to the substrate in an outer-sphere, metal-ligand cooperation (MLC) mechanism (Fig. 4, left) [24 – 26]; this effect may be weaker in the case of RuL1, which presents a -CH_2- bridge, while RuL2 does not have a bridge group, thereby, diminishing its catalytic performance in the

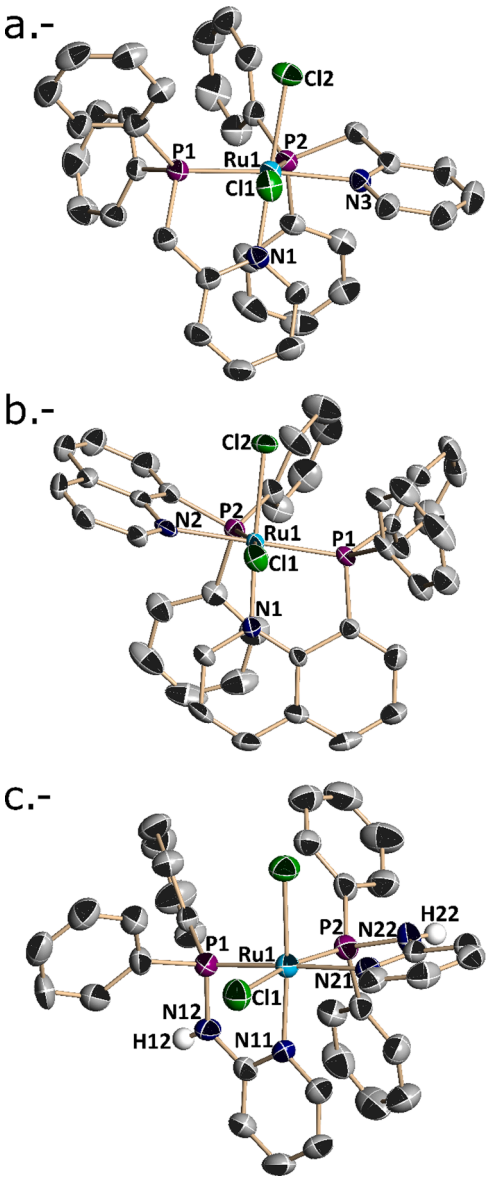


Fig. 2. Molecular structure for a.- RuL1, b.- RuL2, and c.- RuL3. Displacement ellipsoids at 50% level of probability. Hydrogen atoms, except –NH- bond in complex RuL3, and solvating molecules of ethanol and dichloromethane in the structure of RuL1 and RuL3 respectively, were omitted for clarity.

Table 1
Hydrogen transfer of acetophenone using ruthenium complexes bearing phosphorus-nitrogen ligands.

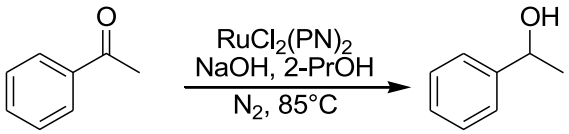
Entry	Complex	Conversion%;(TOF h^{-1})					
		5 min	10 min	30 min	60 min	120 min	180 min
1	RuL1	4;(580)	11; (647)	28; (560)	48; (480)	66; (330)	73; (243)
2	RuL2	1;(125)	3;(180)	10; (200)	20; (200)	43; (215)	56; (187)
3	RuL3	16; (2000)	33; (1941)	65; (1300)	83; (830)	90; (450)	91; (303)

Substrate/catalyst= 1000/1; Catalyst= 0.01 mmol; Temperature= 85 °C; Solvent = 2-propanol; NaOH/Catalyst= 24/1.

Table 2
Hydrogen transfer of acetophenone using different bases and base/catalyst ratios (conversions in%).

Entry	Complex	NaOH (ratio)		Sodium tert-butoxide (ratio)	
		24/1	48/1	24/1	48/1
1	RuL1	48%	42%	47%	34%
2	RuL2	20%	19%	18%	25%
3	RuL3	83%	50%	42%	33%

Substrate/catalyst= 1000/1; Catalyst= 0.01 mmol; Solvent= 2-propanol; Temperature= 85 °C.

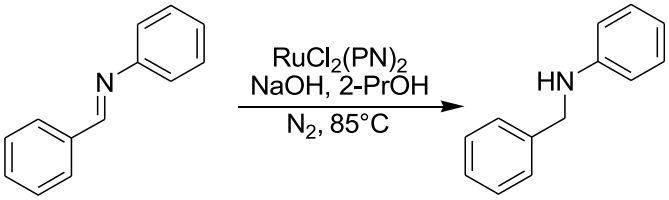


Scheme 3. Hydrogen transfer reaction of acetophenone to 1-phenylethanol.

Table 3
Hydrogenation of N-benzylideneaniline using ruthenium complexes bearing phosphorus-nitrogen ligands.

Entry	Complex	%; (TOF h^{-1})					
		5 min	10 min	30 min	60 min	120 min	180 min
1	RuL1	2;(48)	13; (156)	68; (272)	89; (178)	96; (96)	100; (67)
2	RuL2	11; (264)	32; (385)	86; (344)	97; (194)	98; (98)	100; (67)
3	RuL3	10; (240)	12; (145)	26; (104)	46; (92)	78; (78)	92; (61)

Substrate/catalyst= 200/1; Catalyst= 0.01 mmol; Temperature= 85 °C; Solvent = 2-propanol; NaOH/Catalyst= 24/1.



Scheme 4. Catalytic hydrogen transfer reaction of N-benzylideneaniline using 2-propanol as the hydrogen source.

hydrogen transfer reaction. Also, the more voluminous quinoline group, present in L2, might hinder the interaction between the complex and the substrate or the hydrogen donor molecule. The use of higher base loads might affect this mechanism (Table 2), as this base excess could interact with the bridge's hydrogen, present in ligands L1 and L3, lowering the catalytic activity, while RuL2 does not show a substantial difference in its activity, as L2 lacks this hydrogen.

In the imine hydrogen transfer reaction, on the other hand, RuL2 was the most active catalyst, although all three complexes achieve near complete conversion up to three hours. In this case, the presence of the quinoline group does not hinder the catalytic activity of the RuL2 complex, which suggest that the reaction might follow a different mechanism, in which the stability of the complex is more important than the possible steric effect or the assistance provided by the ligand over the formation of the metal-hydride intermediate, in an inner-sphere mode metal-ligand cooperation (MLC) mechanism (Fig. 4, right) [24–27].

Considering that the imine might interact with the catalyst in an inner-sphere MLC, it is possible to propose a reaction mechanism (Scheme 5) [24]. In this mechanism, the reaction starts with the addition

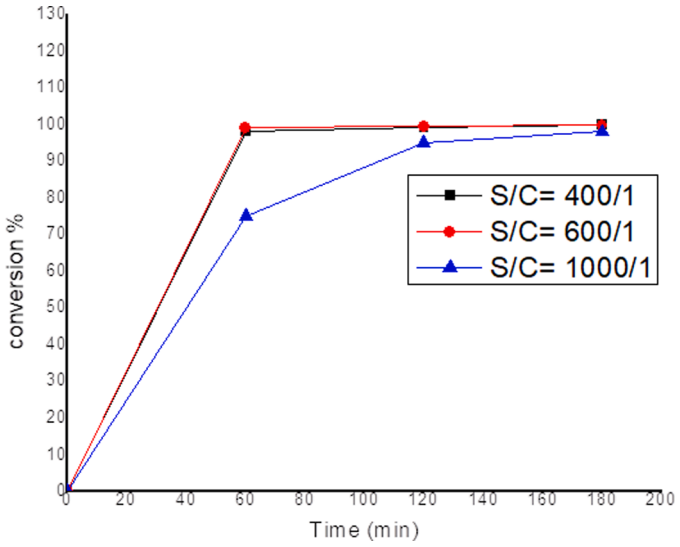
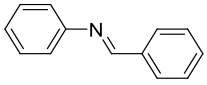
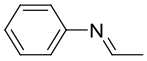
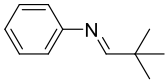
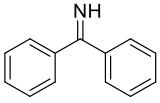


Fig. 3. Hydrogenation of N-benzylideneaniline catalyzed by RuL2 complex (0.01 mmol), using different substrate/catalyst ratios.

Table 4
Hydrogenation of different imines using ruthenium complexes bearing phosphorus-nitrogen ligands.

Substrate	Entry	Complex	Conv. (%)	TOF (h^{-1})
	1	RuL1	100	67
	2	RuL2	100	67
N-Benzylideneaniline (A)	3	RuL3	92	61
	4	RuL1	19	13
	5	RuL2	95	63
N-Benzylidenemethylamine (B)	6	RuL3	52	35
	7	RuL1	0	0
	8	RuL2	0	0
N-Benzylidene-tertbutyl amine (C)	9	RuL3	0	0
	10	RuL1	11	7
	11	RuL2	8	5
Benzophenoneimine (D)	12	RuL3	77	51

Substrate/catalyst= 200/1; Catalyst= 0.01 mmol; Temperature= 85 °C; Solvent= 2-propanol; NaOH/Catalyst= 24/1; Reaction time= 3 h.

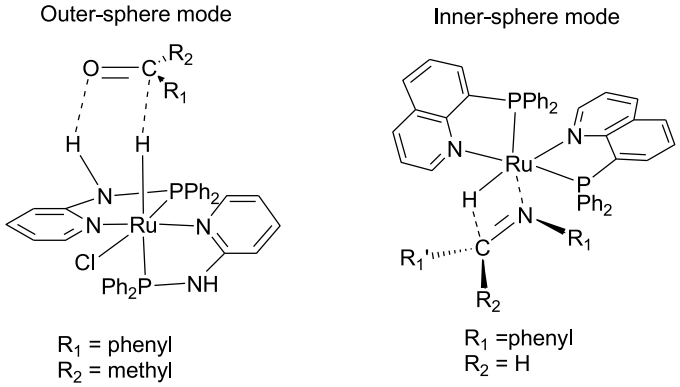


Fig. 4. Proposed metal-ligand cooperation (MLC) mechanism for hydrogen transfer reaction of acetophenone (left) and N-benzylideneaniline (right) [24].

of 2-propanol/sodium hydroxide mixture (or sodium isopropoxide), evidenced by the change of color of the reaction (A). This addition is quickly followed by the formation of a metal hydride intermediate (B), which is followed by the addition of the imine. The first hydrogen transfer step (C) is followed by the addition of a solvent molecule, which provides the second hydrogen atom and yielding the amine product (D).

The main reason to decrease the substrate/catalyst ratio in the imine hydrogenation was to initially study if the complexes are active enough to convert the imine into the corresponding amine, as it was found that N-benzylideneaniline could hydrolyze into its corresponding aldehyde and amine in a basic medium if the catalytic activity is not high enough. Complex RuL2 was active enough to avoid such decomposition at higher substrate concentration; however, when a 1000/1 substrate/catalyst ratio was used, a slight decrease in the activity was observed, although the reaction reached almost complete conversion. This behavior is classic considering that the catalyst/ substrate ratio was 1000/1, as there are fewer catalyst molecules available, but still managed to remain stable and active until near-complete conversion.

Our group has previously studied this reaction catalyzed by ruthenium(II) complexes bearing naphthyridine-derived ligands [10], achieving lower conversions under similar reaction conditions (89% after 6 h of reaction), which indicates how important is the coordination sphere in the catalytic performance. Most of the reported imine hydrogenation studies, catalyzed by homogeneous or heterogeneous systems, focused on asymmetric reactions using molecular hydrogen instead of a hydrogen-donor molecule such as 2-propanol, with reaction times ranging from 30 min up to 5 days to achieve complete conversions with mild reaction conditions [28–33]. Vaquero et al. [34] reported the use of ruthenium (II) complexes bearing a chiral phosphine ligand, under mild conditions and using a 2-propanol/potassium tert-butoxide mixture similar to what was reported in this work, achieving high conversions and enantioselectivities; however, it still requires the use of molecular hydrogen, and the reaction was carried out in a glove box instead of a simple two-necked flask.

Substituting the substrate's methyl moiety with a tert-butyl group (table 4, entries 7 – 9) yields no conversion with any complex, as the substrate might be too basic, or the tert-butyl moiety might create an additional steric effect. On the other hand, RuL3 was the most active catalyst in the benzophenoneimine hydrogenation (Table 4, entries 10–12), similar to what was observed when acetophenone was used as substrate [26].

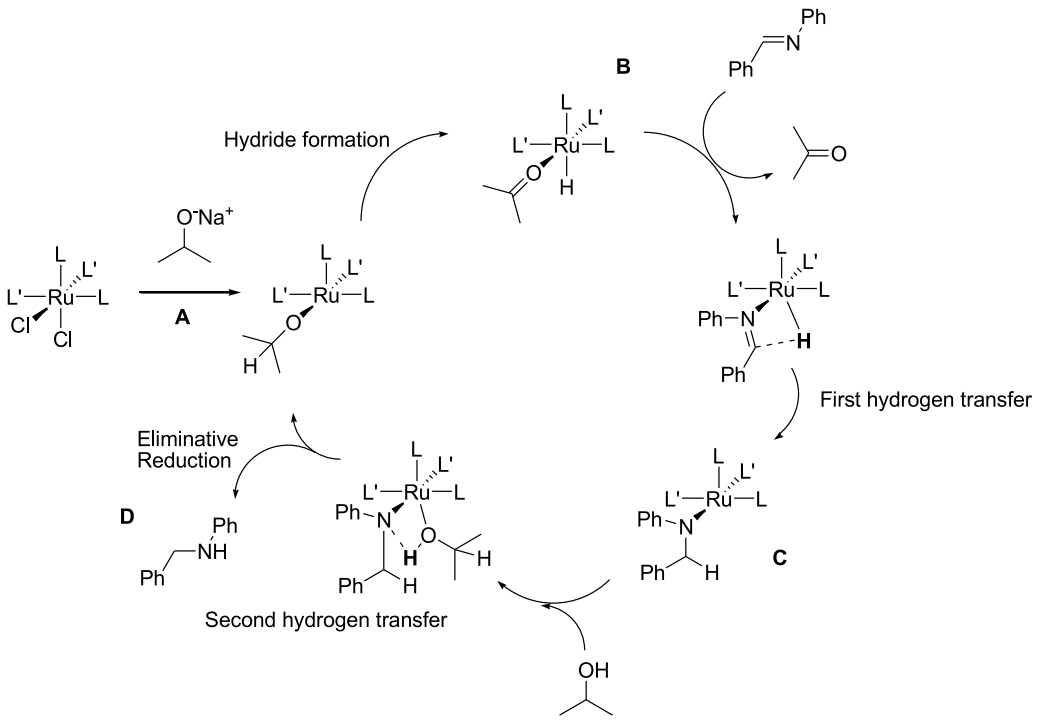
Overall, the ruthenium(II) complexes bearing phosphine-nitrogen ligands reported in this study are active catalysts in ketone and imine reductions under mild conditions and using a secondary molecule, in this case, the same solvent, as the hydrogen source.

5. Conclusions

Ruthenium(II) complexes bearing phosphorus-nitrogen (PN) ligands were obtained in high yields and fully characterized via x-ray diffraction, evidencing a non-equivalent cis-Cl, cis-P, cis-N isometry in a non-regular octahedral geometry. These complexes are active catalysts in N-benzylideneaniline and acetophenone hydrogenation under mild conditions and can use 2-propanol as a hydrogen source instead of traditional molecular hydrogen (H_2). It was found that the ligand's electronic, structural, and steric properties can influence the catalytic activity of the studied ruthenium(II) complexes, as the reaction might follow an inner-sphere mechanism in the imine hydrogenation reaction. The versatility and high activity in imine hydrogenation of these ruthenium(II) complexes represents an alternative to similar catalytic systems, avoiding the use of high pressure and temperature conditions.

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Scheme 5. Proposed mechanism for hydrogen transfer reaction of imines, using the solvent as hydrogen source [24].

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CRediT authorship contribution statement

Braulio Aranda: Investigation, Validation, Visualization. **Gonzalo Valdebenito:** Validation, Methodology. **Sebastián Parra-Melipán:** Investigation, Validation, Methodology. **Vicente López:** Investigation. **Sergio Moya:** Investigation. **Andrés Vega:** Investigation. **Pedro Aguirre:** Writing – original draft, Conceptualization, Resources, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mcat.2022.112374.

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