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From a Sequential to a True One-pot Cascade Reaction in Aqueous Medium: Concurrent Ruthenium-Catalysed Allylic Alcohol Isomerisation-Asymmetric Bioreduction**

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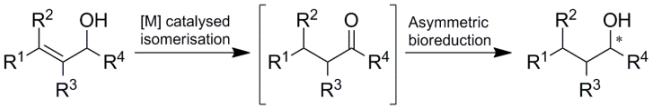
Dedication ((optional))

***Abstract**: The Ru-catalysed redox isomerisation of allylic alcohols was successfully coupled with the enantioselective enzymatic ketone reduction (mediated by KREDs) in a concurrent process in aqueous medium. The overall transformation, formally the asymmetric reduction of allylic alcohols, took place: (i) with excellent conversions and enantioselectivities, (ii) under mild reaction conditions, (iii) employing commercially and readily available catalytic systems, and (iv) without external coenzymes or cofactors. A concise medium engineering optimisation allowed us to cross the frontier between a multi-step approach and a genuine cascade reaction where the metal and biocatalyst coexist from the beginning.*

At the dawn of the 21st century a new awareness arose to strive towards chemical processes which are not only aimed at productivity but also at ecological efficiency and environmental sustainability.[1] In this sense, new cleaner and more efficient one-pot multistep cascades in green solvents (*i.e.*, water)[2] are emerging as exciting alternatives to classical step-by-step processes, which also minimise chemical waste, save time, and simplify practical aspects,[3] being enantioselective one-pot processes one of the most recalcitrant challenges to solve. In particular, the combination of metal- and bio-catalysts working hand in hand[4] in water has recently attracted the attention of several research groups, being able to assemble a Cu-catalysed 'click' reaction,[5] the Wacker oxidation[6] or Suzuki and Heck cross-coupling reactions with bioreductions[7] or olefin metathesis followed by enzymatic hydrolysis or hydroxylation.[8] However, all these examples presented an important and common pitfall, the coexistence of both catalysts, which leads to: (i) reciprocal poisoning, (ii) degradation due to the presence of additives, cofactors or co-solvents, and (iii) incompatibility of the different reaction conditions for both transformations.[9] To tackle these hurdles, these cascades were performed in a sequential mode or, alternatively, the catalysts were site-isolated by compartmentalisation or encapsulation techniques.

Recently, we reported the first example of coupling of the ruthenium-catalysed isomerisation of allylic alcohols with an ω-transaminase (ω-TA).[10] Although the resulting amines were isolated in very high yields and enantiomeric excesses, the process had to be accomplished in a sequential fashion due to the inactivation of the metal catalyst by both ω-TA and pyridoxal-5'-phosphate (cofactor). In order to design a genuine chemoenzymatic one-pot concurrent process (which formally involves the asymmetric reduction of racemic allylic alcohols, see Scheme 1),[11-13] we decided to employ ketoreductases (KREDs) as biocatalyst,[14] which are able to work even under very low cofactor concentrations ($NADP^+$ or NADPH).[15]

Scheme 1. Ru-catalysed allylic alcohol isomerisation combined with an enantioselective enzymatic reduction in a one-pot process.



First, we tested the catalytic activity of the bis(allyl)-ruthenium(IV) complexes **1-3** in the redox isomerisation of *α*-vinylbenzyl alcohol (**4a**) in the medium required by KREDs, that is, a phosphate buffer (125 mM, pH 7.0) containing 1.25 mM magnesium sulfate (see Scheme 2).[16] Under these conditions, complexes **2** and **3** achieved the complete isomerisation of **4a** in just 2.5 h at 50 ºC, while complex **1** required a longer reaction time (7.5 h). Next, we checked if the most active catalysts (complexes **2-3**) worked upon addition of propan-2-ol (*i*-PrOH), a requirement imposed in KRED-mediated reductions for recycling the cofactor and drive the equilibrium. Complex **2** retained indeed its catalytic activity (99% in 2.5 h) and chemoselectivity, as concomitant reduction of ketone **4b** (*via* ruthenium-catalysed transfer hydrogenation) was not observed.[17] In contrast, complex **3** needed a longer reaction time (5 h) to achieve quantitative conversion (99%).

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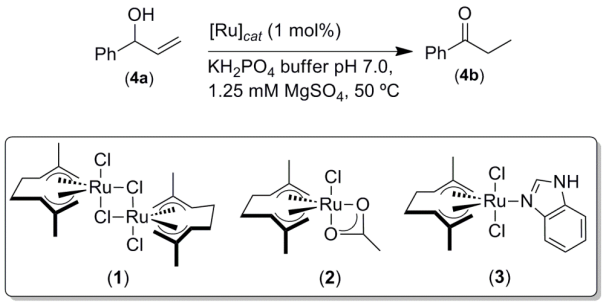
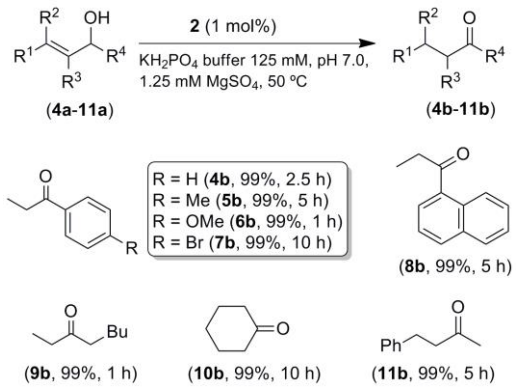
Thus, complex **2** was selected as the candidate catalyst for the chemoenzymatic system.

Scheme 2. Optimisation of the isomerisation of α-vinylbenzyl alcohol (**4a**, 1 mmol) catalysed by Ru(IV) complexes **1-3** in the phosphate buffer of KREDs.



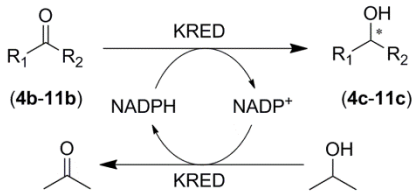
In our previous report,[10] the inhibition caused by ω-TAs on the ruthenium complex prevented us from achieving a concurrent process and a sequential procedure had to be developed. Consequently, the compatibility of complex **2** with the NADPH-dependent KREDs was investigated by performing the isomerisation in the presence of both metal and biocatalyst.[18] We were delighted to find that the impact of the biocatalyst on complex **2** was negligible, as similar conversion (99%) and reaction time (2.5 h) were observed upon addition of KREDs. Similarly, no inhibition (99% of **4b** after 2.5 h) was observed in the presence of NADPH (10 mM), the cofactor needed for the KRED enzyme activity. In order to have a better understanding of the role of cofactor inhibition, we also tested the reaction in the presence of $NADP^+$ (1 mM), since it would be present during the recycling of NADPH mediated by *i*-PrOH. Under these conditions, the isomerisation of **4a** reached only a 70% conversion after 24 h, probably due to poisoning of metal complex **2**. Based on these results, we evaluated Ru-complex **2** for the selective isomerisation of a variety of aryl and aliphatic allylic alcohols under KREDs-compatible reaction conditions (see Scheme 3). Particularly, 1-(*p*-methoxyphenyl)prop-2-en-1-ol (**6a**) and the aliphatic 1-octen-3-ol (**9a**) were completely converted in only one hour. However, cyclohexen-1-ol (**10a**) and 4-phenylbut-3-en-2-ol (**11a**), requiered increased catalyst loading (10 mol% for **10a**; 5 mol% for **11a**) and reaction time (10 h for **10a**; 5 h for **11a**) to reach complete conversion, as typically observed in previous studies.[16a]

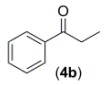
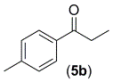
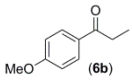
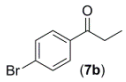


Scheme 3. Isomerisation of the allylic alcohols **4a-11a** (1 mmol) into ketones **4b-11b** catalysed by the Ru(IV) complex **2** in a phosphate buffer 125 mM pH 7.0 (1.25 mM $MgSO_4$) at 50 ºC.

Encouraged by these initial findings, which suggest the potential of complex **2** in the isomerisation of allylic alcohols under the reaction conditions required for the biocatalytic step of the cascade, we then assessed the scope of the reduction of the isolated ketones **4b-11b** by using the ketoreductases from the Codex® KRED Screening Kit.[19] Table 1 shows selected results of this screening.

Table 1. KRED-catalysed bioreduction of ketones **4b-11b**.[a]



Entry	Substrate	Product	KRED	*c* (%)[b]	*ee* (%)[c]
1	 (4b)	**4c**	P1-A04	>99	>99 (*R*)
2			P3-B03	>99	97 (*S*)
3	 (5b)	**5c**	P1-A04	>99	98 (*R*)
4			P3-G09	>99	99 (*S*)
5	 (6b)	**6c**	P1-A04	>99	>99 (*R*)
6			P3-H12	>99	98 (*S*)
7	 (7b)	**7c**	P1-A04	>99	99 (*R*)
8			P3-H12	>99	99 (*S*)
9	(8b)	**8c**	P1-B02	>99	98 (*R*)
10			P2-D11	>99	97 (*S*)
11	(9b)	**9c**	P1-A04	>99	>99 (*R*)
12			P3-G09	>99	>99 (*S*)
13	(10b)	**10c**	P1-A04	>99	-
14	(11b)	**11c**	P1-H10	>99	93 (*R*)

[a] Reaction conditions: Substrate (20 mM) in KH_2PO_4 buffer 125 mM (1.25 mM $MgSO_4$, 1 mM NADPH) pH 7.0 (900 μL), KRED (2 mg), *i*-PrOH (190 μL), for 24 h at 250 rpm and 30 ºC. [b] Measured by GC or HPLC. [c] Measured by chiral GC or HPLC.

Under the standard conditions for screening, the majority of KREDs were very active and reached complete conversion after 24 h with ketones substituted with both electron-withdrawing or electron-donating substituents on the aryl moiety. Regarding enantioselectivity, results depended on the biocatalyst and to a lesser degree on the ketone substrate. Nevertheless, it was possible to identify KREDs which afforded either enantiomer of chiral alcohols **4c-9c** with *ee* in the range 97- >99%. In the case of **11c**, an immediate precursor for antihypertensive agents such as bufeniode and labetalol,[20] the bioreduction was challenging, leading to enantiomeric excesses up to 93% for the (*R*)-enantiomer. Next, we evaluated the possibility of enzyme inhibition by the Ru-complex and, gratifyingly, no effect was observed in either conversion or selectivity upon addition of a significant amount of complex **2** (20 mol%), reinforcing the suitability of this combination. On the other hand, the concentration was increased from 20 mM to 200 mM, to resemble that used in the metal-catalysed step. Under these

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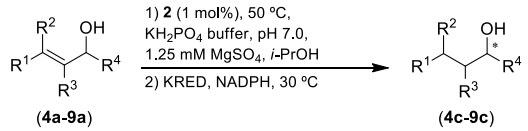
conditions, the enzymatic step worked again very efficiently, solving one of the key drawbacks to carry out chemical and biocatalytic reactions simultaneously, namely finding a compatible concentration. With both steps optimised independently and overpassing preliminary issues such as reaction medium, concentration or compatibility of catalysts, we carried out the one-pot process in a sequential mode using **4a** (200 mM) as a model substrate. Once the initial isomerisation of **4a** was completed at 50 ºC (as judged by GC), the selected KRED and NADPH were added and the reaction mixture stirred for 24 h at 30 ºC (Table 2, entry 1). Thus, the saturated alcohol **4c** was obtained with 95% of overall conversion and >99% *ee*. Under an identical protocol, some selected allylic alcohols of the series (**5a**-**9a**) gave rise to the corresponding saturated alcohols with very high enantiomeric excess (98- >99%, Table 2, entries 2-6). Moreover, along with being an operationally simple methodology, the excellent levels of conversion led to the products with high yield. At this point, we should mention that this methodology allows us to produce enantiopure alcohols starting from racemic substrates (*i.e.* without using prochiral reagents). Once an efficient stepwise process was validated, we focused on developing a true cascade where the metal catalyst and the enzyme coexisted from the beginning. Bearing in mind the observed absence of inhibition between KREDs and complex **2**, we selected for an initial experimental setup **4a** as starting allylic alcohol and KRED-P1-A04 as the biocatalyst. The substrate concentration was fixed to 200 mM with 1 mol% of complex **2** and 100% w/w of enzyme powder/substrate in the previous buffer. Likewise, the temperature was adjusted to 30 ºC to preserve the stability of the enzyme. Under these conditions, the catalytic system worked poorly and the allylic alcohol was recovered as the major product (Table 3, entry 1).

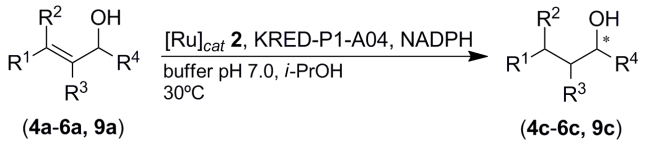
Table 2. Chemoenzymatic one-pot process in a sequential mode.[a]



Entry	Substrate	Product	KRED	Conv. (%)[b]	Yield (%)[c]	*ee* (%)[d]
1	**4a**	**4c**	P1-A04	95	86	>99 (*R*)
2	**5a**	**5c**	P3-G09	97	90	99 (*S*)
3	**6a**	**6c**	P1-B05	92	85	>99 (*R*)
4	**7a**	**7c**	P3-H12	95	88	99 (*S*)
5	**8a**	**8c**	P1-B10	94	90	98 (*R*)
6	**9a**	**9c**	P1-A04	96	90	>99 (*R*)

[a] Reaction conditions: **4a-9a** (200 mM) under Ar, KH_2PO_4 buffer 125 mM (1.25 mM $MgSO_4$) pH 7.0, *i*-PrOH (15% v/v), 1 mol% of **2** and 50 ºC (buffer solution previously degassed with Ar). Once completed the isomerisation (GC), addition of KRED (100% w/w) and NADPH (1 mM) and stirring at 30 ºC. [b] Conversion by GC/HPLC. [c] Isolated yield. [d] Measured by chiral GC or HPLC.

Table 3. Concurrent (one-pot cascade) metal catalysed isomerisation-enzymatic reduction combining ruthenium catalyst **2** and KRED-P1-A04.[a]



Entry	Allylic Alcohol	Substrate [mM]	**2** (mol%)	% w/w (KRED)	NADPH (mM)	*i*-PrOH (% v/v)	T (ºC)	Product ratio (%)[b] Allylic alcohol	Ketone intermediate	Reduced alcohol	Isolated yield	*ee* (%)[c]	Absolute config.
1	**4a**	200	1	100	1	15	30	90	5	5	-	-	-
2	**4a**	200	5	100	1	15	30	0	15	85	-	>99	(*R*)
3	**4a**	200	5	50	1	15	30	0	60	40	-	>99	(*R*)
4	**4a**	200	5	100	1	30	30	4	94	1	-	-	-
5	**4a**	200	5	100	1	15	45	0	17	83	-	>99	(*R*)
6	**4a**	200	5	100	10	15	30	0	15	85	-	>99	(*R*)
7	**4a**	200	5	100	-	15	30	0	15	85	80	>99	(*R*)
8	**6a**	200	5	100	-	15	30	0	6	94	86	>99	(*R*)
9	**9a**	200	5	100	-	15	30	0	9	91	85	>99	(*R*)
10	**5a**	200	5	100	-	15	30	0	30	70	60	>99	(*R*)

[a] Reaction conditions: Substrate (200 mM) under Ar atmosphere in KH_2PO_4 buffer 125 mM (1.25 mM $MgSO_4$) pH 7.0 (buffer solution previously degassed with Ar) and stirring for 24 h. [b] Measured by HPLC except for **9a** (GC).[c] Measured by chiral HPLC except for **9a** (GC).

In the following attempt, the metal catalyst loading was increased to 5 mol%, **4a** being completely isomerised and the saturated alcohol **4c** obtained with >99% *ee* as the major product (85%, entry 2).[21] Remarkably, the absence of the starting alcohol in the resulting mixture enabled an easy purification of **4c**. Next, a decrease in the biocatalyst loading to 50% w/w changed the outcome dramatically, with a significant accumulation of intermediate ketone **4b** (entry 3). Further optimisation included screening the amount of hydride donor (*i*-PrOH), temperature and higher cofactor levels (NADPH). First of all, the increase of *i*-PrOH concentration to 30% v/v turned out to be critical for the bioreduction and the cascade halted in the ketone intermediate (entry 4). Regarding the temperature, an increase to 45 ºC did not impact the outcome of the process (entry 5). On the other hand, in an effort to drive the bioreduction of the ketone to completion, the amount of NADPH was increased to 10 mM (entry 6). However, the overall conversion was again anchored in the previous 85%. Accordingly, we run an identical reaction in the absence of NADPH and, surprisingly, the process worked just as well as in presence of the cofactor (entry 7).[15] A plausible explanation would be that the enzyme powder may contain cofactor from the manufacturing process, according to literature from the supplier of KREDs.[22,23] On the basis of these findings, we hypothesized that the reason for not reaching quantitative conversion in the concurrent approach lies in

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the stability of the biocatalyst. Hence, the KRED would be rapidly deactivated in the reaction medium, leading to a fixed conversion of 85%. In the sequential approach, on the contrary, accumulation of ketone prior to addition of biocatalyst would enable complete reduction before enzyme inactivation. In order to demonstrate these assumptions, we studied in more detail the kinetics of the reactions. First, the allylic isomerisation of **4a** into **4b** was assayed under the conditions of the concurrent process, namely 5 mol% catalyst loading at 30 ºC (Table 3, entry 2). Thus, these milder conditions demanded a longer reaction time (4 h) for complete conversion, despite using 5 mol% of complex **2** (see Figure S1 in the ESI). On the other hand, the bioreduction of ketone **4b** catalysed by KRED-P1-A04 (Table 1, entry 1) was monitored periodically, **4b** being almost completely reduced in just 30 min (90%) and then taking 20 h longer for consuming the substrate (see Figure S2 in the ESI). Hence, the reaction slowed down drastically after 30 min, perhaps due to the lack of robustness of the biocatalyst. Alternatively, this enzymatic reaction was also performed but incubating 3 h the KRED in the buffer prior to the addition of **4b**. Now, the bioreduction reached 85% conversion very quickly, although it did not evolve further. Indeed, this outcome was identical to that achieved in the concurrent process (Table 3, entry 2), in which **4b** is being gradually formed by the action of complex **2** while the enzyme decomposes concomitantly. Finally, the distribution of products of the concurrent process (conversion of **4a** into **4c**) was checked over time (Table 3, entry 2), showing as the overall transformation occurs mainly in the first 4 h, period during which the enzyme remains highly active (Figure 1). Collectively, these facts indicate that the faster the isomerisation takes place, the higher the overall yield of the cascade. Bearing this in mind, the concurrent approach was extended to allylic alcohols **6a** and **9a** with the same catalytic system (complex **2** and KRED-P1-A04, without cofactor). Pleasantly, the outcome agreed our expectations, and furnished enantiopure **6c** and **9c** in 94% and 91% conversion (free of unsaturated alcohol), respectively (entries 8-9). On the contrary, the slower isomerisation of **5a** consequently brought a moderate overall conversion of **5c** (70%, entry 10).

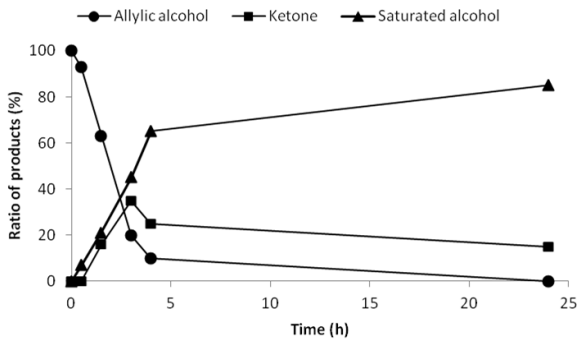

Figure 1. Product distribution as a function of time for the conversion of **4a** into **4c** concurrently catalysed by complex **2** and KRED-P1-A04 (Table 3, entry 2).

In summary, we have developed a chemoenzymatic one-pot process in aqueous medium, in both sequential and concurrent fashion, which provides enantiomerically pure alcohols from racemic allylic alcohols by combining a Ru(IV)-catalysed isomerisation with a bioreduction promoted by KREDs. The sequential process was highly efficient and operationally simple, the only adjustment before KRED and cofactor addition being a slight decrease on the temperature. Regarding the concurrent process, both the metal- and biocatalyst were able to coexist and work simultaneously from the beginning, furnishing the final products with yields close to 85%. Clearly, this first example of a genuine concurrent metal and biocatalysed reaction in water is an important contribution to the field of cascade processes, and opens up a new frontier for its practical application, as it does not require the isolation or compartmentalisation of the catalysts.

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[18] A parametric study of the catalytic activity of complexes **1-3** with **4a** under different catalytic conditions is shown in Table S1 in the ESI.

[19] The Codex® KRED Screening Kit (Codexis) contains 24 ketoreketoreductases. For the full panel of enzymatic results, see ESI.

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[23] Three different batches of KRED-P1-A04, were tested, the results being on the range of 80-85% of saturated alcohol **4c**.

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Entry for the Table of Contents (Please choose one layout)

Layout 2:

Cascade Synthesis

Nicolas Ríos-Lombardía, Cristian Vidal, Elisa Liardo, Francisco Morís, Joaquín García-Álvarez,* and Javier González-Sabín*

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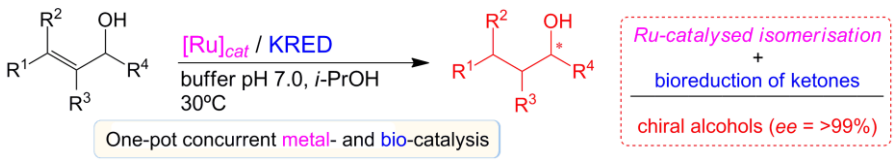

From a sequential to a true one-pot cascade reaction in aqueous medium: Concurrent ruthenium-catalysed allylic alcohol isomerisation-asymmetric bioreduction

Metals and enzymes play together from the beginning: A new concurrent one-pot metal- and biocatalysed protocol for the enantioselective synthesis of alcohols in water is reported, establishing a new bridge between metal catalysed and enzyme mediated enantioselective organic reactions.