Enzyme Catalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201601840
Internationale Ausgabe: DOI: 10.1002/anie.201601840

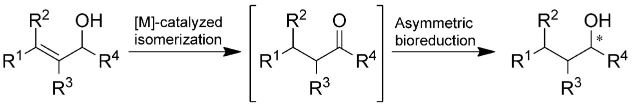
From a Sequential to a Concurrent Reaction in Aqueous Medium: Ruthenium-Catalyzed Allylic Alcohol Isomerization and Asymmetric Bioreduction

Nicolás Ríos-Lombardía[+], *Cristian Vidal*[+], *Elisa Liardo, Francisco Morís, Joaquín García-Álvarez,* and Javier González-Sabín**

Abstract: *The ruthenium-catalyzed redox isomerization 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 with excellent conversions and enantioselectivities, under mild reaction conditions, employing commercially and readily available catalytic systems, and without external coenzymes or cofactors. Optimization resulted in a multistep approach and a genuine cascade reaction where the metal catalyst and biocatalyst coexist from the beginning.*

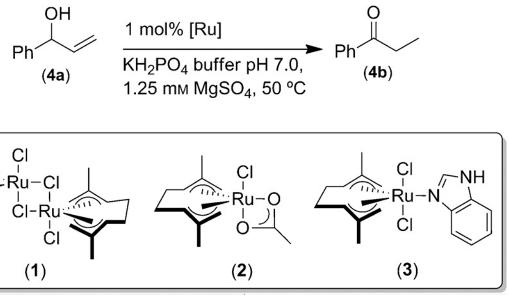
At the dawn of the twenty-first century a new challenge arose, challenge to strive towards chemical processes which are not only aimed at productivity but also at ecological efficiency and environmental sustainability.[1] In this sense, new, cleaner, and more-efficient one-pot multistep sequences in green solvents (i.e., water)[2] are emerging as exciting alternatives to classical step-by-step processes, and they minimize chemical waste, save time, and simplify practical aspects.[3] The enantioselective one-pot processes is one of the most difficult challenges to solve. In particular, the combination of metal catalysts and biocatalysts working hand in hand[4] in water has recently attracted the attention of several research groups, some examples being a copper-catalyzed "click" reaction,[5] either the Wacker oxidation[6] or Suzuki and Heck cross-coupling reactions with bioreductions,[7] and olefin metathesis followed by either enzymatic hydrolysis or hydroxylation.[8] However, all these examples presented an important and common pitfall, the coexistence of both catalysts leading to: 1) reciprocal poisoning, 2) degradation because of the presence of additives, cofactors, or cosolvents, and 3) incompatibility of the different reaction conditions for both transformations.[9] To tackle these hurdles, these reaction sequences were performed in a sequential mode or, alternatively, the catalysts were site-isolated by compartmentalization or encapsulation techniques.

Recently, we reported the first example of coupling of the ruthenium-catalyzed isomerization 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 because of the inactivation of the metal catalyst by both ω-TA and pyridoxal-5′-phosphate (cofactor). To design a genuine concurrent chemoenzymatic one-pot process (which formally involves the asymmetric reduction of racemic allylic alcohols; Scheme 1),[11–13] we decided to employ ketoreductases (KREDs) as biocatalysts,[14] which are able to work even under very low cofactor concentrations ($NADP^+$ or NADPH).[15]



Scheme 1. Ruthenium-catalyzed allylic alcohol isomerization 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 isomerization 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 (Scheme 2).[16] Under these reaction conditions, **2** and **3** achieved the complete



Scheme 2. Optimization of the isomerization of α-vinylbenzyl alcohol (**4a**; 1 mmol) catalyzed by the ruthenium(IV) complexes **1**–**3** in a phosphate buffer of KREDs.

---

[*] Dr. N. Ríos-Lombardía,[+] E. Liardo, Dr. F. Morís, Dr. J. González-Sabín
EntreChem SL, Edificio Científico Tecnológico
Campus El Cristo, 33006 Oviedo (Spain)
E-mail: jgsabin@entrechem.com
Dr. C. Vidal,[+] Dr. J. García-Álvarez
Laboratorio de Compuestos OrganometálicosyCatálisis (Unidad Asociada al CSIC), Centro de Innovación en Química Avanzada (ORFEO-CINQA), Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo (Spain)
E-mail: garciajoaquin@uniovi.es

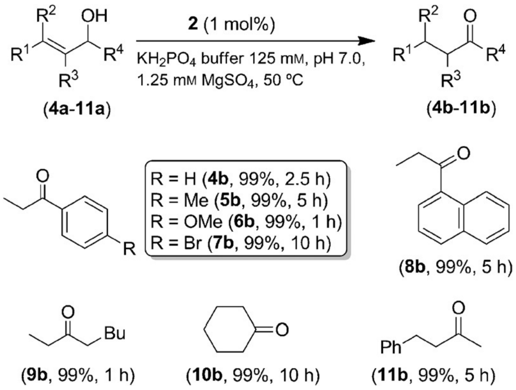
[+] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201601840.

isomerization of **4a** in just 2.5 hours at 50 °C, while **1** required a longer reaction time (7.5 h). Next, we checked if the most active catalysts (**2** and **3**) worked upon addition of propan-2-ol (*i*PrOH), a requirement imposed in KRED-mediated reductions for recycling the cofactor and driving the equilibrium. The complex **2** retained its catalytic activity (99 % in 2.5 h) and chemoselectivity, as concomitant reduction **4b** (via ruthenium-catalyzed transfer hydrogenation) was not observed.[17] In contrast, **3** needed a longer reaction time (5 h) to achieve quantitative conversion (99 %). Thus, **2** was selected as the candidate catalyst for the chemoenzymatic system.

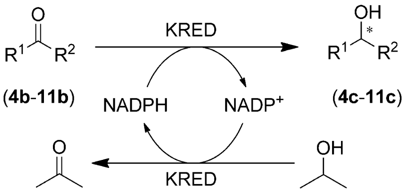
In our previous report,[10] the inhibition caused by ω-TAs on the ruthenium complex prevented us from achieving a concurrent process and a sequential procedure had to be developed. Consequently, the compatibility of **2** with the NADPH-dependent KREDs was investigated by performing the isomerization in the presence of both metal catalyst and biocatalyst.[18] We were delighted to find that the impact of the biocatalyst on **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. 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 reaction conditions, the isomerization of **4a** reached only a 70 % conversion after 24 hours, probably because of poisoning of **2**. Based on these results, we evaluated **2** for the selective isomerization of a variety of aryl and aliphatic allylic alcohols under KREDs-compatible reaction conditions (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**), required 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]

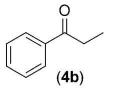
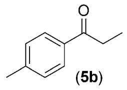
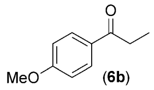
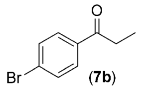
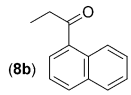
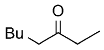
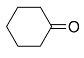
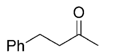
Encouraged by these initial findings, which suggest the potential of **2** in the isomerization of allylic alcohols under the reaction conditions required for the biocatalytic step of the cascade, we then assessed the scope of the reduction of the isolated ketones **4b**–**11b** by using the ketoreductases from the Codex® KRED Screening Kit.[19] Table 1 shows selected results of this screening. Under the standard reaction conditions for screening, the majority of KREDs were very active and reached complete conversion after 24 hours using ketones having either 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 both enantiomers of **4c**–**9c** with *ee* values in the 97–> 99 % range. In the case of **11c**, an immediate precursor for antihypertensive agents such as bufeniode and labetalol,[20] the bioreduction was challenging, thus leading to enantiomeric excesses up to 93 % for the *R* enantiomer. Next, we evaluated the possibility of enzyme



Scheme 3. Isomerization of the allylic alcohols **4a**–**11a** (1 mmol) into ketones **4b**–**11b** catalyzed by the **2** in a phosphate buffer 125 mM pH 7.0 (1.25 mM $MgSO_4$) at 50 °C.

Table 1: KRED-catalyzed bioreduction of **4b-11b**.[a]



Entry	Substrate	Product	KRED	Conv. [%][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*)

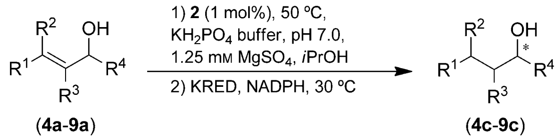
[a] Reaction conditions: Substrate (20 mM) in KH_2PO_4 buffer 125 mM (1.25 mM $MgSO_4$, 1 mM NADPH) pH 7.0 (900 μL), KRED (2 mg), *i*PrOH (190 μL), for 24 h at 250 rpm and 30 °C. [b] Measured by GC or HPLC. [c] Measured by chiral-phase GC or HPLC. Absolute configurations were determined by comparing the corresponding optical rotations with the values reported in the literature (see SI).

inhibition by the ruthenium complex and, gratifyingly, no effect was observed in either conversion or selectivity upon addition of a significant amount of **2** (20 mol %), thus reinforcing the suitability of this combination. Likewise, the concentration was increased from 20 to 200 mm, to resemble that used in the metal-catalyzed step. Under these reaction conditions, the enzymatic step worked very efficiently again, thus solving one of the key drawbacks, namely finding a compatible concentration, to carrying out chemical and biocatalytic reactions simultaneously.

With both steps optimized independently and addressing preliminary issues such as reaction medium, concentration, or compatibility of catalysts, we carried out the one-pot process in a sequential fashion using **4a** (200 mm) as a model substrate. Once the initial isomerization of **4a** was complete at 50 °C (as judged by GC), the selected KRED and NADPH were added and the reaction mixture stirred for 24 hours at 30 °C (Table 2, entry 1). Thus, the saturated alcohol **4c** was obtained with 95 % overall conversion and greater than 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 (entries 2–6). Moreover, along with being an operationally simple methodology, the excellent levels of conversion led to the products in 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 **2**, we selected **4a** as a starting allylic alcohol and KRED-P1-A04 as the biocatalyst for an initial experimental setup. The substrate concentration was fixed to 200 mm with 1 mol % of **2** and 100 % w/w of enzyme powder/substrate in the previous buffer. Likewise, the temperature was adjusted to 30 °C to preserve the stability of the enzyme. Under these reaction conditions, the catalytic system worked poorly and the allylic alcohol was recovered as the major product (Table 3, entry 1). In the following attempt, the metal catalyst loading was increased to 5 mol %, and **4a** was completely isomerized and the saturated alcohol **4c** obtained with greater than 99 % *ee* as the major product (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 the intermediate ketone **4b** (entry 3). Further optimization 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

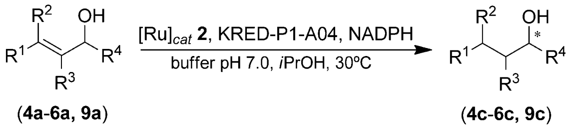
Table 2: Chemoenzymatic one-pot process in a sequential mode.[a]



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 °C (buffer solution previously degassed with Ar). Once the isomerization was complete (GC), KRED (100 % w/w) and NADPH (1 mm) were added and the reaction mixture stirred at 30 °C. [b] Determines by GC/HPLC. [c] Yield of isolated product. [d] Measured by chiral-phase GC or HPLC.

Table 3: Concurrent (one-pot cascade) metal-catalyzed isomerization/enzymatic reduction by combining **2** and KRED-P1-A04.[a]



Entry	Allylic alcohol	**2** (mol %)	% w/w (KRED)	NADPH [mm]	*i*PrOH [% v/v]	*T* [°C]	Product ratio [%][b] Allylic alcohol	 Ketone intermediate	 Reduced alcohol	Yield [%][c]	*ee* [%][d]	Absolute config.
1	**4a**	1	100	1	15	30	90	5	5	–	–	–
2	**4a**	5	100	1	15	30	0	15	85	–	> 99	*R*
3	**4a**	5	50	1	15	30	0	60	40	–	> 99	*R*
4	**4a**	5	100	1	30	30	4	94	1	–	–	–
5	**4a**	5	100	1	15	45	0	17	83	–	> 99	*R*
6	**4a**	5	100	10	15	30	0	15	85	–	> 99	*R*
7	**4a**	5	100	–	15	30	0	15	85	80	> 99	*R*
8	**6a**	5	100	–	15	30	0	6	94	86	> 99	*R*
9	**9a**	5	100	–	15	30	0	9	91	85	> 99	*R*
10	**5a**	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] Yield of isolated product. [d] Measured by chiral-phase HPLC except for **9a** (GC).

bioreduction and the cascade halted at the ketone intermediate (entry 4). Regarding the temperature, an increase to 45 °C did not impact the outcome of the process (entry 5). Moreover, 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 at the previous 85 %. Accordingly, we ran 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 the stability of the biocatalyst. Hence, the KRED would be rapidly deactivated in the reaction medium, thus 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. To demonstrate these assumptions, we studied the kinetics of the reactions in more detail. First, the allylic isomerization of **4a** into **4b** was assayed under the reaction conditions of the concurrent process, namely 5 mol % catalyst loading at 30 °C (entry 2). Thus, these milder reaction conditions demanded a longer reaction time (4 h) for complete conversion, despite using 5 mol % of **2** (see Figure S1 in the Supporting Information). Likewise, the bioreduction of **4b**, catalyzed by KRED-P1-A04 (Table 1, entry 1), was monitored periodically and **4b** was almost completely reduced in just 30 minutes (90 %), then taking more 20 hours for consumption of the substrate (see Figure S2). Hence, the reaction slowed down drastically after 30 minutes, perhaps because of the lack of robustness of the biocatalyst. Alternatively, this enzymatic reaction was also performed but the KRED in the buffer was incubated for 3 hours 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 gradually formed by the action of **2** while the enzyme decomposed. Finally, the distribution of products of the concurrent process (conversion of **4a** into **4c**) was checked over time (entry 2), thus showing that the overall transformation occurs mainly in the first 4 hours, a period during which the enzyme remains highly active (Figure 1). Collectively, these facts indicate that the faster the isomerization takes place, the higher the overall yield of the cascade. Bearing this information in mind, the concurrent approach was extended to the allylic alcohols **6a** and **9a** with the same catalytic system (**2** and KRED-P1-A04, without cofactor). Pleasantly, the outcome agreed with our expectations, and furnished enantiopure **6c** and **9c** in 94 and 91 % conversion (free of unsaturated alcohol), respectively (entries 8 and 9). On the contrary, the slower isomerization of **5a** consequently brought a moderate overall conversion of **5c** (entry 10).

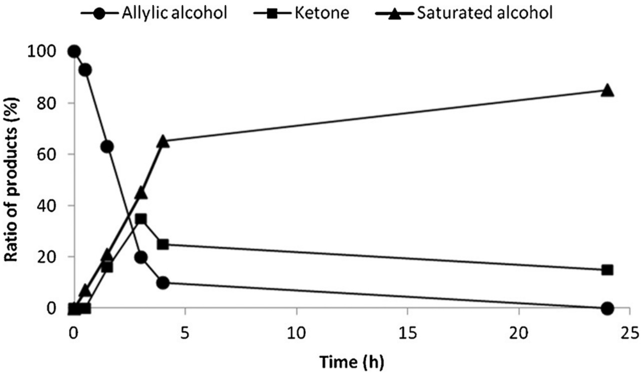


Figure 1. Product distribution as a function of time for the conversion of **4a** into **4c** concurrently catalyzed by **2** and KRED-P1-A04 (see Table 3, entry 2 for reaction conditions).

In summary, we have developed a chemoenzymatic one-pot process in aqueous medium, in both sequential and concurrent fashion, and it provides enantiomerically pure alcohols from racemic allylic alcohols by combining a ruthenium(IV)-catalyzed isomerization 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 catalyst and biocatalyst were able to coexist and work simultaneously from the beginning, thus furnishing the final products with yields close to 85 %. Clearly, this first example of a genuine concurrent metal-catalyzed and biocatalyzed 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 compartmentalization of the catalysts.

Acknowledgments

We are indebted to the MINECO of Spain (RYC-2011-08451 and CTQ2013-40591-P), the Gobierno del Principado de Asturias (Project GRUPIN14-006), and the COST Action SIPs-CM1302 for financial support. J.G.-A. thanks the MINECO and the European Social Fund for a "Ramón y Cajal" contract. E.L. acknowledges funding from the European Union's Horizon 2020 MSCA ITN-EID program (grant agreement No 634200). N.R.-L. acknowledges MINECO for funding under Torres-Quevedo program (PTQ-12-05 407).

Keywords: alcohols · chirality · enzyme catalysis · isomerization · transition metals

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 8691–8695
Angew. Chem. **2016**, *128*, 8833–8837

---

[1] P. T. Anastas, J. C. Warner, *Green Chemistry Theory and Practice*, Oxford University Press, Oxford, **1998**.

[2] a) U. M. Lindström, *Organic Reactions in Water: Principles, Strategies and Applications*, Blackwell Publishing, Oxford, **2007**; b) M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415.

[3] a) S. F. Mayer, W. Kroutil, K. Faber, *Chem. Soc. Rev.* **2001**, *30*, 332; b) A. Bruggink, R. Schoevaart, T. Kieboom, *Org. Process Res. Dev.* **2003**, *7*, 622; c) J. M. Lee, Y. Na, H. Han, S. Chang,

Chem. Soc. Rev. **2004**, *33*, 302; d) Y. Hayashi, *Chem. Sci.* **2016**, *7*, 866.

[4] For combinations of metal catalyst and organocatalyst, see: A. Quintard, A. Alexakis, C. Mazet, *Angew. Chem. Int. Ed.* **2011**, *50*, 2354; *Angew. Chem.* **2011**, *123*, 2402; for a combination of an organocatalyst with an enzyme, see: K. Baer, M. Kraußer, E. Burda, W. Hummel, A. Berkessel, H. Gröger, *Angew. Chem. Int. Ed.* **2009**, *48*, 9355; *Angew. Chem.* **2009**, *121*, 9519.

[5] A. Cuetos, F. R. Bisogno, I. Lavandera, V. Gotor, *Chem. Commun.* **2013**, *49*, 2625.

[6] H. Sato, W. Hummel, H. Gröger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4488; *Angew. Chem.* **2015**, *127*, 4570.

[7] a) E. Burda, W. Hummel, H. Gröger, *Angew. Chem. Int. Ed.* **2008**, *47*, 9551; *Angew. Chem.* **2008**, *120*, 9693; b) A. Boffi, S. Cacchi, P. Ceci, R. Cirilli, G. Fabrizi, A. Prastaro, S. Niembro, A. Shafir, A. Vallribera, *ChemCatChem* **2011**, *3*, 347.

[8] a) K. Tenbrink, M. Sebler, J. Schatz, H. Gröger, *Adv. Synth. Catal.* **2011**, *353*, 2363; b) C. A. Denard, H. Huang, M. J. Bartlett, L. Lu, Y. Tan, H. Zhao, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2014**, *53*, 465; *Angew. Chem.* **2014**, *126*, 475.

[9] The only exception would be the dynamic kinetic resolutions (DKRs) combining a racemizing metal catalyst with a biotransformation, although almost exclusively in organic solvent: a) S. Agrawal, E. Martínez-Castro, R. Marcos, B. Martín-Matute, *Org. Lett.* **2014**, *16*, 2256; b) O. Verho, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2015**, *137*, 3996. Additionally, Kroutil and coworkers combined an iridium-catalyzed oxidation with a bioreduction in aqueous medium, but it led to disappointing enantioselectivities: F. G. Mutti, A. Orthaber, J. H. Schrittwieser, J. G. de Vries, R. Pietschnig, W. Kroutil, *Chem. Commun.* **2010**, *46*, 8046.

[10] N. Ríos-Lombardía, C. Vidal, M. Cocina, F. Morís, J. García-Álvarez, J. González-Sabín, *Chem. Commun.* **2015**, *51*, 10937.

[11] Asymmetric reduction of allylic alcohols has proven to be a challenging process: H. Matsuda, S. Ando, T. Morikawa, S. Kataoka, M. Yoshikawa, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1949.

[12] The ruthenium-catalyzed isomerization/asymmetric transfer hydrogenation of allylic alcohols in dry organic solvents and using high temperatures has been reported: a) R. Wu, M. G. Beauchamps, J. M. Laquidara, J. R. Sowa, Jr., *Angew. Chem. Int. Ed.* **2012**, *51*, 2106; *Angew. Chem.* **2012**, *124*, 2148; b) T. Slagbrand, H. Lundberg, H. Adolfsson, *Chem. Eur. J.* **2014**, *20*, 16102.

[13] For a related nonchiral chemoenzymatic process, see: Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100.

[14] S. Gargiulo, D. J. Opperman, U. Hanefeld, I. W. C. E. Arends, F. Hollmann, *Chem. Commun.* **2012**, *48*, 6630.

[15] T. Knaus, C. E. Paul, C. W. Levy, S. De Vries, F. G. Mutti, F. Hollmann, N. S. Scrutton, *J. Am. Chem. Soc.* **2016**, *138*, 1033.

[16] a) J. García-Álvarez, J. Gimeno, F. J. Suárez, *Organometallics* **2011**, *30*, 2893. For recent examples of redox isomerization/hydrogenation or halogenation of allylic alcohols, see: b) L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem. Int. Ed.* **2009**, *48*, 5143; *Angew. Chem.* **2009**, *121*, 5245; c) N. Ahlsten, A. Bermejo Gómez, B. Martín-Matute, *Angew. Chem. Int. Ed.* **2013**, *52*, 6273; *Angew. Chem.* **2013**, *125*, 6393; d) A. Bermejo Gómez, E. Erbing, M. Batuecas, A. Vázquez-Romero, B. Martín-Matute, *Chem. Eur. J.* **2014**, *20*, 10703.

[17] a) V. Cadierno, P. Crochet, J. Francos, S. E. García-Garrido, J. Gimeno, N. Nebra, *Green Chem.* **2009**, *11*, 1992; b) A. E. Díaz-Álvarez, P. Crochet, V. Cadierno, *Catal. Commun.* **2011**, *13*, 91; c) V. Bizet, X. Pannecoucke, J.-L. Renaud, D. Caharda, *Adv. Synth. Catal.* **2013**, *355*, 1394.

[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 ketoreductases. For the full panel of enzymatic results, see the Supporting Information.

[20] a) W. Stampfer, B. Kosjek, K. Faber, W. Kroutil, *J. Org. Chem.* **2003**, *68*, 402; b) J. A. Johnson, W. S. Akers, V. L. Herring, M. S. Wolf, J. M. Sullivan, *Pharmacotherapy* **2000**, *20*, 622.

[21] This fact reveals inhibition by KREDs and NADPH towards **2**, and is in contrast to the previous experiments (Table S1, entries 6 and 7).

[22] N. K. Modukuru, J. Sukumaran, S. J. Collier, A. S. Chan, A. Gohel, G. W. Huisman, R. Keledjian, K. Narayanaswamy, S. J. Novick, S. M. Palanivel, D. Smith, Z. Wei, B. Wong, W. L. Yeo, D. A. Entwistle, *Org. Process Res. Dev.* **2014**, *18*, 810.

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

Received: February 22, 2016