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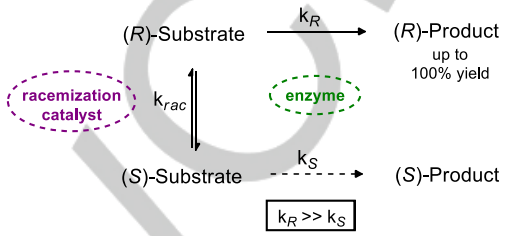
FULL PAPER

Lipase-oxovanadium heterogeneous catalysis system: a robust protocol for the dynamic kinetic resolution of *sec*-alcohols

Laiza A. de Almeida,[a] Thayna H. Marcondes,[a] Cintia D. F. Milagre[a] and Humberto M. S. Milagre*[a]

This paper is dedicated to the memory of Professor José Augusto Rosário Rodrigues.

Abstract: Herein, we present a robust and eco-friendly dynamic kinetic resolution (DKR) protocol for secondary alcohols using a combined heterogeneous catalytic CAL-B/$VOSO_4$ system at 50 °C in the relatively green solvent heptane. This catalytic system is active and chemo- and enantioselective for up to 5 cycles. A set of 13 aromatic and heteroaromatic secondary alcohols were evaluated to determine the substrate scope. The performance of the combined CAL-B/$VOSO_4$ system was improved by employing a low-cost, homemade Teflon tube to compartmentalize the catalysts in one-pot conditions, making this system for up to 8 reaction cycles.



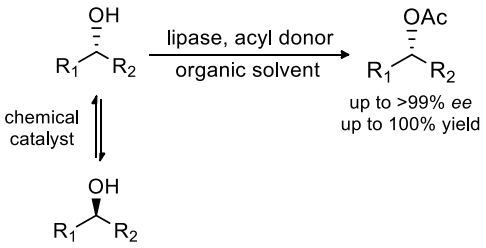
Scheme 1. Chemoenzymatic dynamic kinetic resolution.

Introduction

Optically active secondary alcohols and their derivatives are essential building blocks for pharmaceuticals, agrochemicals, and food products.[1] Several methodologies describe their preparation, including a multitude of synthetic and physicochemical approaches such as chromatographic separation of racemates,[2] chemo- and biocatalytic stereoselective reduction from pro-chiral ketones[3] and enantioselective resolution of racemates.[3a,4] Among these methodologies, those catalysed by enzymes offer notable advantages such as impressive chemo-, regio-, and stereoselectivity, energy-efficient operations and more environmentally friendly processes.[5] Despite of all these methodologies, there is still room for greener and more robust synthetic routes to enantiopure *sec*-alcohols.

In this context, chemoenzymatic dynamic kinetic resolution (DKR), which combines the enzyme-catalysed kinetic resolution (KR) of racemic *sec*-alcohols with the *in situ* chemocatalytic racemization, affords the desired product as a single enantiomer in up to 100% yield (Scheme 1), making it an attractive alternative for preparing enantiopure *sec*-alcohols.[6,7]

Lipases are versatile biocatalysts used in DKR protocols because of their commercial availability in a ready-to-use format, relatively low cost, stability in organic solvents, and high activity and stereoselectivity towards a wide range of substrates.[8,9] In a DKR of *sec*-alcohols in organic media, lipases promote the enantioselective transesterification of one enantiomer of the racemic mixture in the presence of an acyl donor (Scheme 2). The product is an optically active ester that can be subsequently hydrolysed to the enantiopure alcohol.



Scheme 2. Chemoenzymatic DKR of *sec*-alcohol.

In an efficient chemoenzymatic DKR, the main challenge is to combine both bio- and chemocatalysts since this protocol is conducted in a one-pot manner, and those catalysts may require specific reaction conditions.[6,7,10] Metal complexes, such as those with ruthenium,[11,12] iridium,[13] palladium[6] and iron,[14] are useful racemization agents. However, most are expensive, not eco-friendly or not readily available and, in some cases, they require conditions that are harmful to lipases, such as high temperatures or the presence of strong bases. Therefore, substantial effort has been devoted to developing biocompatible and more environmentally benign racemization catalysts, such as solid acids,[15] zeolites[16,17] and vanadium compounds.[18–24]

Vanadium catalysts of type O=V(L)n can efficiently racemize allylic and benzyl secondary alcohols via an addition-elimination mechanism involving carbocation formation (Scheme 3).[19]

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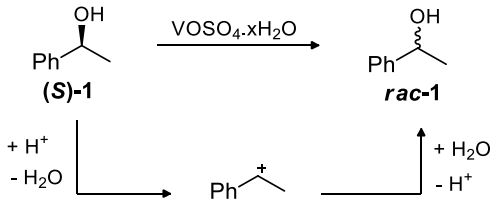
Supporting information for this article is given via a link at the end of the document.



Scheme 3. $VOSO_4$-catalysed racemization of (*S*)-1-phenyletanol ((*S*)-**1**).

The Akai group used the homogeneous catalyst $O=V(OSiPh_3)_3$ and lipase B from *Candida antarctica* (CAL-B) in the DKR of several allylic alcohols and obtained the corresponding chiral esters in up to 99% yield and 99% *ee*.[18,20,21] However, depending on the reaction time and oxovanadium catalyst activity, both the metal and biocatalyst can be deactivated due to catalyst interactions. To overcome this limitation, the Akai group used an immobilization strategy in which the vanadium catalyst was incorporated into a mesoporous silica matrix (V-MPS), allowing low catalyst loading (1 mol%) and high recyclability.[21,22] In the DKR of *rac*-1-phenylbut-2-en-1-ol, this V-MPS racemization catalyst presented excellent recyclability (over six reaction cycles), affording the (*R*)-product in quantitative chemical yield and complete optical purity.[21] Despite these results, the high cost of the MPS matrix and the immobilization procedure, which includes the use of benzene as solvent and inert atmosphere,[21,22] are limiting factors for the application of V-MPS.

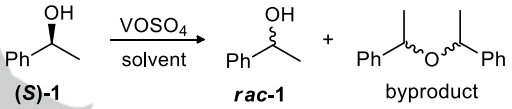
Considering that hydrated vanadyl sulfate ($VOSO_4.XH_2O$) is a less expensive, readily available and less toxic metal complex, this compound is a promising alternative for the development of more economical and eco-friendly DKR processes, particularly when combined with an immobilized lipase to afford a heterogeneous catalytic system, which enables the reuse of both catalysts. Jacobs *et al*. used $VOSO_4$ as a heterogeneous racemization catalyst and immobilized CAL-B in octane (80 °C) for the DKR of *rac*-1-phenylethanol and obtained the (*R*)-product in 93% yield and 99% *ee*.[19] They observed that $VOSO_4$ is incompatible with lipases and to circumvent this issue, the vanadium compound was physically separated through a rotating inox basket containing the lipase. Souza *et al*. also described the DKR of *rac*-1-phenylethanol catalysed by $VOSO_4$ and CAL-B using a continuous flow approach that enabled catalyst compartmentalization.[24] In this work, the DKR was performed in toluene (70 °C) and the (*R*)-product was obtained with 96% yield and 99% *ee*.

Due to the advantages outlined above, herein we report our effort towards a thorough investigation of the chemoenzymatic DKR of *sec*-alcohols using the CAL-B/$VOSO_4$ system. The reaction conditions (solvent and temperature) of the racemization were optimized and the recyclability of $VOSO_4$ in this step was evaluated. Additionally, for the first time, the recyclability of the CAL-B/$VOSO_4$ heterogeneous system for the DKR of 1-phenylethanol was studied, also evaluating the recyclability of both catalysts alone to provide evidence about an incompatibility between lipase and $VOSO_4$. The robustness of the method developed herein was achieved by performing the reaction with a high substrate load, as well as by carrying out the reaction in a larger scale. Lastly, to evaluate the efficiency of this method, the DKR of a set of 12 other aromatic and heteroaromatic *sec*-alcohols was explored.

Results and Discussion

Our study began by examining the $VOSO_4$-catalysed racemization step using (*S*)-1-phenylethanol ((*S*)-**1**) as a model substrate aiming to increase the selectivity of the process previously reported by Jacobs *et al*[19] and Souza *et al*.[24] As shown in Table 1, fast racemization was achieved at 80 °C in all the evaluated solvents, but with low selectivity (high by-product formation). Decreasing the temperature resulted in better selectivity with acceptable racemization rates. The optimum conditions disclosed in this study, heptane at 50 °C (Table 1, entry 6), in addition to being greener than the conditions previously reported in the literature,[19,24] are closer in those required by enzymes, which will be crucial in the DKR.

Table 1. Racemization of (*S*)-1-phenylethanol catalysed by $VOSO_4$.



Entry	Solvent	*T* (°C)	Time (h)	*ee* (%)[a]	*Sel* (%)[b]
1	Toluene	80	1.0	2.9	16
2		50	2.0	14	>99
3	Octane	80	0.5	1.0	78
4		50	1.5	1.7	89
5	Heptane	80	0.5	<1.0	43
6		50	1.0	4.6	93

Conditions: (*S*)-**1** (0.25 mmol), solvent (4 mL), $VOSO_4.XH_2O$ (50 mg), vigorous stirring. [a] Determined by chiral GC-FID analysis. [b] Determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL^{-1}) as internal standard.

To demonstrate the recyclability of $VOSO_4$, the racemization of (*S*)-**1** was carried out under the optimum reaction conditions with consecutive 1 hour-cycles (Figure 1). The oxovanadium catalyst remained active even after 10 cycles and it continued to afford low *ee* values of (*S*)-**1** (*ee* = 2-5%). An increase in by-product formation was observed throughout the cycles (*Sel* = 91-63%). The recyclability of $VOSO_4$ was evaluated by Jacobs *et al*[19] at higher temperatures (80 °C) using octane as the solvent, but in that case the catalyst remained active for only 3 cycles of the racemization of (*S*)-**1**. The optimization of the racemization conditions performed here allowed a significant increase in $VOSO_4$ recyclability.

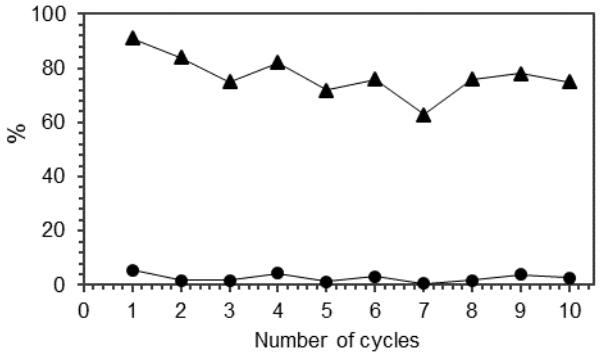
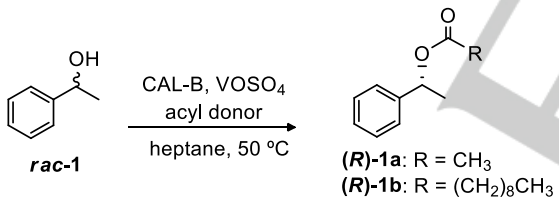


Figure 1. $VOSO_4$ recycling in the racemization of (*S*)-phenylethanol (**1**) (1 h for each cycle; ● *ee* of (*S*)-**1** at the end of each cycle, determined by chiral GC-FID analysis; ▲ selectivity, determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL^{-1}) as internal standard).

Having established the optimal condition for the vanadium-catalysed racemization, $VOSO_4$ and the immobilized *Candida antarctica* lipase B (CAL-B) were combined to perform the DKR of *sec*-alcohols. First, the DKR reaction was performed using *rac*-1-phenylethanol (*rac*-**1**) as a model substrate to evaluate the acyl donor effect since the acylating agent can significantly influence the enzymatic resolution step (Table 2).[25–28]

Table 2. DKR of *rac*-1-phenylethanol (*rac*-**1**) catalysed by CAL-B/$VOSO_4$ using different acyl donors.



Entry	Acyl donor	Time (h)	Product	*c* (%)[a]	ee_P (%)[b]
1	Vinyl acetate	3	(*R*)-**1a**	75	78
2	Ethyl acetate	3	(*R*)-**1a**	43	95
3	Vinyl decanoate	2	(*R*)-**1b**	82	>99
4	Ethyl decanoate	8	(*R*)-**1b**	61	>99

Conditions: *rac*-1 (0.25 mmol), acyl donor (2 equivalents, 0.50 mmol), heptane (4 mL), CAL-B (20 mg), $VOSO_4.XH_2O$ (50 mg), 50 °C, vigorous stirring. [a] Determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL^{-1}) as internal standard. [b] Determined by chiral GC-FID analysis.

The reactions using vinyl and ethyl decanoates (Table 2, entries 3 and 4) presented high enantioselectivities and afforded (*R*)-1-phenylethyl decanoate ((*R*)-**1b**) with *ee* > 99%. These results indicate that acyl donors with longer acyl chains lead to higher enantioselectivities, which is corroborated by the literature.[27,28] Besides this, the commonly used acyl donors such as vinyl acetate resulted in some inhibition of the racemization.[19] The reaction with vinyl decanoate was the most efficient, resulting in (*R*)-**1b** in 87% conversion and *ee* > 99% in 2 h. Thus, vinyl decanoate was selected as the acyl donor for the DKR protocol.

We then evaluated the recyclability of the vanadium-lipase system for DKR to develop a more sustainable and cost-effective methodology. To demonstrate the recyclability of the CAL-B/$VOSO_4$ system, consecutive cycles of DKR reactions were performed and the catalytic system was reused until a significant decrease in the conversion was observed (Figure 2). At the end of each cycle, the combined catalyst was recovered by simple paper filtration and washed three times with heptane. Under these conditions, the system remained stable for up to 5 cycles (c = 86-83%, *ee* of (*R*)-**1b** = 99%).

The decrease in the conversion after the fifth cycle may be related to an incompatibility between CAL-B and $VOSO_4$ due to the extended contact time [19] or an incompatibility between $VOSO_4$ and the acyl donor. To better understand this limitation, we evaluated the recyclability of CAL-B in the KR of *rac*-**1** in the absence of the racemization catalyst, and the lipase remained active and enantioselective even after 6 cycles (Figure 3). In addition, we evaluated the performance of $VOSO_4$ in the racemization of (*S*)-**1** in the presence of vinyl decanoate. The catalyst remained highly active in the presence of the acyl donor even after 5 reaction cycles, reproducing previously described observations (Figure 4). These results show that CAL-B and $VOSO_4$ are stable and remain active for several cycles when they are not in the same reaction system. However, during the cycles of DKR, the catalysts gradually lose their performance due to their mutual incompatibility.

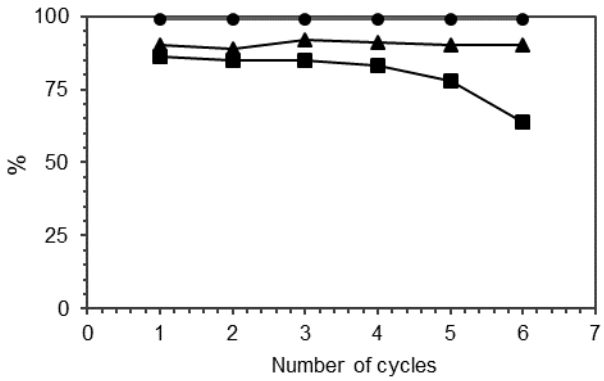


Figure 2. Recycling of CAL-B and $VOSO_4$ in the DKR of *rac*-**1** (2 h of each cycle; ● *ee* of the product (*R*)-**1b** at the end of each cycle, determined by chiral GC-FID analysis; ■ conversion; ▲ selectivity). Conversion and selectivity were determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL^{-1}) as internal standard. Conditions: *rac*-**1** (0.25 mmol), vinyl decanoate (2 equivalents, 0.50 mmol), heptane (4 mL), CAL-B (20 mg), $VOSO_4.XH_2O$ (50 mg), 50 °C, vigorous stirring.

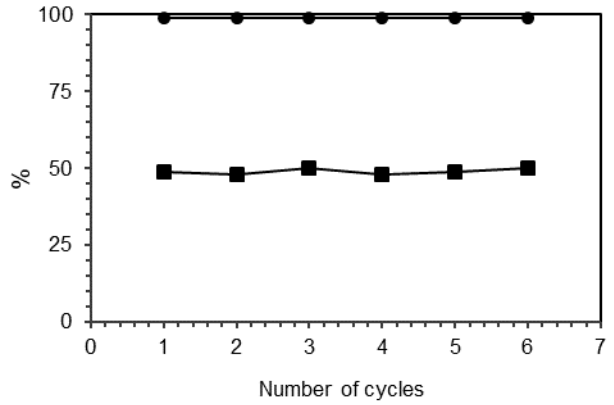


Figure 3. Recycling of CAL-B in the KR of *rac*-**1** (3 h for each cycle; ● *ee* of the product (*R*)-**1b** at the end of each cycle, determined by chiral GC-FID analysis; ■ conversion, determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL^{-1}) as internal standard). Conditions: *rac*-**1** (0.25 mmol), vinyl decanoate (2 equivalents, 0.50 mmol), heptane (4 mL), CAL-B (20 mg) 50 °C.

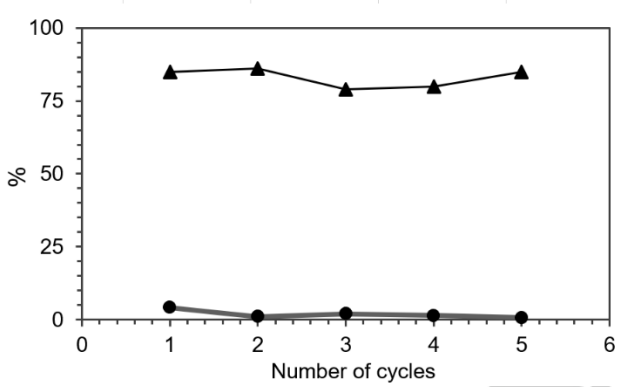
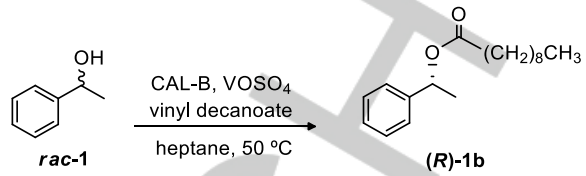


Figure 4. Recycling of $VOSO_4$ in the racemization of (*S*)-**1** in the presence of 0.50 mmol of vinyl decanoate (1 h for each cycle; ● *ee* of (*S*)-**1** at the end of each cycle, determined by chiral GC-FID analysis; ▲ selectivity, determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL-1) as internal standard). Conditions: (*S*)-**1** (0.25 mmol), vinyl decanoate (2 equivalents, 0.50 mmol), heptane (4 mL), $VOSO_4.XH_2O$ (50 mg), 50 °C, vigorous stirring.

To evaluate the tolerance of the catalyst system to high substrate loads, we performed the DKR of *rac*-1-phenylethanol (*rac*-**1**), keeping the other reaction conditions fixed and only varying the substrate concentration from 0.0625 to 0.250 M (Table 3). The results show that the catalytic system can hold up to 2 times the increase in substrate loading, with a small drop in conversion and selectivity. However, this effect is more pronounced at higher substrate loading with a significant decrease in selectivity.

Table 3. Increasing substrate load on DKR of rac-1-phenylethanol (*rac*-1): Evaluation of catalytic tolerance.



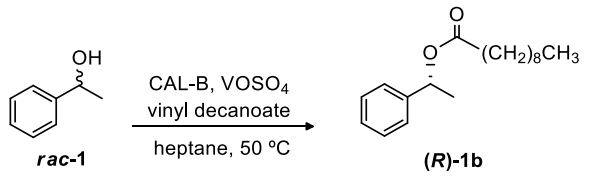
Entry	Substrate concentration (M)	Time (h)	*c* (%)[a]	ee_P (%)[b]	*Sel.*(%)[a]	*E*
1	0.0625	2	82	>99	92	>200
2	0.125	3	79	>99	87	>200
3	0.250	3	76	>99	77	>200

Conditions: *rac*-**1** (0.25, 0.50 or 1.00 mmol), acyl donor (2 equivalents, 0.50, 1.00 or 2.00mmol), heptane (4 mL), CAL-B (20 mg), $VOSO_4.XH_2O$ (50 mg), 50 °C, vigorous stirring. [a] Determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL^{-1}) as internal standard. [b] Determined by chiral GC-FID analysis.

With these results in hands, the substrate scope was evaluated based on 13 aromatic and heteroaromatic *sec*-alcohols (Table 4). High yields (73 to 91%) and high enantiomeric excesses (up to 99%) were observed for the heteroaromatic and substituted aromatic *sec*-alcohols. These results indicate that the incompatibility between CAL-B and $VOSO_4$ is an issue for substrates that require extended reaction times. In these cases, better conversions and selectivities can be obtained by physically separating CAL-B and $VOSO_4$, which has been mentioned in previous works.[19,21,24] On the other hand, no conversions were observed in the substitution of the side chain with groups larger than ethyl (substrates **11-13**, Table 4). According to the literature, the size difference between the groups bound to the stereocenter of the alcohol is important for lipase-catalysed kinetic resolution.[9,29a] Reports in the literature point out that CAL-B is less reactive towards substrates **11**[29b,c] and **12**[29d], while for substrate **13** no kinetic resolution is observed.[29e]

Compartmentalization of incompatible catalysts is a strategy inspired by natural systems, as compartments in cells allow incompatible and concurrent catalytic transformations to occur simultaneously for the synthesis of complex molecules.[30] Herein, we decided to use this strategy to prolong the high performance of the CAL-B/$VOSO_4$ system to beyond the fourth cycle of use. To do this, a homemade Teflon tube with micro holes was built (see the Supporting Information), and one of the catalysts was placed inside the tube to prevent physical contact between the two catalysts. In the first test, we placed the CAL-B inside the Teflon tube (Table 5).

Table 5. Results of the DKR of *rac*-1-phenylethanol (*rac*-**1**) with and without compartmentalization of the catalysts.

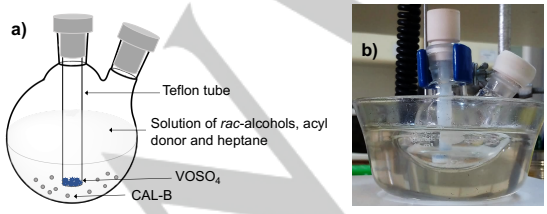


Entry		Time (h)	*c* (%)[a]	*ee*P (%)[b]	*Sel* (%)[a]	*E*
1	without tube	2	82	>99	92	>200
2	CAL-B into the tube	2	20	>99	>99	>200
3	$VOSO_4$ into the tube	1	91	>99	98	>200

Conditions: *rac*-**1** (0.25 mmol), acyl donor (2 equivalents, 0.50 mmol), heptane (4 mL), CAL-B (20 mg), $VOSO_4.XH_2O$ (50 mg) into a Teflon tube, 50 °C, magnetic stirring. [a] Determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL^{-1}) as internal standard. [b] Determined by chiral GC-FID analysis.

The DKR reaction was carried out in a 25-mL glass round-bottomed flask containing the Teflon tube loaded with lipase, using *rac*-**1** as the substrate and the optimal reaction conditions defined in this work (Table 5, entry 2). After 2 h, a 20% conversion of *rac*-**1** into (*R*)-**1b** (*ee* > 99%) and no by-product formation was observed. This lower conversion rate could be attributed to poor mass transfer of the substrate to the inside of the tube containing the immobilized enzyme. Other than the lower conversion rate, this result indicates that compartmentalization is promising for optimization of the DKR since this strategy did not interfere with the enantioselectivity of the process and it inhibited the formation of by-product. In the second test, we placed the $VOSO_4$ inside the Teflon tube (Table 5, entry 3) and product (*R*)-**1b** was obtained with 96% conversion, 98% selectivity and *ee* > 99% in only 1 h, making the protocol developed in this work even more efficient. The results for the DKR of *rac*-**1** with and without compartmentalization prove the importance of the physical separation of the heterogeneous catalysts.

A schematic of the system under the optimized conditions is shown in Scheme 4.



Scheme 4. a) Schematic representation of DKR reaction setup with compartmentalization of the catalysts; b) DKR reaction: tube with $VOSO_4$ in contact with the reaction media containing the substrate (a racemic *sec*-alcohol), vinyl decanoate (acyl donor), immobilized CAL-B and heptane.

Once the compartmentalization system was optimized, the next step was to evaluate its recyclability after 8 cycles. As shown in Figure 5, the system remained active throughout the experiments and only a slight decrease in the conversion, from 94% in the first cycle to 87% in the 8th cycle, was observed. The tube was removed at the end of each cycle and washed three times with heptane. CAL-B was recovered by simple paper filtration and washed three times with heptane. No leaching was observed in either situation (visual inspection).

These results show that this compartmentalization strategy improves the recyclability of the CAL-B/$VOSO_4$ system, as both catalysts maintained their performance for 8 cycles (c = 94-87%, *ee* of (*R*)-**1b** = 99%) as well as their high selectivity (no by-products formation), confirming that it is possible to overcome catalyst incompatibility issues in this DKR protocol using only a low-cost and homemade tube. In addition, the simple compartmentalization strategy adopted in this work facilitated the removal and recovery of $VOSO_4$ from the reaction system during workup.

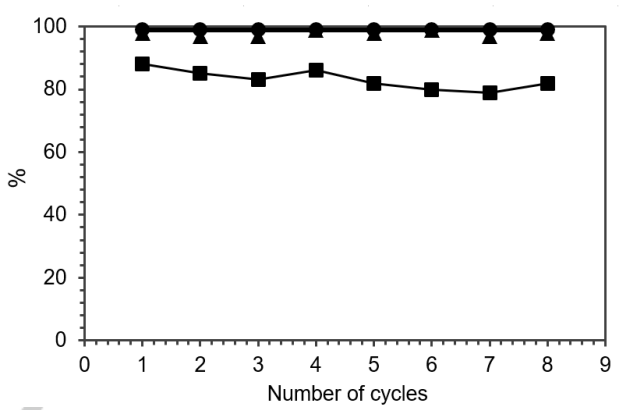


Figure 5. Recycling of CAL-B and $VOSO_4$ in the DKR of *rac*-**1** with compartmentalization ($VOSO_4$ into a Teflon tube; 1 h for each cycle; ● *ee* of the product (*R*)-**1b** at the end of each cycle, determined by chiral GC-FID analysis; ■ conversion; ▲ selectivity). Conversion and selectivity were determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL^{-1}) as internal standard. Conditions: *rac*-**1** (0.25 mmol), vinyl decanoate (2 equivalents, 0.50 mmol), heptane (4 mL), CAL-B (20 mg), $VOSO_4.XH_2O$ (50 mg) into the tube, 50 °C, vigorous stirring.

To evaluate the extension and applicability of the compartmentalization system developed herein, we carried out the DKR of the substrates that exhibited the lowest conversions and selectivities (substrates **3**, **6** and **10**, Table 6) in the previously non-compartmentalized tests. The DKR reactions performed with the compartmentalization system resulted in higher selectivities, similar to what was observed for model substrate *rac*-**1**.

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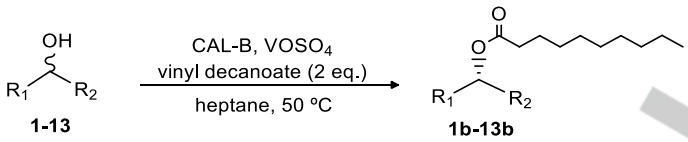
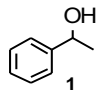
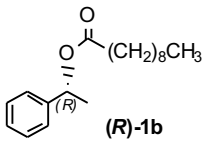
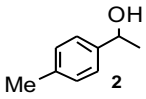
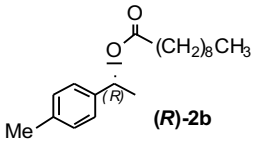
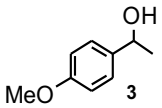
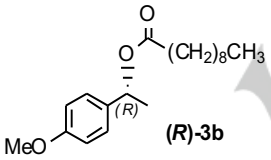
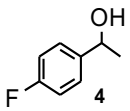
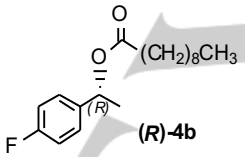
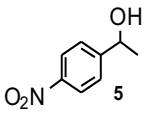
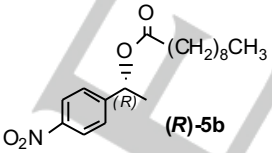
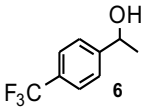
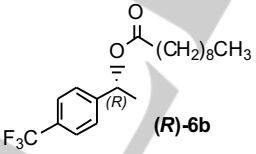
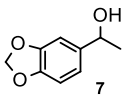
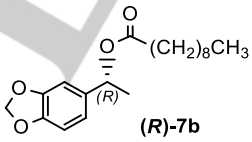
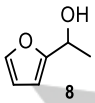
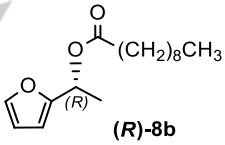
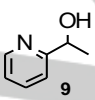
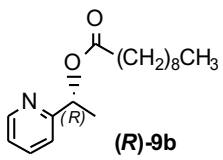
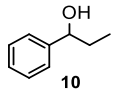
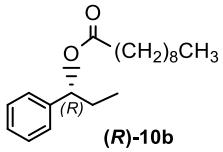
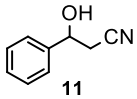
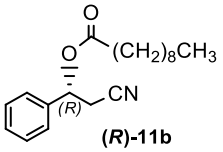
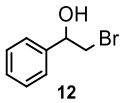
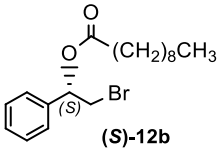
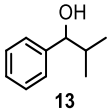
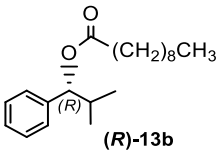
Table 4. DKR of aromatic and heteroaromatic *sec*-alcohols catalysed by CAL-B and $VOSO_4$.

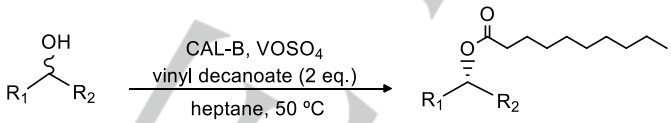


Substrate	Time	Product	Yield (%)[a]	*ee*P. (%)[b]	*E*	*Sel.* (%)[c]
 **1**	2 h	 **(*R*)-1b**	85	>99	>200	92
 **2**	45 min	 **(*R*)-2b**	87	>99	>200	93
 **3**	30 min	 **(*R*)-3b**	73	>99	>200	87
 **4**	1 h	 **(*R*)-4b**	79	>99	>200	96
 **5**	1 h	 **(*R*)-5b**	82	96	194	91
 **6**	2 h	 **(*R*)-6b**	80	>99	>200	90
 **7**	30 min	 **(*R*)-7b**	90	91	110	96
 **8**	30 min	 **(*R*)-8b**	88	>99	>200	97
 **9**	1 h	 **(*R*)-9b**	91	89	90	>99

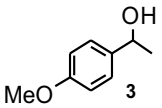
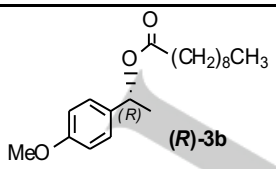
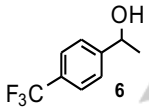
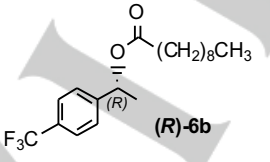
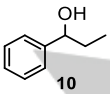
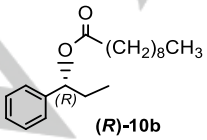
 **10**	2 h	 **(*R*)-10b**	74	>99	>200	77
 **11**	24 h	 **(*R*)-11b**	n.r.	n.d.	-	-
 **12**	24 h	 **(*S*)-12b**	n.r.	n.d.	-	-
 **13**	24 h	 **(*R*)-13b**	n.r.	n.d.	-	-

Conditions: 0.25 mmol of *rac*-alcohol, 0.50 mmol of vinyl decanoate (2 equivalents), heptane (4 mL), $VOSO_4.XH_2O$ (50 mg), CAL-B (20 mg), 50 °C, vigorous stirring. [a] Isolated yield after flash chromatography. [b] Determined by chiral GC-FID analysis after hydrolysis of the product into the (*R*)-alcohol and compared to the racemic standard. [c] Determined by GC-FID comparing the relative peak areas of substrate, product, and by-products. n.r. = no reaction observed, n.d. = not determined

Table 6. DKR of *sec*-alcohols with compartmentalization of the catalysts.



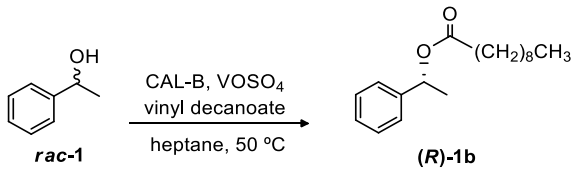
3, 6 or 10 **(*R*)-3b, (*R*)-6b or (*R*)-10b**

Substrate	Product	Time	Compartmentalization	Yield(%)[a]	ee_P (%)[b]	*E*	*Sel.* (%)[c]
 **3**	 **(*R*)-3b**	30 min	without	83	>99[b)]	>200	87
			with	88	>99[b)]	>200	92
 **6**	 **(*R*)-6b**	2 h	without	78	>99	>200	90
			with	80	>99	>200	96
 **10**	 **(*R*)-10b**	2 h	without	80	>99	>200	76
			with	90	>99	>200	98

Conditions: 0.25 mmol of *rac*-alcohol, 0.50 mmol of vinyl decanoate (2 equivalents), heptane (4 mL), $VOSO_4.XH_2O$ (50 mg) into the tube, CAL-B (20 mg), 50 °C, magnetic stirring. [a] Isolated yield after flash chromatography. [b] Determined by chiral GC-FID analysis after hydrolysis of the product into the (*R*)-alcohol and compared to the racemic standard. [c] Determined by GC-FID comparing the relative peak areas of substrate, product, and by-products. n.r. = no reaction observed, n.d. = not determined.

To assess the robustness of the catalytic system, we performed a large-scale DKR of *rac*-1-phenylethanol (*rac*-**1**) (Table 7) with a substrate loading of 5.00 mmol (See the Supporting Information for details). These experiments revealed that there were no significant differences between the lowest and the large scale, and high selectivity was also reached for the model substrate *rac*-**1**, under these reaction conditions.

Table 7. Large-scale DKR of *rac*-1-phenylethanol (*rac*-**1**) with compartmentalization of the catalysts: Evaluation of robustness of the protocol



***rac*-1** **(*R*)-1b**

Entry	Substrate load (mmol)	Time (h)	Yield (%)[a]	ee_P (%)[b]	*Sel* (%)[c]	*E*
1	0.25	2	**91**	>99	**98**	>200
2[d]	5.00	2	**88**	>99	**98**	>200

[a] Isolated yield after flash chromatography. [b] Determined by chiral GC-FID. [c] Determined by GC-FID analysis with *n*-tetradecane (0.050 mmol mL^{-1}) as internal standard. Conditions: [d] *rac*-**1** (5 mmol, 0.61 g), acyl donor (2 equivalents, 10 mmol, 1.98 g), heptane (80 mL), CAL-B (0.40 g), $VOSO_4.XH_2O$ (1.00 g) into the tube, 50 ºC, magnetic stirring.

Conclusions

In this work, a robust DKR protocol for aromatic and heteroaromatic *sec*-alcohols has been developed using the heterogeneous catalysts CAL-B and $VOSO_4$, and high conversions, *ee* values and more important, selectivity, were achieved. The recyclability of the CAL-B/$VOSO_4$ system was investigated for the first time, and this catalytic system remained active for 4 DKR cycles. To further increase the recyclability, the catalysts were compartmentalized through the physical separation of $VOSO_4$ from CAL-B by employing a low-cost, homemade Teflon tube, which allowed 8 reaction cycles without a loss in performance or selectivity. In addition to preventing performance loss of the catalysts due to contact, the Teflon tube facilitated the removal of the catalysts during reaction workup and their reuse. Moreover, this methodology proved to be robust for gram scale experiments. In summary, the combination of these readily commercially available and non-toxic catalysts, CAL-B and $VOSO_4$, presents itself as an environmentally attractive alternative for the resolution of aromatic and heteroaromatic *sec*-alcohols.

Experimental Section

General

Ketones and aldehydes, (*S*)-1-phenylethanol ((*S*)-**1**), *rac*-1-phenylpropanol (**10**), vinyl and ethyl decanoates, vanadyl sulfate hydrate ($VOSO_4 \cdot XH_2O$), methylmagnesium bromide solution (3.0 M in diethyl ether) and immobilized *Candida antarctica* lipase B (Novozym 435; CAL-B; ≥ 5000 U/g, recombinant, expressed in *Aspergillus niger* and adsorbed on a macroporous resin) were purchased from Sigma-Aldrich. All solvents (p.a. grade), and reagents were used as received.

Racemic alcohols **1**-**6** and **11-13** were synthesized via reduction of their corresponding ketones with $NaBH_4$ following a previously described procedure.[31] Racemic alcohols **7**-**9** were obtained from their respective aldehydes via Grignard reactions following a previously described procedure.[32] See the Supporting Information for details related to procedures and for the full characterization data of the synthesized alcohols.

GC-MS analysis was performed on an Agilent 7890B GC coupled to an Agilent 5977A MS (electron impact ionization at 70 eV) with a (5%-phenyl)-methylpolysiloxane column (30 m × 0.25 mm ID; HP5-MS) and using helium as the carrier gas (1 mL min^{-1}). The injector and interface temperatures were 260 °C and 280 °C, respectively. The GC-MS temperature program was as follows: 80 °C for 3 min, then ramp to 280 °C at 30 °C min^{-1}, then hold 3 min.

GC-FID analysis was performed on a Shimadzu GC-2010 Plus equipped with an AOC-20i autosampler and using hydrogen as the carrier gas (1 mL min^{-1}). To determine the conversion and selectivity values, a (5%-diphenyl)-dimethylpolysiloxane column (30 m × 0.25 mm ID; Rtx-5) was used. In these analyses, the injector and interface temperatures were 260 °C and 280 °C, respectively. The GC-FID temperature program was as follows: 80 °C for 3 min, ramp to 280 °C at 30 °C min^{-1}, then hold 10 min. In DKR reactions of 1-phenylethanol, conversions and selectivities were calculated by determining the concentration of 1-phenylethyl acetate or 1-phenylethyl decanoate using a calibration curve with *n*-tetradecane as internal standard. In other DKR reactions, selectivity values were determined using the equation *Sel* (%) = $[(A_S + A_P)/(A_S + A_P + A_{byP})] \times 100$, where A_S, A_P, and A_{byP} are the relative peak areas of substrate, product and by-products, respectively, in the chromatograms. To determine the enantiomeric excess (*ee*) values, two chiral columns were used: Hydrodex β-3P (heptakis-(2,6-di-O-methyl-3-O-pentyl)-β-cyclodextrin, 25 m × 0.25 mm ID) and Lipodex E (octakis-(2,6-di-O-pentyl-3-O-butyryl)-γ-cyclodextrin, 25 m × 0.25 mm ID). In these analyses, the injector and interface temperatures were 160 °C and 180 °C, respectively. For 1-phenylethanol, 1-phenylethyl acetate and 1-phenylethyl decanoate, the *ee* values were determined directly using the relative peak areas of their enantiomers. For other DKR products, the *ee* were obtained indirectly after determining the *ee* values of the correspondent alcohols obtained from esters hydrolysis. See the Supporting Information for details related to the temperature program for chiral GC-FID analysis.

^1H NMR and ^{13}C NMR (DEPTQ) spectra were acquired on a Bruker Fourier 600 (B0 14.1 T) using $CDCl_3$ as the solvent, operating at a frequency of 600.13 MHz for the ^1H nucleus and 150.90 MHz for the ^{13}C nucleus. Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS). Signal multiplicities are indicated by the letters s (singlet), brs (broad singlet), d (doublet), dd (doublet of doublets), doublet of doublets of doublets (ddd), t (triplet), q (quartet), qnt (quintet) and m (multiplet).

Optical rotations were measured in $CHCl_3$ solutions on a Perkin Elmer 341 LC polarimeter at the sodium D line (589 nm) and with a 1.00 dm quartz cell.

Racemization reactions

Solvent screening. To 0.25 mmol (30.5 mg) of (*S*)-1-phenylethanol was added 4.0 mL of solvent (toluene, octane or heptane) and 50 mg of $VOSO_4 \cdot XH_2O$. The resulting suspension was stirred at 50 °C or 80 °C using a magnetic bar, and the reactions were monitored by chiral GC-FID until reaching the lowest *ee* for the (*S*)-enantiomer.

Recycling of $VOSO_4$. To 0.25 mmol (30.5 mg) of (*S*)-1-phenylethanol was added 4.0 mL of heptane and 50 mg of $VOSO_4 \cdot XH_2O$. The resulting suspension was stirred at 50 °C using a magnetic bar for 1 h. Then, the catalyst ($VOSO_4$) was filtered off by simple paper filtration, washed with heptane (3 x 2 mL) and used in a new racemization cycle under the same reaction conditions described. The procedure was repeated for 10 cycles.

DKR reactions

Acyl donor screening. To 0.25 mmol (30.5 mg) of *rac*-1-phenylethanol was added 4.0 mL of heptane and 0.50 mmol (2 equivalents) of acyl donor (vinyl acetate, ethyl acetate, vinyl decanoate or ethyl decanoate). To the resulting solution were added 20 mg of immobilized *Candida antarctica* lipase B (CAL-B) and 50 mg of $VOSO_4 \cdot XH_2O$. The resulting suspension was stirred at 50 °C using a magnetic bar, and the reactions were monitored on GC-FID. After reaching maximum substrate conversions to the (*R*)-products and lower by-product formation, the catalysts were removed by simple paper filtration, and the reaction solution was concentrated under reduced pressure. The residues were purified by flash chromatography (heptane:ethyl acetate, 95 : 5) to afford (*R*)-1-phenylethyl acetate and (*R*)-1-phenylethyl decanoate.

Recycling of CAL-B and $VOSO_4$. To 0.25 mmol (30.5 mg) of *rac*-1-phenylethanol was added 4.0 mL of heptane and 0.50 mmol (112 µL) of vinyl decanoate. To this resulting solution were added 20 mg of immobilized *Candida antarctica* lipase B (CAL-B) and 50 mg of $VOSO_4 \cdot XH_2O$. The resulting suspension was stirred at 50 °C using a magnetic bar for 2 h. Then, the catalysts (CAL-B and $VOSO_4$) were filtered off by simple paper filtration, washed with heptane (3 x 2 mL) and added in a new DKR cycle under the same reaction conditions. The procedure was repeated for 6 consecutive cycles.

Evaluation of catalytic tolerance. To 0.25 mmol (30.5 mg), 0.50 mmol (61.1 mg) or 1.00 mmol (122.2 mg) of *rac*-1-phenylethanol was added, respectively, 0.50 mmol (99.1 mg), 1.00 mmol (198.3 mg) or 2.00 mmol (396.6 mg) of vinyl decanoate and 4.0 mL of heptane. To the resulting solutions were added 20 mg of immobilized *Candida antarctica* lipase B (CAL-B) and 50 mg of $VOSO_4 \cdot XH_2O$. The resulting suspensions were stirred at 50 °C using a magnetic bar, and the reactions were monitored byGC-FID. After reaching maximum substrate conversions to (*R*)-1-phenylethyl decanoate and lower by-product formation, the catalysts were removed by simple paper filtration and the reaction solutions were concentrated under reduced pressure.

Substrate scope. To 0.25 mmol of each racemic alcohol were added 4.0 mL of heptane and 0.50 mmol (99.1 mg) of vinyl decanoate. To this resulting solution were added 20 mg of immobilized *Candida antarctica* lipase B (CAL-B) and 50 mg of $VOSO_4 \cdot XH_2O$. The resulting suspension was stirred at 50 °C using a magnetic bar, and the reactions were monitored on GC-FID. After reaching the maximum conversion to the (*R*)-decanoate esters and lower by-product formation, the catalysts were removed by simple paper filtration, and the reaction solutions were concentrated under reduced pressure. The residues were purified by flash chromatography (heptane:ethyl acetate, 95 : 5) to give the (*R*)-decanoates.

Compartmentalization of the catalysts. To a 25-mL two-neck round bottom flask were added 20 mg of immobilized *Candida antarctica* B lipase (CAL-B) and 4.0 mL of heptane. A Teflon tube containing 50 mg of $VOSO_4 \cdot XH_2O$ was added into the reaction flask by fitting it into a septum. The flask was closed with this septum connect to the tube, and then, using syringes, 0.25 mmol of *rac*-alcohol and 0.50 mmol (99.1 mg) of vinyl decanoate were added into the reaction system. The resulting suspension was stirred at 50 °C using a magnetic bar. After maximum conversion of the (*R*)-decanoates and lower by-product formation was achieved, the tube with $VOSO_4$ was removed, and CAL-B was filtered off by simple paper filtration. For recycling analyses (performed for the DKR of *rac*-1-phenylethanol), the catalysts were removed from the reaction flask, washed with heptane (3 x 2 mL; $VOSO_4$ was washed inside the tube) and used in a new DKR cycle under the same reaction conditions. This procedure was repeated for 8 consecutive cycles.

Large-scale DKR. To a 250-mL three-neck round bottom flask were added 0.40 g of immobilized *Candida antarctica* B lipase (CAL-B) and 80.0 mL of heptane. A tube containing 1.00 g of $VOSO_4 \cdot XH_2O$ was added into the reaction flask by fitting it into a septum. The flask was closed with this septum connect to the tube, and then, using syringes, 5.00 mmol of *rac*-1-phenylethanol (0.61 g) and 10.0 mmol (1.98 g) of vinyl decanoate were added into the reaction system. The resulting suspension was stirred at 50 °C using a magnetic bar and the reaction was monitored by GC-FID. After maximum substrate conversion to the respective (*R*)-1-phenylethyl decanoate and lower by-product formation was achieved, the tube with $VOSO_4$ was removed and CAL-B was filtered off by simple paper filtration.

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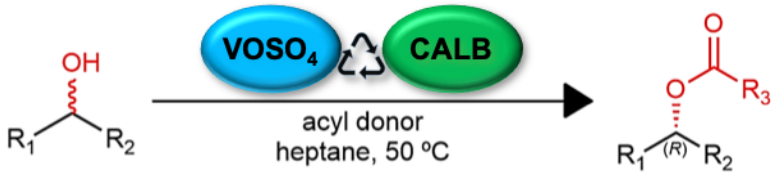

A robust and eco-friendly dynamic kinetic resolution (DKR) protocol for secondary alcohols using a combined heterogeneous catalytic CAL-B/$VOSO_4$ system.

*L. A. de Almeida, T. H. Marcondes, C. D. F. Milagre, H. M. S. Milagre**

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Lipase-oxovanadium heterogeneous catalysis system: a robust protocol for the dynamic kinetic resolution of *sec*-alcohols