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COMMUNICATION

Good isomerization of 2-cyclohexenol by two Ru(II) complexes, synthesis and characterization of the reaction intermediate.

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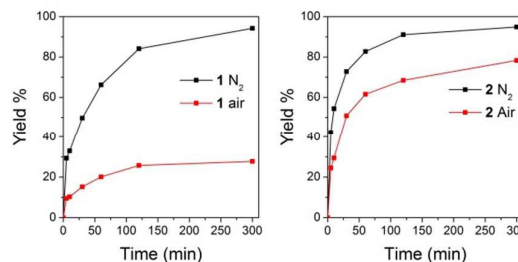
The catalytic activity of [RuClCp(PTA)₂] (**1**) and [RuCp(PTA)₂(H₂O-κO)]OTf (**2**) was assessed for the redox isomerization of the cyclic allylic alcohol 2-cyclohexenol into cyclohexanone in water and biphasic media. Complex **2** showed unprecedented good TONs for the studied conversion both in water (TON = 647) and biphasic of cyclohexen/H₂O (TON = 3420) while **1** showed a lower but also good activity (water TON = 95, biphasic TON = 100). The catalytic reaction intermediate [RuCp(PTA)₂(η²-C₆H₉OH)CF₃SO₃ (**3**) was synthesized and characterized by NMR.

The isomerization of allylic alcohols into the corresponding aldehydes and ketones conventionally proceeds by a succession of oxidation and reduction steps. This time consuming and energetically expensive synthetic route can be bypassed by using the appropriate metal catalyst that allows the isomerization process with 100% atom efficiency. The catalytic route usually avoids high reaction temperature and toxic reactants and solvents. The reaction can also be performed in water if the appropriate catalyst is used.^{1–10} Nowadays various complexes, mainly with metals of groups 8, 9 and 10, have demonstrated to catalyse this transformation. From the mechanistic point of view, a tentative explanation of the catalytic process invokes three possible pathways depending on the nature of the catalytically active moiety: a) the metal hydride addition-elimination mechanism, b) the η³-allyl mechanism and c) the enone mechanism.¹¹ Nevertheless, none of these models takes into account the participation of the solvent that can drive the geometry taken by the intermediates or even participate in the mechanism itself.^{12,13} Our group have showed that complexes [RuClCp(PTA)₂] (**1**) and [RuCp(PTA)₂(H₂O-κO)]OTf (**2**) can effectively catalyse the isomerization of linear allylic alcohols from 3-buten-2-ol to 1-octen-3-ol in water (PTA = 1,3,5-triaza-7-phosphaadamantane,

OTf = trifluoromethanesulfonate), revealing that, in many cases, the presence of water in the medium is mandatory for accomplishing the reaction.⁸ The study of the isomerization of 2-propen-1-ol in water by neutron scattering and molecular dynamics showed that water is required for the catalytic process. The detected reaction intermediate for this reaction, the complex [RuCp(exo-η²-CH₂=CH-CH₂-OH)(PTA)₂]OTf, was showed to be stabilized by a structured and stable water bridge between the alcohol and the N_{PTA}.⁹

This behaviour can justify why water is needed in the medium but does not explain why in the series of allylic alcohols from 3-buten-2-ol to 1-octen-3-ol the conversion to ketone depends on the length of the tail of the alcohol and why 1-hexen-3-ol is the most reluctant to undergo isomerization.¹⁶ The possible reason for this behaviour could come from the tail of the alcohol that sterically hinders the reaction, but this hypothesis needs to be supported by experimental and theoretical evidences. With this target in mind, the assessment of how **1** and **2** catalyze the isomerization of the secondary allylic alcohol 2-cyclohexenol, the cyclic analogue of the 1-hexen-3-ol, can provide valuable information to solve this question. Additionally, catalytic isomerization of secondary allylic alcohols has a potential industrial importance as there are significant examples in nature of this family of chemical compounds, such as the natural opioids morphine and codeine, that could be easily transformed in their corresponding ketones. The effective and practical

Figure 1. Conversion of 2-cyclohexenol to cyclohexanone catalysed by **1** and **2** (H₂O, 70°C, [Ru] 1 mol%). Yields determined by GC.



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isomerization of these natural products is a useful procedure

Table 1. Catalytic isomerization of 2-cyclohexenol by published catalysts.

Catalyst	[cat] mol %	Additive	Solvent	T [°C]	Time	TON	TOF (h ⁻¹)	Yield %	Ref
2	0.1		H ₂ O/ Cyclohexane	70	7 cycles of 3h	3420 ^a	1 st cycle: >333 7 th cycle: 20	1 st cycle: >99 ^b 7 th cycle: 6 ^b	This paper
2	0.01		H ₂ O	70	2h	650	325	6.5 ^b	This paper
2	1		MeOH	70	2h	97	48.5	97	This paper
2	1		MeOH	70	2h	97	48.5	97	This paper
[Ir(OH)(COD)(i ^t Pr)]	0.25		Toluene	110	1.5 h	328	219	82 ^b	17
[Ru(η ⁵ -C ₅ ,k-N-CpN)(CH ₃ CN) ₂]PF ₆	0.5		THF- <i>d</i> 8	60	10 min	200	1205	85 ^c	18
[RuCl(η ⁵ -3-phenylindenyl)(PPh ₃) ₂]	0.5	Base	Toluene	RT	1.5 h	198	132	>99 ^b	19
[Ru ₂ (μ-H)((C ₅ Ph ₄ O) ₂ H)(CO) ₄]	0.5		THF	65	7	166	24	56	17
[Ru(η ⁵ -C ₅ ,k-P-CpP)(CH ₃ CN) ₂]PF ₆	4		THF- <i>d</i> 8	60	5 h	140	28	97 ^c	12
[Rh(COD)(CH ₃ CN) ₂]BF ₄	2	PTA		23	12 h	49.5	4	>99 ^b	20
[RuCp*(MeCN) ₃]PF ₆	2	K ₂ CO ₃	CH ₃ CN	Reflux	1 h	48	48	96 ^b	21
[Ru(η ⁴ -1,3,5-COT)(PEt ₃) ₃]	5		C ₆ H ₆	70	2 h	17.2	9	86 ^b	22
[RuClCp(PPh ₃) ₂]	5	Et ₃ NHPF ₆	Dioxane	100	24 h	15.4	0.7	60 ^b	23
[[RuCl ₂ (η ³ :η ³ -C ₁₀ H ₁₆)(Pyr)]	10		H ₂ O	75	15 h	9.9	0.7	99 ^b	12

a) TON after 7 cycles (H₂O/cyclohexane 1:1, 70°C, [Ru] 0.1 mol%, 3 h/cycle); b) Yield determined by GC; c) Yield determined by NMR.

for synthesising biologically active chemicals from natural and most of the time economical sources.

In contrast to the expectations based on the low conversion of 1-hexen-3-ol, complexes **1** and **2** catalyse the clean isomerization of 2-cyclohexen-1-ol to cyclohexanone with higher conversion rates than any previously catalyst published (Table 1), under relatively mild conditions (70 °C), in water and a biphasic medium of cyclohexane/H₂O (Figure 1). It is important to stress that the allylic alcohol is only isomerized into the ketone, without any trace of by-products as cyclohexanol or 2-cyclohexenone.

The TOF of 1 mol% of **1** at 70°C under N₂ is 352 h⁻¹ at 5 min reaction, which is slower than that for **2** (511 h⁻¹) and agrees with the suspicion that **1** is a precatalyst and **2** the real active catalyst. This suspicion was supported by the fact that after 5 h the conversions obtained with both complexes in water are almost identical (**1**: 94%; **2**: 95%). It is known that complex **1** is in equilibrium with **2** in water but in presence of a large excess of Cl⁻ only complex **1** is observed in solution.⁸ When the isomerization reaction was carried out under the same reaction conditions in presence of 10 equivalents of NaCl the alcohol was not significantly converted by any of the two complexes (Figure S1).

Interestingly, while the catalytic activity of **1** for the isomerization of 2-cyclohexen-1-ol in water slightly depends on the pH, in the case of **2** this dependency is not observed (Figure S2). This behaviour contrasts with the strong pH dependence observed for the catalytic isomerization of linear allylic alcohols with both catalysts.¹⁰

Nevertheless, the reaction mediated by **1** clearly relies on the presence of water in solution: in dry methanol the

isomerization does not work, but when 10 equivalents of water were added it proceeded. This fact could not be surprising as water is needed to originate the catalytically active aqua-complex **2**. The activity of **2** is irrespective of the amount of water in the reaction medium, as its conversion to cyclohexanone can be obtained also in dry methanol with similar TONs than in water. This behaviour is completely different to what observed when **2** was used for catalysing the isomerization of linear allylic alcohols: that reactions were very sensitive to the presence and amount of water.¹⁰ It is interesting to point out that in methanol approximately only the 10% of the linear 1-hexen-3-ol was converted into the corresponding ketone (See ESI).

Another interesting fact is that the lesser concentration of **2** the larger TON is obtained: in 2 h and under N₂ the resulting TON with 0.1 mol% of **2** was 304 (conversion = 30.4%, TOF = 152 h⁻¹) while with 0.01 mol% the TON was 650 (conversion = 6.5%, TOF = 325). At the best of our knowledge, the latter reaction gave the highest TON found in bibliography for the isomerization of 2-cyclohexenol. Under air the resulting TON with 0.1 mol% of **2** was 97 (TOF = 48.5 h⁻¹) while with 0.01 mol% was 177 (TOF = 88.5 h⁻¹), both of them are lower than under N₂ but larger than any other previously produced by a catalyst published for this reaction in water (Table 1). This behavior was not observed when **1** was used as catalyst for the isomerization of 2-cyclohexenol in the same reaction conditions (Table S1).

The catalytic activity of **2** for the isomerization of 2-cyclohexenol significantly improves in the biphasic system cyclohexane/water 1:1, reaching TONs >99 in 30 min with 1 mol% of catalyst under N₂ and 70.5 under air. It is interesting

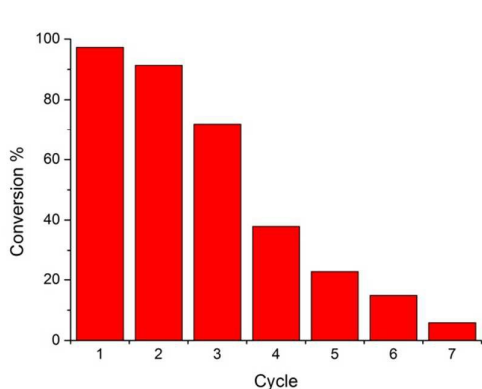


Figure 2. Isomerization of 2-cyclohexanol catalyzed by **2** in biphase ($\text{H}_2\text{O}/\text{cyclohexane}$ 1:1), at 70°C , $[\text{Ru}]$ 0.1 mol%, 3 h/cycle) in successive recycling runs.

to stress that when 0.1 mol% of **2** was used the full conversion of the alcohol under inert atmosphere was achieved in 3 hours ($\text{TON} > 999$, $\text{TOF} > 333 \text{ h}^{-1}$). In the same conditions but under air the conversion is markedly worse as reaches a TON of 500 after 15h ($\text{TOF} = 33.3 \text{ h}^{-1}$). When 0.02 mol% of catalyst was used the conversion under N_2 was 31% with TON of 1550 ($\text{TOF} = 103 \text{ h}^{-1}$). Under the same biphasic conditions but using complex **1** as catalyst, the conversion did not significantly improve with respect to that obtained in water (Table S1).

One of the advantages of the biphasic systems is the recyclability of the catalyst. This possibility was tested on the biphasic reaction conditions that produced the best conversion (reaction time of 3 h, under N_2 and 0.1 mol% of **2**). The two first runs displayed a similar conversion that begins to decrease significantly after the third cycle, dropping down to the 6% after the seventh. Nevertheless, the final overall TON (considering the 7 cycles) was of 3420 (Figure 2) that is the largest known so far.

The study of the reaction by NMR spectroscopy showed that in water, methanol or biphasic conditions there is a common main intermediate independently of the catalyst used (**1** or **2**). It was possible to synthesize this intermediate by reaction of **2** with 2-cyclohexenol in MeOH at 5°C (Scheme 1). The complex precipitated from the solution due to its reduced solubility in MeOH. The resulting white microcrystalline powder was characterized by IR and NMR spectroscopy as $[\text{RuCp}(\text{PTA})_2(\eta^2\text{-C}_6\text{H}_9\text{OH})\text{CF}_3\text{SO}_3]$ (**3**) (See ESI).

The NMR studies run on solutions of **3** in D_2O and $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ (10:1) showed that the 2-cyclohexenol ligand is weakly coordinated to the ruthenium and tends to be substituted by

Scheme 1. Synthesis of **3**.

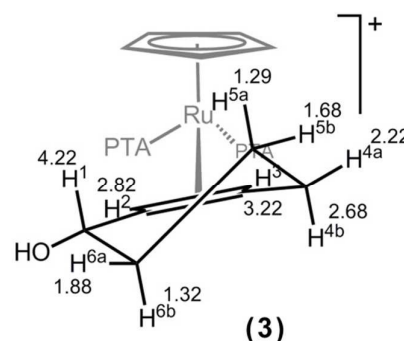
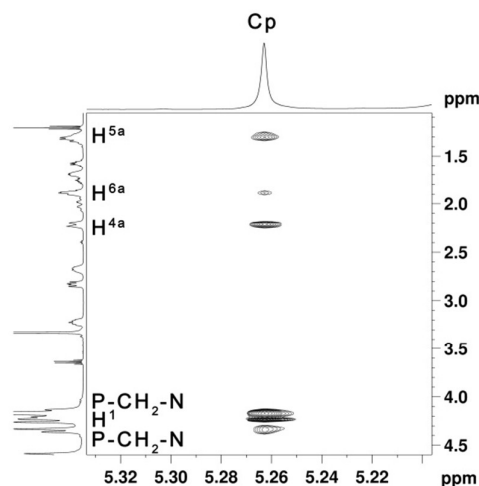
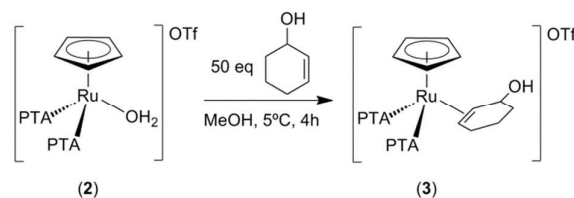
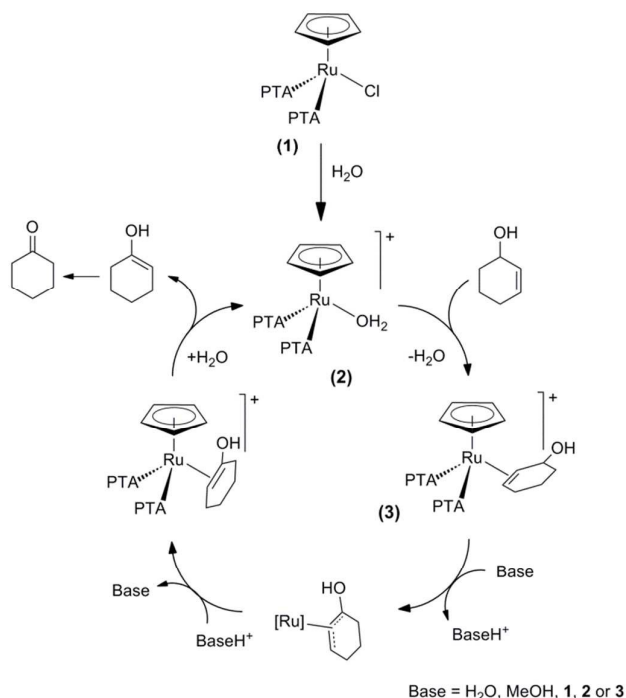


Figure 3. Top: ROE cross peaks between Cp and H^1 , H^{5a} , H^{6a} and H^{4a} . Bottom: propose structure for **3** containing hydrogen chemical shifts of the 2-cyclohexenol ligand.

water molecules to give rise to complex **2**. At room temperature complexes **2** and **3** are in a ratio of about 60:40, but the equilibrium can be pushed toward the formation of **3** by decreasing the temperature at -20°C where the proportion is 20:80, which remains stable up to -80°C (See ESI). Upon coordination of a molecule of 2-cyclohexenol to the ruthenium centre the phosphorous of the PTA ligands become inequivalent as indicated by the two doublets in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum, which are shifted to lower field than the singlet of **2** (**2**: -24.25 ppm (s); **3**: -23.24 ppm (d), -21.97 ppm (d), $^2J_{\text{P-P}} = 42 \text{ Hz}$). The η^2 -bonding alkene hydrogens appear in the ^1H NMR spectrum at 2.82 (H^2) and 3.22 ppm (H^3) (See ESI) as observed for the allyl alcohol complex $[\text{RuCp}(\eta^2\text{-CH}_2=\text{CH-CH}_2\text{-OH})(\text{PTA})_2](\text{CF}_3\text{SO}_3)$, which was studied theoretically and by neutron scattering.¹³ The disposition adopted in solution by the ligands in complex **3** has been investigated by means of a ^1H - ^1H ROESY experiment, revealing that the 2-cyclohexenol is placed almost parallel to the Cp ring, resembling the *exo* geometry adopted by the allyl alcohol in complex $[\text{RuCp}(\eta^2\text{-CH}_2=\text{CH-CH}_2\text{-OH})(\text{PTA})_2](\text{CF}_3\text{SO}_3)$, as indicated by the ROE cross peaks between the hydrogens of the Cp and sp^3 carbons H^1 , H^{4a} , H^{5a} and H^{6a} of the 2-cyclohexenol (Figure 3). This coordination mode, that is recurrent in the catalytic isomerization reactions mediated by **1** and **2**, must determine the conversion and the kinetics. Nevertheless, and in contrast



Scheme 2. Proposed mechanism for the isomerization of 2-cyclohexenol to cyclohexanone mediated by 1 and 2.

with the isomerization of linear allylic alcohols, the possible catalytic isomerization process (Scheme 2) of 2-cyclohexenol does not depend on the presence of water in the reaction medium and needs to be studied by theoretical simulations and scattering techniques to characterize whether the water molecules as acting as spectators.

Conclusions

In conclusion we found that complexes 1 and 2 can catalyse the difficult isomerization of 2-cyclohexenol to cyclohexanone under mild conditions with outstanding conversion rates both in water and water/cyclohexane biphasic system, in which medium it is possible to recycle the catalyst up to 7 times. The reaction is currently under study to unravel the catalytic mechanism, as well as to explore its potentiality in the isomerization of the allylic alcohol moiety in the natural opioids.

Conflicts of interest

There are no conflicts to declare.

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The catalytic isomerization of 2-cyclohexenol to cyclohexanone has been accomplished with large conversion rates by using two Ru(II) catalysts containing PTA under mild reaction conditions in both water and biphasic media.

