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COMMUNICATION

Dynamic Kinetic Resolution of a Tertiary Alcohol

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Abstract: In spite of the tremendous success of dynamic kinetic resolutions for a broad range of compound classes, tertiary alcohols and their corresponding esters have still remained as one of the most challenging substrates for this type of process. This is due to the size and steric hindrance of the tertiary alcohol as well as to the difficulty in finding reaction conditions for the racemization of such compounds being at the same time compatible with the resolution reaction, which preferably is carried out with an enzyme. In this study the first example of a dynamic kinetic resolution of a racemic tertiary alcohol is presented. The desired synthesis of the resulting enantiomerically pure ester was achieved by combining a lipase-catalyzed kinetic resolution with an *in situ* racemization utilizing a bio-compatible oxovanadium-catalyst. First, the two individual reactions were examined, improved and adjusted to be compatible with each other. Subsequently, addition of both catalysts in tailor-made portions led to the desired combined process and delivered the product with >99% *ee* and a conversion exceeding 50%, thus proving such a desired dynamic kinetic resolution of a tertiary alcohol.

Despite of tremendous achievements in the field of asymmetric catalysis in general [1] and its application to tertiary alcohols in particular,[1] enantioselective synthesis of tertiary alcohols with the aid of dynamic kinetic resolution using enzymes has remained an unsolved challenge so far. Such an access would be highly desirable due to the need of enantiomerically pure forms of tertiary alcohols or acylated derivatives thereof in the field of pharmaceuticals and natural product synthesis.[2] For example; the tertiary alcohol-derived pharmaceutical Efavirenz® represents an important drug for the treatment of HIV infections.[3]

From a synthetic point of view, one of the favoured overall concepts for the enantioselective approach to tertiary alcohols is dynamic kinetic resolution (DKR), since such a process engineering could provide access to a wide range of enantiomerically pure tertiary alcohols. An advantage of this DKR approach is that the racemic substrates are typically easily accessible by various chemical methods and that the desired product could be obtained in an irreversible fashion in theoretically 100% yield and in enantiomerically pure form (>99% *ee*). The chemoenzymatic DKR is very well established in the field of secondary alcohols by combining metal-catalyzed racemization and a lipase-catalyzed acylation as concurrently occurring reaction steps.[4] Prominent examples of such DKRs have been demonstrated by Bäckvall *et al.*,[4,5] Kim *et al.*,[6] and Berkessel *et al.* [7] with the first one being applied already on technical scale in modified form.[4]

Remarkably, however, no successful extension of this concept towards tertiary alcohols was achieved so far. Very recently, an efficient racemization protocol for tertiary alcohols has been reported for the first time by the Bäckvall group,[8] although compatibility with an enzymatic resolution, thus leading to a DKR, has remained an unsolved task up to now. The difficulty in developing racemization strategies for tertiary alcohols might be in particular due to two reasons: first, the well-established metal-catalyzed racemization through a redox process being successful for secondary alcohols cannot be utilized in the case of tertiary alcohols, as there is a lack of an oxidizable C–H-bond. Second, the tertiary alcohols are prone to decomposition leading to elimination side-products even under slightly acidic conditions and the resulting esters are even more sensitive.[4b] Recently, some of us developed an alternative way for a DKR of secondary alcohols proceeding by means of oxovanadium-catalyzed C–O bond cleavage generating a cation followed by the reformation of the C–O bond.[4b,9] We envisioned that such a

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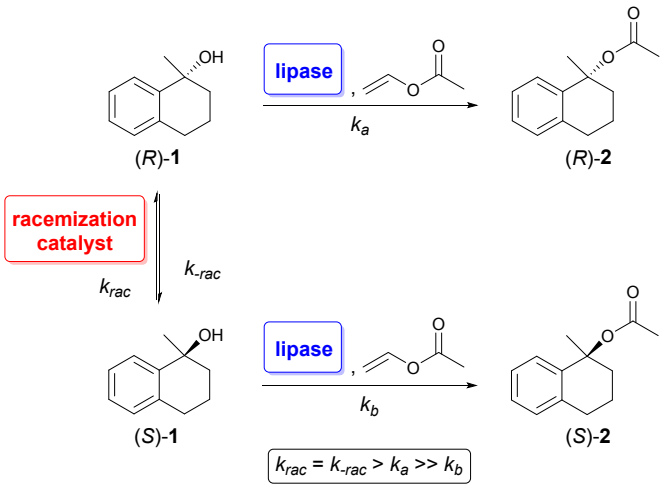
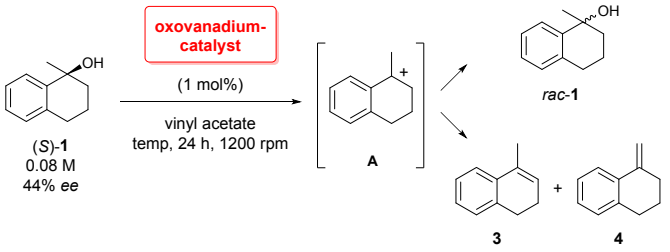
type of racemization could also be suitable for tertiary alcohols, and in the following we report the first example of a DKR of a tertiary alcohol, which is based on the combination of an oxovanadium-catalyzed racemization and enzymatic resolution through esterification with a lipase in an organic medium (Scheme 1). In order to make such a DKR process efficient, the KR should proceed in a highly enantioselective fashion (k_a>>k_b), thus enabling the formation of the desired enantiomer in enantiomerically pure form.



Scheme 1. General principle of a DKR of the model substrate *rac*-**1**.

Toward this end, we first focused on the development of a robust racemization process of the tertiary alcohol **1** as a key step for such a DKR process. Starting from enantiomerically enriched (*S*)-**1** (44% *ee*) three different oxovanadium-catalysts, namely O=V(OSiPh$_3$)$_3$,[9a,12] V-MPS4 (immobilized on mesoporous silica (MPS))[9c,d] and PhosphonicS™ POVO (immobilized on silica)[9b] were evaluated with respect to their potential for catalyzing a racemization process (Table 1). The V-MPS4 (pore diameter of the MPS is 4 nm), which was prepared as reported in literature[1c] yielded promising results in terms of the racemization rate and an acceptable racemization was achieved within 24 hours when using this V-MPS4-catalyst (Table 1, entries 3-5). The *ee*-value could be reduced from 44% *ee* to 16% *ee*. However, when using this catalyst, a relatively large amount of side-products **3** and **4** was observed, in contrast to the use of the other two catalysts (entries 1,2), O=V(OSiPh$_3$)$_3$ and the PhosphonicS™ POVO. In addition, the racemization was tremendously decreased when using the PS-POVO (44% *ee* to 38% *ee*) and the tris(triphenylsilyloxy)oxovanadium catalyst (44% *ee* to 41% *ee*). In order to further enhance the racemization process, different reaction temperatures were tested (Table 1, entries 3-5). It turned out that the side-product formation could be somewhat reduced at lower reaction temperature (15 °C), although the racemization proceeded much slower. On the other hand, complete formation of side-products **3** and **4** was observed at higher temperature (50 C). Based on these findings, we decided to use 25 °C for all further experiments.

Table 1. Impact of catalysts and temperatures on the racemization of alcohol (*S*)-**1**. The reactions were carried out in an Eppendorf tube under argon atmosphere.

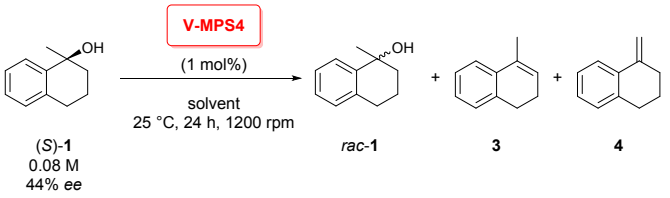


Oxo-vanadium catalyst	T (°C)	Yield of alcohol[a] **1** (%)	*ee*-value **1** (%)	Yield of side-product[a] **3** (%)	Yield of side-product[a] **4** (%)
O=V(OSiPh$_3$)$_3$	25	86	41	11	3
PS-POVO	25	100	38	0	0
V-MPS4	25	66	16	29	5
V-MPS4	15	73	34	23	4
V-MPS4	50	1	0	91	8

[a] NMR yield.

Another critical parameter, which has been identified to have a significant influence on the course of the racemization, is the type of solvent component (Table 2). Isooctane and diisopropyl ether provided the best results, since with these solvents the side-product formation could be completely suppressed and in addition the racemization rates (44% *ee* to 15% *ee* in isooctane and 44% *ee* to 21% *ee* in diisopropyl ether) were acceptable.

Table 2. Impact of organic solvents on the racemization of alcohol (*S*)-**1**. The reactions were carried out in a Schlenk-tube under argon atmosphere.



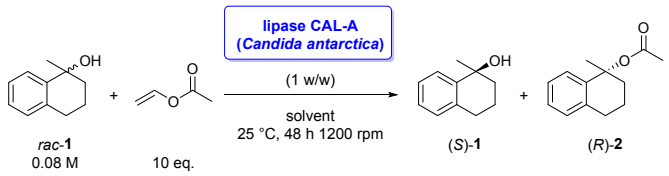
Solvent	Yield of alcohol[a] **1** (%)	*ee*-value **1** (%)	Yield of side-product[a] **3** (%)	Yield of side-product[a] **4** (%)
Vinyl acetate[b]	67	4	28	5
Isooctane	100	15	0	0
Cyclohexane	90	16	8	2
MeO^{t}Bu	94	28	6	0
Diisopropyl ether	100	21	0	0

[a] NMR yield.

Methyl *tert*-butyl ether (MTBE) and cyclohexane provided higher side-product formation, thus being less suitable. These results show that the choice of solvent is of high importance for the reaction process.

Based on these results (Table 2), kinetic resolution of *rac*-**1** was tested in various solvents being suited for the racemization as both processes have to be combined later with each other for achieving the envisaged chemoenzymatic DKR. As an enzyme we chose the *Candida antarctica* lipase A (CAL-A) as this biocatalyst has been described to be useful for tertiary alcohols.[10,11] In our kinetic resolution study (Table 3), cyclohexane and diisopropyl ether turned out as the most promising solvents with 28% or 32% conversion to the desired product after 48 hours reaction time (Table 3, entries 1, 3).

Table 3. Kinetic resolution of alcohol *rac*-**1** in different solvents.

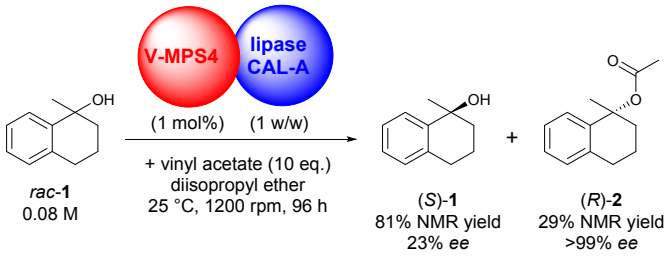


Solvent	Yield of alcohol[a] (*S*)-**1** (%)	*ee*-value (*S*)-**1** (%)	Yield of acetate[a] (*R*)-**2** (%)	*ee*-value (*R*)-**2** (%)	E-value
Isooctane	77	23	23	>99	>200
Cyclohexane	72	39	28	>99	>200
MeO^{t}Bu	91	14	9	>99	>200
Diisopropyl ether	68	50	32	>99	>200

[a] NMR yield.

In every case the *ee*-value of the resulting acetate was excellent with >99% *ee*, which corresponds to an E-value of each reaction of >200. In addition, no side-products were observed in these kinetic resolutions of *rac*-**1** with lipase CAL-A.

For the combined DKR process diisopropyl ether turned out as a promising solvent since racemization as well as kinetic resolution furnished good results when conducting these reactions in separated fashion. Thus, our initial attempt for a combined process consisted in a one pot process in diisopropyl ether. Accordingly, a 0.08 M solution of the substrate *rac*-**1** in diisopropyl ether, containing 10 eq. of vinyl acetate, was treated with CAL-A (1 w/w) and V-MPS4 (1 mol%) under argon atmosphere (Scheme 2). Although in this initial experiment we observed a conversion of only 29% to the expected product (*R*)-**2** after 96 h, we were pleased to find that no side-product formation was observed under these reaction conditions. Another promising result was the relatively low optical purity (23% *ee*) of the remaining alcohol **1** (in comparison to the calculated theoretical *ee*-value of 41% ee for a "pure" kinetic resolution), which indicated that a racemization in parallel to the kinetic resolution of *rac*-**1** took place as desired.

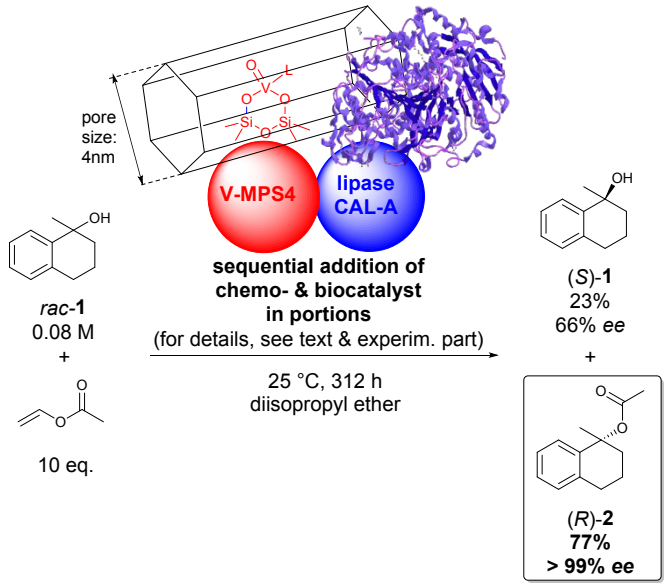


Scheme 2. DKR of *rac*-1 in a one pot process.

As in this initial DKR experiment the formation of the desired product (*R*)-**2** was relatively low with 29%, this result indicates that the CAL-A was deactivated in the reaction solution over a certain period of time. This hypothesis could be confirmed by a stability test of CAL-A (see Supporting Information), in which fresh solution of starting material and vinyl acetate were added to a recycled portion of the lipase CAL-A.

With this insight into enzyme stability under process conditions in hand and in order to increase the conversion, we added CAL-A and V-MPS4 stepwise. Under these experimental conditions, it was ensured that fresh, active CAL-A was constantly added to the reaction mixture and that the kinetic resolution could therefore be maintained over the whole reaction time (Scheme 3). For the stepwise addition we started initially with a kinetic resolution of *rac*-**1** in the presence of only CAL-A and could reach a formation of (*R*)-**2** in 38% yield (according to NMR) after 72 hours with 0.5 w/w of CAL-A. At this stage, we added a mixture of V-MPS4 (1 mol%) and CAL-A (0.5 w/w) and stirred the reaction mixture for another 24 hours. A further addition of CAL-A (2 w/w) yielded in 41% of (*R*)-**2**. Although at this point the consumption of **1** was still below 50%, we were glad to find that side-product formation was completely suppressed even after such a prolonged reaction time. Therefore, we decided to conduct the second cycle of DKR after filtration, evaporation and re-dissolving the reaction mixture of the first cycle in diisopropyl ether. These steps were not necessary from the perspective of the DKR, but turned out to be beneficial in terms of practicability and handling reasons. Since still a large portion of lipase is needed due to the known low activity of existing lipases for tertiary alcohols[10] in combination with their limited stability, for better stirring ability we decided to remove the inactivated biocatalyst portion by filtration prior to adding new portions of lipase and oxovanadium racemization catalyst to the reaction mixture. Thus, the resulting solution was then again treated with further portions of the enzyme CAL-A and oxovanadium-complex V-MPS4 for racemization (for details, see Supporting Information). After the catalysts had been filtered off, we obtained a 77% yield of (*R*)-**2** with an excellent excess of >99% *ee* (determined again by NMR), thus indicating that through this stepwise catalyst addition a DKR process has been realized. Thus, by means of this approach, to the best of our

knowledge, for the first time a DKR of a tertiary alcohol was successfully carried out.



Scheme 3. DKR of *rac*-**1** in a sequential batch process. All reactions were done with a stirring rate of 1200 rpm under an argon atmosphere.

In conclusion, the first example of a DRK of a tertiary alcohol, exemplified for the transformation of *rac*-**1** into (*R*)-**2**, has been achieved. The concept is based on a chemoenzymatic approach combining a lipase-catalyzed resolution and an oxovanadium-catalyzed racemization. In a sequential batch process with a stepwise addition of the catalysts in various portions, we could overcome the limitations caused by the deactivation of the biocatalyst CAL-A under the process conditions. The continuous addition of fresh, active CAL-A ensures that kinetic resolution can take place permanently in combination with the desired racemization, so that a final conversion of 77% to the desired acetate (*R*)-**2** with an excellent *ee*-value of >99% *ee* was achieved, thus representing a proof-of-concept for such a DKR. Tasks for future work are the improvement of the reaction conditions and the extension of this method to other substrates. As a major hurdle is not the DKR itself but the stability of enzyme and, in part, esters, as well as the substrate scope[13] of enzyme and racemization catalyst. Thus, currently our major focus is on developing CAL-A mutants and vanadium catalysts with improved performance in the DKR.

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Conflicts of interest

There are no conflicts to declare.

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13 The challenge of the substrate scope is illustrated by some selected examples in the Supporting Information.