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Good isomerization of 2-cyclohexenol by two Ru(II) complexes, synthesis and characterization of a reaction intermediate[†]

Franco Scalambra, 🔟 Belen López-Sanchez 🔟 and Antonio Romerosa 🕩 *

The catalytic activities of $[RuClCp(PTA)_2]$ (1) and $[RuCp(PTA)_2 (H_2O \cdot \kappa O)]OTf$ (2) were 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 in the biphase of cyclohexene/H₂O (TON = 3420) while 1 showed a lower but also good activity (water TON = 95, biphasic TON = 100). The catalytic reaction intermediate $[RuCp(PTA)_2(\eta^2-C_6H_9OH)]$ CF₃SO₃ (3) was synthesized and characterized using 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 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 η^3 -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 adopted by the intermediates or even participate in the mechanism itself.^{12,13} Our group has shown that complexes $[RuClCp(PTA)_2]$ (1) and $[RuCp(PTA)_2(H_2O-\kappa O)]OTf (2)$ 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-phosphaadamentane, OTf = trifluromethanesulfonate), revealing that, in many cases, the presence of water in the medium is mandatory for accomplishing the reaction.¹⁴ The study of the isomerization of 2-propen-1-ol in water using 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*- η^2 -CH₂=CH-CH₂-OH) (PTA)₂]OTf, was shown to be stabilized by a structured and stable water bridge between the alcohol oxygen and the N_{PTA}.¹⁵

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 chain 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 chain of the alcohol that sterically hinders the reaction, but this hypothesis needs to be supported by experimental and theoretical evidence. 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 in answering this question. Additionally, the 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 into the corresponding ketones. The effective and practical isomerization of these natural products is a useful procedure for synthesising biologically active chemicals from natural and mainly economical sources.

In contrast with 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 published catalyst (Table 1), under relatively mild conditions (70 °C), in water and a biphasic medium of cyclohexane/H₂O (Fig. 1). It is important to stress that this allylic alcohol is only isomerized into the ketone, without any trace of by-products such as cyclohexanol or 2-cyclohexenone.



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Área de Química Inorgánica-CIESOL, Facultad de Ciencias, Universidad de Almería, Almería, Spain. E-mail: romerosa@ual.es

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Catalyst	[cat] mol%	Additive	Solvent	$[O_{\circ}]_{L}$	Time	NOL	$\operatorname{TOF}(h^{-1})$	Yield %	Ref.
2	0.1		H ₂ O/cyclohexane	70	7 cycles of 3 h	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_2O	70	2 h	650	325	6.5^{b}	This paper
2	1		MeOH	70	2 h	97	48.5	97	This paper
2	1		MeOH	70	2 h	97	48.5	97	This paper
[Ir(OH)(COD)(I ⁱ Pr)]	0.25		Toluene	110	$1.5 \mathrm{h}$	328	219	82^b	17
Ru(n ⁵ -C5,k-N-CpN)(CH ₃ CN) ₂]PF ₆	0.5		THF-d8	60	10 min	200	1205	85^c	18
RuCl(h ⁵ -3-phenylindenyl)(PPh ₃) ₂]	0.5	Base	Toluene	\mathbf{RT}	$1.5 \mathrm{h}$	198	132	>99 ^b	19
Ru ₂ (µ-H){(Ĉ ₅ Ph ₄ O) ₂ H}(ČÔ) ₄]	0.5		THF	65	7	166	24	56	17
Ru(n ⁵ -C5,k-P-CpP)(CH ₃ CN) ₂]PF ₆	4		THF-d8	60	5 h	140	28	67^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_2CO_3	CH ₃ CN	Reflux	1 h	48	48	66^{b}	21
$Ru(n^4-1,3,5-COT)(PEt_3)_3$	5)	$C_6 H_6$	70	2 h	17.2	6	86^b	22
RuClCp(PPh ₃) ₂]	5	Et_3NHPF_6	Dioxane	100	24 h	15.4	0.7	60^{b}	23
$[{\rm RuCl}_2(\eta^3:\eta^3-{\rm C}_{10}{\rm H}_{16})({\rm Pyr})]$	10		H_2O	75	15 h	9.9	0.7	66	12

100 100 80 80 1 N, - 2 N Yield % Yield % 60 60 1 air - 2 Air 40 40 20 20 0 0 50 100 150 200 250 300 50 100 150 200 250 300 ò ò Time (min) Time (min)

Fig. 1 Conversion of 2-cyclohexenol to cyclohexanone catalysed by 1 and 2 (H_2O , 70 °C, [Ru] 1 mol%). Yields determined using GC.

The TOF of 1 mol% of 1 at 70 °C under a N_2 atmosphere is 352 h⁻¹ in 5 min, which is slower than that for 2 (511 h⁻¹) and agrees with the hypothesis that 1 is a precatalyst and 2 is the actual active catalyst. This hypothesis 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 the 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 the presence of 10 equivalents of NaCl, the alcohol was not significantly converted by the two complexes (Fig. 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 (Fig. S2[†]). This behaviour contrasts with the strong pH dependence observed for the catalytic isomerization of linear allylic alcohols with both types of catalysts.¹⁰

Nevertheless, the reaction mediated by 1 clearly relies on the presence of water in solution; in anhydrous methanol, the isomerization does not proceed, but when 10 equivalents of water were added it proceeded. This is no surprise 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 anhydrous methanol with similar TONs with that obtaned in water. This behaviour is completely different to what was observed when 2 was used to catalyse the isomerization of linear allylic alcohols; that reactions are very sensitive to the presence and amount of water.¹⁰ It is interesting to point out that in methanol, approximately 10% of the linear 1-hexen-3-ol was converted into the corresponding ketone (see the ESI†).

Another interesting fact is that with lower the concentration of 2, larger the TON obtained in 2 h and under a N₂ atmosphere, 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). To the best of our knowledge, the latter reaction gave the highest TON found in the literature for the isomerization of 2-cyclohexenol. In air, the resulting TON with 0.1 mol% of 2 was 97 (TOF = $48.5 h^{-1}$), while with 0.01 mol%, it was 177 (TOF = $88.5 h^{-1}$),

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Table 1

Catalytic isomerization of 2-cyclohexenol by published catalysts

and both are lower under a N_2 atmosphere but greater 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 a catalyst for the isomerization of 2-cyclohexenol under 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 a N₂ atmosphere and 70.5 in the presence of air. It is interesting to stress that when 0.1 mol% of 2 was used, the full conversion of the alcohol under an inert atmosphere was achieved in 3 hours (TON > 999, TOF > 333 h⁻¹) under the same conditions but in air, the conversion is markedly worse, with a TON of 500 after 15 h (TOF = 33.3 h⁻¹). When 0.02 mol% of the catalyst was used, the conversion under a N₂ atmosphere was 31% with a TON of 1550 (TOF = 103 h⁻¹). Under biphasic conditions, but using complex 1 as the 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 a N_2 atmosphere 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 6% after the seventh cycle. Nevertheless, the final overall TON (considering all 7 cycles) was 3420 (Fig. 2), which is the highest so far recorded.

The study of the reaction using NMR spectroscopy showed that in water or methanol or under the biphasic conditions, there is a common main intermediate independent 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 using IR and NMR spectroscopy as [RuCp(PTA)₂(η^2 -C₆H₉OH)]CF₃SO₃ (3) (see the ESI†).





The NMR studies run on solutions of 3 in D₂O and CD₃OD/ D₂O (10:1) showed that the 2-cyclohexenol ligand is weakly coordinated to the ruthenium centre and tends to be substituted by 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 shifted toward the formation of 3 by decreasing the temperature to -20 °C where the proportion is 20:80, which remains stable down to -80 °C (see the ESI†). Upon coordination of a molecule of 2-cyclohexenol to the ruthenium centre, the phosphorus of the PTA ligands become inequivalent as indicated by the two doublets in the ³¹P{¹H} NMR spectrum, which are shifted to a lower field than the singlet of 2 (2: -24.25 ppm (s); 3: -23.24 ppm (d), -21.97 ppm (d), ²J_{P-P} = 42 Hz). The η^2 -bonding alkene hydrogens appear in



Fig. 2 Isomerization of 2-cyclohexenol catalyzed by 2 in biphase (H_2O /cyclohexane 1:1), at 70 °C, [Ru] 0.1 mol%, 3 h per cycle) in successive recycling runs.

Fig. 3 Top: The ROE cross peaks between Cp and H¹, H^{4a}, H^{6a} and H^{5a}. Bottom: The proposed structure for **3** containing hydrogen chemical shifts of the 2-cyclohexenol ligand.



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

the ¹H NMR spectrum at 2.82 (H^2) and 3.22 ppm (H^3) (see the ESI[†]) as observed for the allyl alcohol complex $[RuCp(\eta^2 -$ CH2=CH-CH2-OH)(PTA)2](CF3SO3), 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 the complex [RuCp(η²-CH₂=CH-CH₂-OH)(PTA)₂](CF₃SO₃), as indicated by the ROE cross peaks between the hydrogens of the Cp and sp³ carbons H¹, H^{4a}, H^{5a} and H^{6a} of the alkene bond of 2-cyclohexenol (Fig. 3). This coordination mode, which is recurrent in the catalytic isomerization reactions mediated by 1 and 2, helps to determine the conversion and the kinetics. Nevertheless, and in contrast 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 further study by theoretical simulations and scattering techniques to characterize whether the water molecules act 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 in a water/cyclohexane biphasic system. For the latter medium, it is possible to recycle the catalyst up to 7 times. The reaction is currently under investigation 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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