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Synthesis of the $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(\text{dppb})\text{Cl}]\text{PF}_6$ complex and catalytic activity in the transfer hydrogenation of ketones

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ABSTRACT

Catalysis under mild conditions is of great importance to various chemistry areas, particularly for the development of novel active compounds and for natural products modifications, among others. In this study, the synthesis, characterization, and evaluation of the catalytic activity of a new ruthenium(II) compound, $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(\text{dppb})\text{Cl}]\text{PF}_6$ (**A**) where dppb=1,4-bis(diphenylphosphine)butane, is presented. Catalytic activity of the new Ru(II) compound was tested on hydrogen transfer reaction in various substrates, acetophenone, benzophenone, cyclohexanone, and methyl-ethyl-ketone. Potassium hydroxide was used as base, whereas isopropanol served as both solvent and hydrogen source. Samples comprising substrate: base: catalyst at a 200:20:1 ratio were poured into 5 mm tubes and monitored *in situ* at 40, 50, and 60 °C in a 600 MHz NMR spectrometer. The complex was active in the transfer hydrogenation of ketones, achieving conversions superior to 90% within 4 h at 60 °C, which suggests under mild conditions. Therefore, *in situ* monitoring the reactions through ¹H NMR was a valuable technique to establish the possible catalytic mechanism of Ru(II) precatalyst.

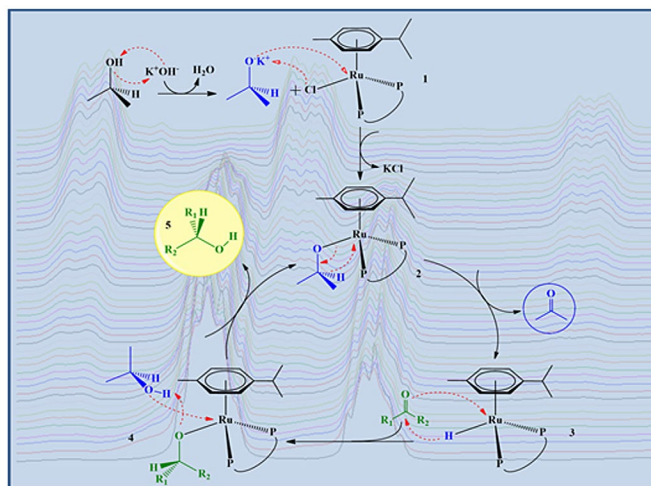
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1. Introduction

There is a significant need for new catalysts with improved performance that are environmentally friendly. In other words, catalysts with higher activity, superior selectivity, and enhanced stability are highly pursued [1]. Ruthenium complexes have been reported to be excellent precursor catalysts for hydrogenation of ketones and alkenes [2, 3], olefin metathesis [4, 5], and hydrogen transfer reaction [6–8], among many other reactions [9–12]. Ru(II) catalysts are considerably cheaper than other metals that are employed in such reactions (e.g. iridium, rhodium, rhenium, and osmium) [13, 14]. Moreover, ruthenium compounds have also been studied as potential anticancer [15–18], antibacterial [19], and antiviral drugs [20]. In this study, high-field NMR spectroscopy has been used to monitor the mechanism *in situ* of the hydrogen transfer reaction catalyzed by Ru complexes [21–26]. Understanding the chemical reaction mechanism may lead to remarkable practical advancements, such as process cost reduction, selective enhancement, and superior environmental consideration [27].

The hydrogen-transfer reaction or transfer hydrogenation is the process of reduction of multiple bonds through abstraction of hydrogen from a reagent (hydrogen-donor) by means of a catalyst, followed by hydrogen addition to the unsaturated functional group of the hydrogen-acceptor (substrate) [28]. There are several substrates that have been successfully reduced employing the hydrogen transfer reaction in the presence of both heterogeneous and homogeneous catalysts. The list includes unsaturated hydrocarbons (alkenes, alkynes), carbonyl (ketones, aldehydes, acids, esters), and nitro compounds (imines, imides, oxides). As catalyst and/or precatalyst, the list includes many complexes of various metals, among them Rh, Ir, Ru, *etc.* [28]. The hydrogen transfer reaction has numerous advantages over conventional hydrogenation processes. The former does not require pressurized hydrogen gas, neither produce hazardous waste, uses an inexpensive hydrogen-donor (2-propanol), and forms a single side-product (*i.e.* acetone), which is easily removed by distillation. Therefore, the hydrogen transfer reaction denotes an environmentally friendly process [29]. Despite recent progress, there is a demand for the development of more sustainable, economic catalytic systems to the hydrogen transfer reaction [30].

In this study, we present an approach using high-field NMR spectroscopy to *in situ* monitor the hydrogen transfer reaction in a real-time fashion using integration of static with rapid injection NMR spectroscopy in conventional 5-mm tubes. NMR spectroscopy is a very useful tool for the structural analysis and quantitative monitoring of complex reaction processes and mixtures. There are several approaches to conducting NMR spectroscopy reaction monitoring [31]. In the method proposed in this paper, the NMR tubes containing substrate and base are placed in the equipment probe for locking, shimming, and temperature settings. The catalyst in the isopropanol solution is injected in the NMR reaction tube *via* a long cannula connected to a plastic syringe. Measurements began once catalysts had been injected and the system had been mechanically stirred. This procedure avoids data loss in the initial portion of reaction. Therefore, *in situ* ^1H NMR spectroscopy was demonstrated to be a valuable technique for monitoring the hydrogen transfer reactions as well as for establishing the possible catalytic mechanism of Ru(II) precatalyst.

2. Experimental

2.1. Materials and methods

All reactions were carried out under argon using standard Schlenk techniques. Solvents were purified by standardized methods and degassed prior to use. $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ was obtained from MetalPrecious, whereas PPh_3 , dppb, α -phellandrene, and NH_4PF_6 were obtained from Sigma-Aldrich and used as received (*i.e.* without further treatment).

Elemental analyses were performed in a Perkin Elmer Series II CHNS/O Analyzer, model 2400. The FT-IR spectra of the powder complexes were recorded from KBr pellets at wavenumbers ranging from 4000 to 200 cm^{-1} in a Bomem-Michelson FT MB-102 instrument. ^1H , $^{13}\text{C}\{^1\text{H}\}$ and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra were recorded in the following spectrometers: BRUKER DRX 400 MHz, using a BBO 5 mm probe, and BRUKER Ascend 600 MHz, using a BBO 5 mm probe at 298 K. $(\text{CD}_3)_2\text{CO}$, CDCl_3 (^1H , $^{13}\text{C}\{^1\text{H}\}$) and, in some cases, CH_2Cl_2 ($^{31}\text{P}\{^1\text{H}\}$) were used as solvents, as well as PF_6^- for internal reference related to $^{31}\text{P}\{^1\text{H}\}$ and TMS for ^1H and $^{13}\text{C}\{^1\text{H}\}$.

2.2. Synthesis of $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(\text{dppb})\text{Cl}]\text{PF}_6$ (**A**)

A solution of 1.00 g of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ dissolved in methanol with 5 mL of α -phellandrene was maintained under reflux during 5 h (see Figure 1). The solution was concentrated and the obtained dark red precipitate $[(\eta^6\text{-}p\text{-cymene})_2\text{Ru}_2\text{Cl}_4]$ (**a**) was filtered off and vacuum dried [32]. The red solid $[(\eta^6\text{-}p\text{-cymene})\text{Ru}(\text{PPh}_3)\text{Cl}_2]$ (**b**) was obtained by placing 850 mg of **a** in methanol with 804 mg of PPh_3 under reduced pressure during 2 h. To 200 mg of **b** in 10 mL of toluene were added 121 mg of NH_4PF_6 and 3 mL of ethanol. The solution was stirred, slightly warmed for 10 min, and added by 132 mg of dppb. This solution was placed under reflux for 3 h. Subsequently, the solution was cooled and the obtained yellow solid was filtered off, washed with diethylether, and vacuum dried. Yield: 76%. Anal. Calcd for $\text{C}_{38}\text{H}_{42}\text{ClF}_6\text{P}_3\text{Ru} \cdot \text{H}_2\text{O}$; C, 53.06; H, 5.16. Found: C, 53.49; H, 4.74. IR (KBr, cm^{-1}): $\nu(\text{C-H})$, 3069; $\nu(\text{C=C})$, 1479; $\nu(\text{P-F})$, 841; $\nu(\text{Ru-P})$, 512; $\nu(\text{Ru-Cl})$, 295. ^1H NMR $[(\text{CD}_3)_2\text{CO}]$, δ (ppm) (*m*, *l*): 7.73–7.53 (m, 20H, Ph^{dppb}), 6.06 (d, 2H, $J_{\text{HH}} = 5.18$ Hz, 3- $\text{CH}^p\text{-cymene}$), 5.31 (d, 2H, $J_{\text{HH}} = 5.35$ Hz, 4- $\text{CH}^p\text{-cymene}$), 3.56 (m, 2H, *a*- $\text{CH}_2^{\text{dppb}}$), 2.62 (sep, 1H, $J_{\text{HH}} = 6.91$ Hz, 6- $\text{CH}^p\text{-cymene}$), 2.27 (m, 2H, *d*- $\text{CH}_2^{\text{dppb}}$), 1.94 (m, 2H, *b*- $\text{CH}_2^{\text{dppb}}$), 1.59 (m, 2H, *c*- $\text{CH}_2^{\text{dppb}}$), 1.19 (s, 3H, 1- $\text{CH}_3^p\text{-cymene}$), 1.04 (d, 6H, $J_{\text{HH}} = 6.95$ Hz, 7- $\text{CH}_3^p\text{-cymene}$). $^{31}\text{P}\{^1\text{H}\}$ NMR $[(\text{CD}_3)_2\text{CO}]$ δ (ppm) (*m*, *l*): 31.19 (s, dppb), -144.10 (sep, PF_6^-). $^{13}\text{C}\{^1\text{H}\}$ NMR $[(\text{CD}_3)_2\text{CO}]$ δ (ppm) (*m*, *l*): 134.12 (t, $\text{CH-Ph}^{\text{dppb}}$), 132.81 (t, $\text{CH-Ph}^{\text{dppb}}$), 132.46 (s, *C-Ph}^{\text{dppb}}), 131.31 (s, *C-Ph}^{\text{dppb}}), 129.94 (t, $\text{CH-Ph}^{\text{dppb}}$), 129.32 (t, $\text{CH-Ph}^{\text{dppb}}$), 99.23 (s, *C-2}^p\text{-cymene}), 97.05 (s, $\text{CH-3}^p\text{-cymene}$), 91.76 (s, $\text{CH-4}^p\text{-cymene}$), 31.27 (s, $\text{CH-6}^p\text{-cymene}$), 30.25 (s, *a-CH}_2^{\text{dppb}}), 28.31 (s, *d-CH}_2^{\text{dppb}}), 28.21 (s, *b-CH}_2^{\text{dppb}}), 28.12 (s, *c-CH}_2^{\text{dppb}}), 23.28 (s, $\text{CH}_3\text{-7}^p\text{-cymene}$), 21.35 (s, $\text{CH}_3\text{-7}^p\text{-cymene}$), 15,29 (s, $\text{CH}_3\text{-1}^p\text{-cymene}$).*******

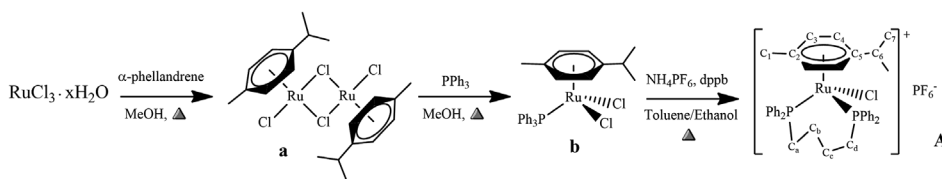


Figure 1. Synthetic pathway of complex A.

2.3. Catalytic studies by NMR

NMR analyses of the hydrogen transfer reaction from 2-propanol to selected ketones were carried out in 5-mm NMR tubes in a Bruker Ascend 600 MHz equipment. ^1H NMR spectra were acquired with eight scans, a single 30° pulse angle, an acquisition time of 1.36 s, and a relaxation delay equal to 1 s. Spectra were recorded at every 30 s (around 500 spectra). The chemicals were added to NMR tubes, mixed by inversion, and inserted into the spectrometer. When the tube was placed in the probe, it is mandatory to allow a suitable time (7–10 min) to achieve thermal equilibrium. Sample temperature was controlled by the variable temperature heater of the probe. After locking and shimming operations, the catalyst was rapidly injected through a cannula coupled to a syringe and mechanically mixed by rapid pushing and pulling. This simpler procedure incorporates modifications to the standard previously reported method [33, 34]. Measurements began upon catalyst injection. The yield of the process was calculated taking into account the relative integrals of ketone and alcohol.

3. Results and discussion

3.1. Synthesis and characterization

Complex **A** was stable in light and in air. Elemental analysis was consistent with the proposed formula. The IR spectrum of the complex displayed characteristic bands that were assigned to the main functional groups of ligands, and to the metal-ligand interaction: aromatic C–H at 3069 cm^{-1} , C=C at 1479 cm^{-1} , P–F at 841 cm^{-1} , Ru–P at 512 cm^{-1} , and Ru–Cl at 295 cm^{-1} . This clearly evidences the complex formation [31]. NMR signals were assigned on the basis of 1-D (^1H , ^{13}C , and ^{31}P NMR) and 2-D NMR experiments, including Correlation Spectroscopy (^1H - ^1H , COSY) and Heteronuclear Single Quantum Coherence (^1H - ^{13}C , HSQC). Complex **A** showed a ^1H NMR spectrum in deuterated acetone comprising ten signals. A multiplet that integrates for 20 protons was observed at 7.6 ppm and assigned to dppb phenyl groups. A doublet that integrates for two protons was noticed close to 6.06 ppm and attributed to CH of *p*-cymene *ortho* to CH_3 - group. Another doublet that integrates for two protons was observed at 5.31 ppm and attributed to CH of *p*-cymene *meta* to CH_3 - group. A multiplet for two protons was observed at 3.56 ppm and assigned to dppb $-\text{CH}_2-$ adjacent to a P atom. The signal septet at 2.62 ppm that integrates for one proton was attributed to CH adjacent to two *p*-cymene CH_3 - groups. The multiplet signals at 2.27, 1.94, and 1.59 ppm, which integrate for two protons each, are attributed to dppb $-\text{CH}_2-$ groups. The singlet at 1.19 ppm that integrates for three protons corresponds to the alone *p*-cymene CH_3 group, whereas the doublet at 1.04 ppm for six protons belongs to the two *p*-cymene CH_3 - groups. All signals were confirmed by the ^1H - ^1H COSY and ^1H - ^{13}C HSQC experiments. The presence of dppb and PF_6 in ruthenium(II) complex **A** was confirmed by ^{31}P NMR spectroscopy, in which one singlet and one septet were observed at 31.19 and -144.10 ppm, respectively. Based on these data, we proposed a piano-stool structure with a ruthenium atom that binds η^6 to a *p*-cymene ligand, a dppb bidentate ligand, a chlorido ligand, and a PF_6 anion as counter ion (Figure 2).

3.2. Catalytic studies by NMR

Complex **A** was designed as catalyst precursor to study the activity for the hydrogen transfer reaction from isopropanol (2-propanol) to ketones (Figure 3). NMR techniques provide

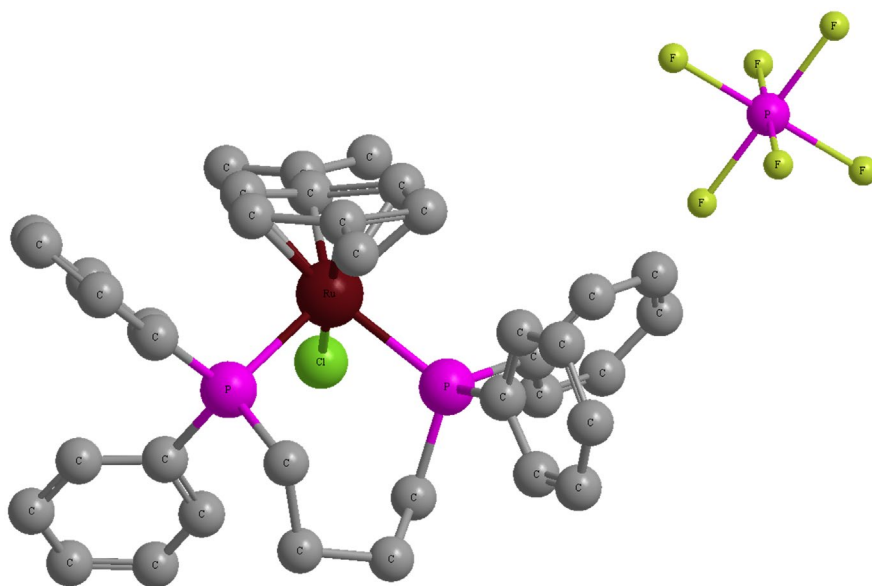


Figure 2. Optimized molecular structure of the Ru(II) complex (hydrogens omitted for clarity).

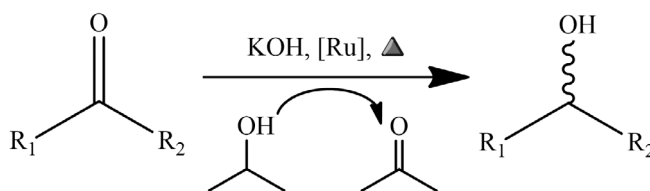


Figure 3. Schematic Ru(II) base-assisted transfer hydrogenation reaction of ketones from isopropanol.

valuable mechanistic information to comprehend this reaction. Complex **A** was evaluated within an air atmosphere employing isopropanol as hydrogen source and different ketone substrates (acetophenone, benzophenone, cyclohexanone, and methyl-ethyl-ketone), 0.5, and 1 mol% of precatalyst concentration. A KOH content of 10 mol% and temperatures of 40, 50, and 60 °C were investigated. Although reaction duration may vary from 3 to 6 h depending on temperature and precatalyst combination, the measuring time was fixed in 4 h.

Initially, a mixture consisting of isopropanol, substrate, and base, and then deuterated solvent was added into the 5-mm NMR tube. This tube was then placed in the equipment (probe) and heated to the desirable reaction temperature (40, 50, or 60 °C). When thermal equilibrium was reached (7–10 min), locking and shimming processes were performed and the spectrum for $t < 0$ was acquired. After these adjustments, the catalyst solution was rapidly injected through a cannula and mechanically mixed by pushing and pulling the syringe plunger for approximately 30 s. This procedure was intended to avoid the loss of important data at the beginning of the reaction. Once mixed, the system was analyzed through ^1H NMR by means of acquiring spectra at every 30 s until achieved 4 h duration.

Figure 4 presents NMR spectrum of the solution containing isopropanol, base and the precatalyst **A**. The inset shows the triplet signal at approximately -11 ppm. This weak triplet was attributed to the coupling between hydrogen and phosphorous atoms of the hydride intermediate, which occurs in a low concentration (0.1%). Therefore, the ^1H NMR spectrum demonstrates the formation of ruthenium-hydride specie as the initial stage of hydrogen transfer reaction [35]. The hydride may be observed until the end of the reaction [36].

NMR techniques are widely known to enable direct observation of multiple reactive intermediates, providing important information concerning the involved reaction mechanism. As excess of isopropanol was used, it was uncomplicated to evaluate the reaction rate by the formation of acetone and the reduced substrate. Figure 5 shows the expansion of ^1H NMR spectra of hydrogen transfer reaction using precatalyst **A**, and using cyclohexanone as substrate. The NMR spectra from 1.3 to 2.2 ppm show an acetone singlet at 1.9 ppm, which increases throughout the reaction. The spectra also denoted three cyclohexanone signals at 2.25, 1.64, and 1.52 ppm that decayed throughout the reaction. Three cyclohexanol signals also appeared at 1.74, 1.58 and 1.38 ppm, which consequently increase with reaction time. The spectra demonstrate the continuous formation of these products during 4 h. This figure clearly shows that ^1H NMR spectroscopy can be easily used to *in situ* monitor the hydrogen transfer reaction.

The NMR data may also be used to extract quantitative information about relative concentration and reaction rates. Figure 6 displays the increase in the relative methyl concentration in phenylethanol at 40, 50, and 60 °C. In accordance to expectations, this figure corroborates the elevated reaction rates at higher temperatures. The data were fitted using an exponential curve to obtain reaction half-life time ($t_{1/2}$, min) and rate constants (k , s^{-1}) (Table 1). These information were used to calculate energy of activation, ΔH^\ddagger , and ΔS^\ddagger (Table 1). The energy of activation (E_a) was calculated by Arrhenius plots ($\ln k = -E_a/RT + \ln A$), wherein k is the equation rate constant, R is the universal gas constant, and T is

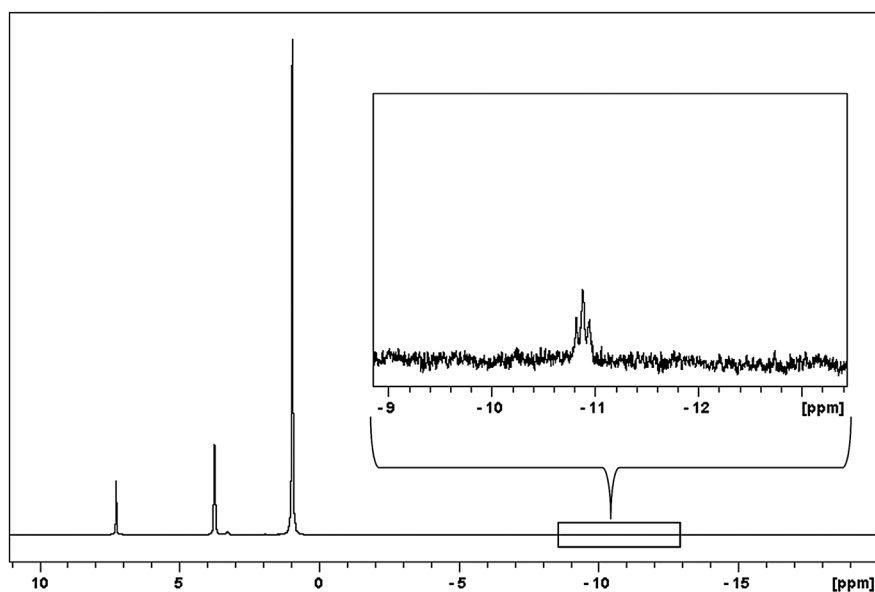


Figure 4. ^1H NMR spectra showing the triplet signal for complex **A**.

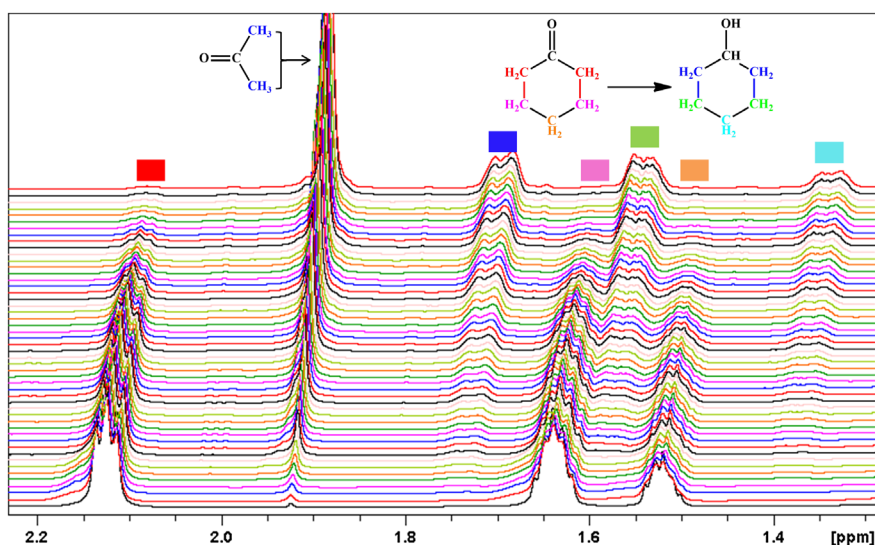


Figure 5. Monitoring of the hydrogen transfer reaction on cyclohexanone, during 4 h, by ^1H NMR spectroscopy.

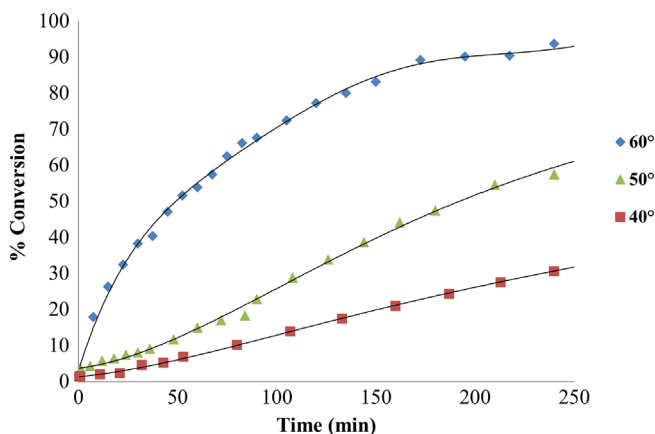


Figure 6. Variation of phenylethanol relative concentration (%) throughout time, measured for 4 h by ^1H NMR spectroscopy. Acetophenone, isopropanol and compound **A** were used as substrate, hydrogen donor, and catalyst, respectively.

Table 1. Activation parameters for the catalytic activity of the catalyst **A**.

| T (K) | $t_{1/2}$ (min) | k ($\times 10^5 \text{ s}^{-1}$) | E_a ($\text{J mol}^{-1} \text{ K}^{-1}$) | ΔH^\ddagger | ΔS^\ddagger |
|---------|-----------------|--------------------------------------|--|---------------------|---------------------|
| 313 | 248 | 4.65 | 4.62×10^4 | 43.50 | -2.74 |
| 323 | 182 | 6.34 | | | |
| 333 | 82 | 14.08 | | | |

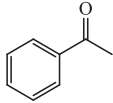
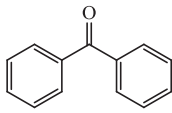


the temperature (K). A $\ln(k)$ versus T^{-1} plot results in a straight line, whose gradient was used to determine E_a . The thermodynamic parameters of such equation (ΔH and ΔS) were determined by the Eyring-Polanyi equation ($\ln(k/T) = (-\Delta H^\ddagger/RT) + [\ln(k_B/h) + (\Delta S^\ddagger/R)]$),

wherein k_B and h are the Boltzmann's and Planck's constant, respectively. The $\ln(k/T)$ versus T^{-1} plot gives a straight line with a slope equal to $-\Delta H^\ddagger/RT$ and an intercept equal to $\ln(k_B/h) + (\Delta S^\ddagger/R)$, from which the enthalpy and entropy of activation, respectively, may be derived (Table 1). Belkova *et al.* previously suggested that these values indicate an ordered (associative) transition state that is typical of proton transfer reactions [37]. Although significant conversions (90%) were obtained in a relatively short period of time (4 h) without continuous mixing, it is always possible to enhance the yield by stirring the reaction mixture.

Table 2 presents the efficiency of the Ru(II) precatalyst on the hydrogen transfer reaction. The conversion to product was observed to vary remarkably (*i.e.* from 24 to 99%) depending on the applied conditions. Most of the reported works use nitrogen atmosphere, temperature of 82 °C, and catalyst load between 0.1 to 1 mol % [29, 38, 39]. A recent work employed temperatures of 40 and 50 °C, a catalyst load of 5%, and reaction time between 24 to 30 h [40]. These results indicate that the conditions carried out here are very mild, because we do not use inert atmosphere, the temperature is lower, the reaction time is acceptable, the catalyst load is similar, and the *in situ* conditions were completely done in the NMR equipment, approaching a combined methodology between rapid injection and static tube. The reaction itself occurs only in the presence of both precatalyst and base. Table 2 also illustrates that the conversion to product is clearly dependent on the catalyst concentration: the higher the catalyst content, the higher the conversion to ketone and vice versa.

A broadly accepted mechanism for catalytic activity of ruthenium complexes involves the dissociation of the chloride ligand as well as the coordination of the hydride species [41]. In the case of base-assisted transfer hydrogenation from isopropanol to ketones, a widely accepted mechanism follows a monohydride route, in which the base transports isopropanol protic hydrogens and the catalyst delivers the hydrides from the carbinol to the carbonyl carbons of the studied ketones. A plausible mechanism for the catalytic activity of the Ru(II)

Table 2. Performance of the Ru(II) complex in the transfer hydrogenation of ketones.^a

| Entry | Substrate | Conversion ^b (%) | | | TON ^c | | |
|-------|---|-----------------------------|-----------------|-----------------|------------------|-------|-------|
| | | 40 °C | 50 °C | 60 °C | 40 °C | 50 °C | 60 °C |
| 1 |  | 24 | 55 | 91 | 48 | 110 | 182 |
| 2 |  | 32 | 88 ^d | 90 | 64 | 88 | 180 |
| 3 |  | 40 | 58 | 99 ^e | 80 | 116 | 198 |
| 4 |  | 29 | 69 ^f | 87 | 58 | 69 | 174 |

^aReactions were carried out at 60 °C during 4 h using isopropanol (520 μ L), ketone (0.5 mmol), base (10 mol%), and catalyst (0.5 mol%).

^bConversion was monitored by ¹H NMR spectroscopy using C₆D₆ as internal standard.

^cTON: Turnover number: ratio of formed product moles to consumed catalyst moles.

^dUsing 1 mol% of catalyst.

^eAfter 6 h.

^fAfter 3 h with 1 mol% of catalyst.

complex is presented in Figure 7. It was previously proposed by Aydemir *et al.* that the first step comprised the removal of isopropanol protic hydrogens by the base [7], as well as the formation of ions that react with precatalyst **A**, forming the Ru-*iso*-propoxyde species **B**. The **B** intermediate undergoes β -hydride elimination and forms the ruthenium metal species **C** and acetone. Then, the hydride intermediate **C** reacts with the carbonyl carbons of ketones substrate and leads to the alkoxyde substrate **D**. Finally, the alkoxyde substrate reacts with another isopropanol molecule (in excess), restoring the intermediate **B** by releasing the respective alcohol derived from the substrate.

In order to corroborate the proposed catalytic mechanism, ^{31}P NMR spectroscopy experiments were performed. Figure 8(a) and (b) display the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of the precatalyst **A** as well as of isopropanol in CDCl_3 , and after addition of the KOH solution in isopropanol, respectively. The difference between the spectra before and after KOH addition becomes evident. The spectra acquired after KOH incorporation denote new peaks with different chemical shifts, suggesting the formation of the intermediate reactive specie **B**. Therefore, the ^1H and ^{31}P NMR spectra played an important role in the understanding of base-assisted

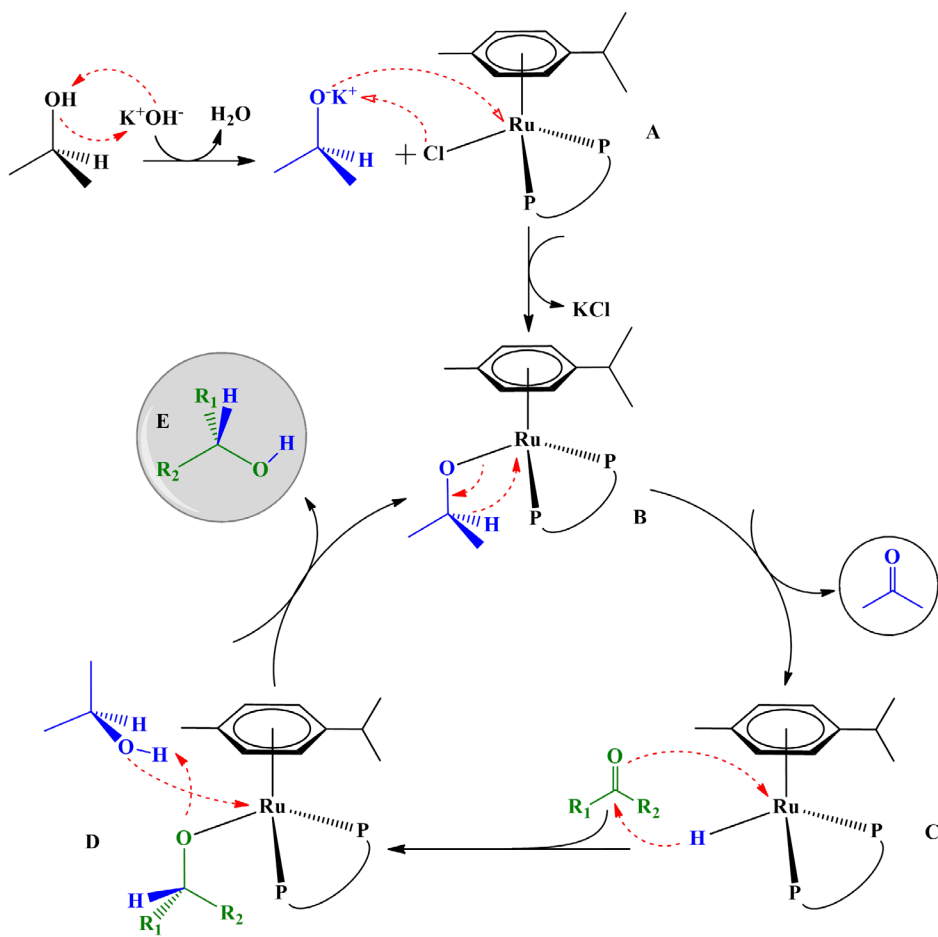


Figure 7. Proposed mechanism for the transfer hydrogenation of ketones catalyzed by the Ru(II) complex **A**.

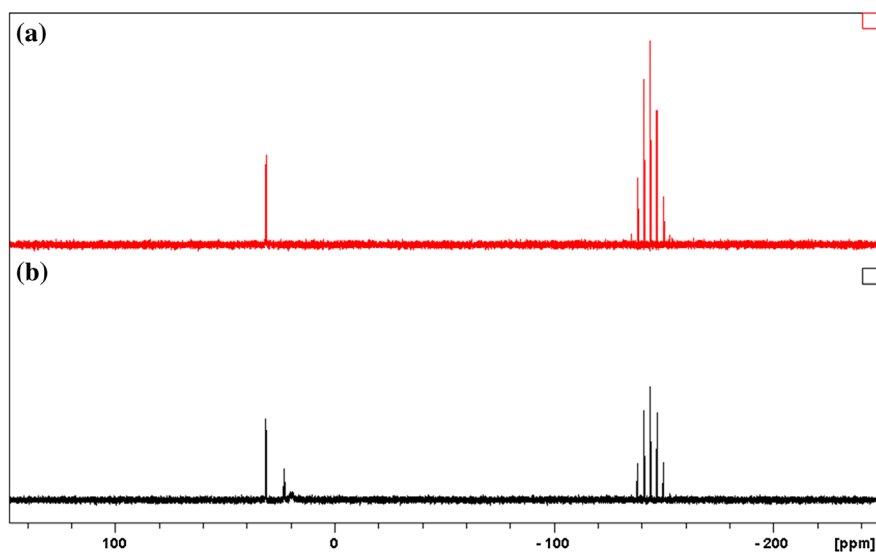


Figure 8. $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of precatalyst A in CDCl_3 with (a) isopropanol and (b) KOH (0.9 M).

transfer hydrogenation of ketones catalyzed by Ru(II) complexes as well as the catalytic mechanism proposed in Figure 7.

4. Conclusion

A new organometallic Ru(II) complex was synthesized, characterized, and tested regarding hydrogen transfer reaction, showing notable catalytic activity in the transfer hydrogenation of ketones, achieving conversions superior to 90% within 4 h at 60 °C, which denote mild conditions. The reaction *in situ* monitored by rapid injection and in real time through ^1H NMR spectroscopy was demonstrated to be a valuable technique for the establishment of the complex catalytic mechanism. This involves the formation of a hydride specie and acetone followed by the reduction of ketone substrates to obtain the desirable compounds. This *in situ* NMR spectroscopy method comprised by probe tuning, locking, magnetic field shimming, and reaction temperature setting may also be easily applied to investigate several other chemical reactions.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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