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Multistep Oxidase–Lyase Reactions: Synthesis of Optically Active 2-Hydroxyketones by Using Biobased Aliphatic Alcohols

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Enzymatic multistep reactions are presently an important research field, from which integrated and efficient synthetic protocols can be created, accompanied by a diminished waste formation (avoiding downstream units operations). This article explores the benzaldehyde lyase (BAL) catalyzed crossed carboligation of benzaldehyde with different aliphatic aldehydes to afford optically active α-hydroxyketones. To this end, different biobased aliphatic alcohols were in situ oxidized to aldehydes by oxidase from *Hansenula* sp. and subsequently carboligated with benzaldehyde by BAL in the same reactor system. For short nonbranched aliphatic alcohols, moderate to high conversions in carboligations (15–99%) with excellent enantioselectivities (98–99%, *R*), were achieved. Both enzymes also exhibited activities at high concentrations of benzaldehyde (up to 200 mM) and with butanol as cosolvent, albeit at the cost of lower conversions, presumably owing to kinetic reasons. After needed optimization of the biocatalyst (e.g., through genetic evolution, whole-cell setup) and the process setup (e.g., stepwise addition of substrates, reaction time), the herein reported concept might provide promising entries in the field of asymmetric synthesis, delivering useful building blocks starting from biobased materials, and in an integrative manner.

Introduction

Biocatalysis has been established in the last decades as a powerful tool for the synthesis of a broad array of optically active chemicals. The main reasons for such interest are the exquisite regio-, enantio-, and chemoselectivity that enzymes often display for many substrates. Aligned to this, advances in molecular biology have enabled the cost-effective provision of large-scale, reproducible, and genetically improved biocatalysts.[1] Adding to that selectivity, enzymatic processes have been typically addressed as "green" processes, owing to the mild (aqueous) reaction conditions in which those reactions are conducted. In recent years, however, considering the wastewater production that biocatalytic process actually create, investigations have also focused on the use of biobased cosolvents (e.g., 2-methyltetrahydrofuran, 2-MeTHF),[2] ionic liquids, and deep-eutectic solvents,[3] as well as solvent-free and nonaqueous processes.[4] The combination of the high efficiency and selectivity of enzymes with a more environmentally friendly process setup may certainly boost even more the interest and the scope of biocatalysis on an industrial level.

In this respect, another emerging approximation to provide "greener" biocatalysis is the setup of multistep catalytic processes, involving the performance of several enzymes in the same reactor, and, therefore, diminishing the waste formation upon the reduction of downstream processing units.[5] Several outstanding examples have been reported in recent years, focusing on lipases, oxidoreductases, transaminases, and lyases.[6] Among these examples, the combination of oxidoreductases[7] and lyases[8] led to promising entries for the synthesis of highly valuable optically active alcohols with diminished waste formation, starting from accessible substrates (e.g., aldehydes, ketones). The enantioselective reduction of ketones is an industrially proven useful method to afford chiral alcohols under extremely mild reaction conditions.[1b,4c,7] Likewise, the enzymatic enantioselective C–C bond formation represents an outstanding alternative to create novel optically active compounds starting from aldehydes as inexpensive substrates.[8] On this basis, several examples on combinations of enzymatic oxidations and C–C bond formation have been reported, either in two-pot or in one-pot setups.[6d,9]

Following these considerations, aiming at combining sustainable chemistry with biocatalysis, the present paper explores the use of (biobased) aliphatic alcohols as substrates for the production of optically active α-hydroxyketones. To this end, the oxidase-catalyzed oxidation of aliphatic alcohols—to form aldehydes—would be in situ coupled with a lyase-catalyzed enantioselective C–C bond formation, to yield the desired chiral α-hydroxyketones in a one-pot, two-steps process. Besides the introduction of biobased alcohols,[10] the envisaged approach would avoid the use of highly volatile and hazardous aliphatic aldehydes, as they would be only formed in situ in millimolar amounts. To validate the concept, benzaldehyde lyase (BAL) was used for the enantioselective C–C bond formation, the core step of the process. BAL is a thiamine diphosphate dependent enzyme (ThDP lyase) with a broad substrate acceptance, that is, it accepts aromatic and aliphatic aldehydes, to afford a wide range of optically active

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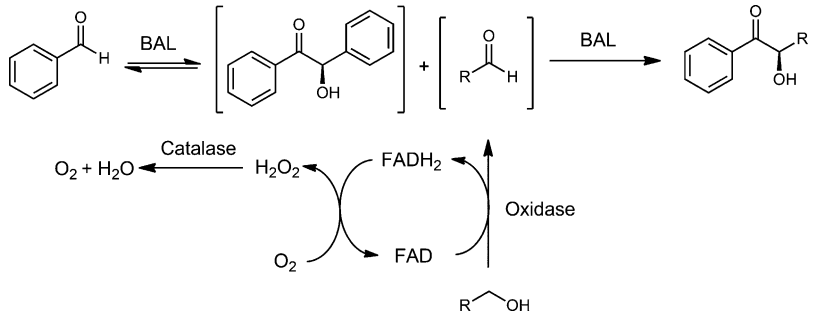


Scheme 1. Conceptual approach of an oxidase–lyase system to afford optically active α-hydroxyketones in a multistep process starting from benzaldehyde[10] and from biobased aliphatic alcohols. Catalase is added to eliminate the formed hydrogen peroxide.

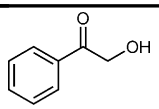
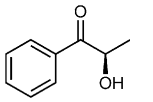
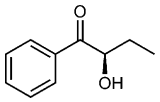
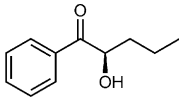
α-hydroxyketones.[8,11] Very recently, diastereoselective reactions catalyzed by BAL were reported as well.[12] The use of BAL in multistep reactions has been so far scarcely addressed, with preliminary examples on lipase–BAL and oxidase–BAL combinations.[6c,d] The overall reaction process is depicted in Scheme 1.

Results and Discussion

Following our previous work,[6d] in which oxidases were able to oxidize methanol to produce, in situ, formaldehyde for the further BAL-catalyzed hydroxymethylation, in the first set of experiments different aliphatic alcohols were tested as substrates for the oxidase from *Hansenula* sp. In the same pot, benzaldehyde was added for the subsequent BAL-catalyzed carboligation to afford the crossed chiral α-hydroxyketones. The one-pot multistep reactions proceeded in aqueous solution, and as cosolvent the biobased 2-MeTHF was used,[2b] as it has proven to be a useful cosolvent for BAL[13] and for oxidases.[6d] The results are depicted in Table 1.

As observed, oxidase from *Hansenula* sp. was successfully applied for the oxidation of short-chain aliphatic alcohols (from methanol to butanol) to afford aldehydes in catalytic amounts, which were then in situ carboligated by BAL to afford the optically active α-hydroxyketones, in excellent conversions for methanol, ethanol, and butanol. Furthermore, BAL displayed outstanding enantioselectivities in all cases (98–99%, see Experimental Section for details), in agreement with previous literature, in which BAL-catalyzed carboligations with benzaldehyde as the donor always lead to highly enantioselective processes.[8,11–14] In the case of propanol, a lower conversion was observed, with benzoin formed by BAL as reversible product (Scheme 1), which rather indicates a lower oxidase-catalyzed rate for this substrate than deactivation of the enzymes in the combined reactor system. The same assumption may be made for hexanol, allylic alcohol, and the branched substrates (Table 1), though activity of oxidase from *Hansenula* sp. for a broad number of short-chain alcohols has been reported.[15] Herein, however, albeit no crossed carboligation could be observed, the formation of benzoin in quantitative amounts assured the activity of BAL in the presence of such alcohols. Thus, aiming at extending the reaction scope, galactose oxidase from *Dactylium dendroides* was assessed, as this enzyme has shown activity for the oxidation of diols.[15b,16] Yet, no conversions could be observed for any of the branched or allylic alcohols, and only quantitative amounts of benzoin were achieved. Likewise, a 2,2,6,6-tetramethylpyrimidine *N*-oxide (TEMPO) catalyzed organocatalytic alcohol oxidation was attempted,[17] aiming at combining, in one pot, the organocatalytic oxidation of aliphatic alcohols with subsequent BAL-catalyzed carboligations. Disappointingly, attempts to obtain compatible reaction conditions for both catalysts (TEMPO–BAL) were unsuccessful. In any case, given the diversity of oxidases in nature,[7] as well as the possibilities that molecular biology techniques offer nowadays for the genetic

Table 1. One-pot multistep process to afford optically active α-hydroxyketones.[a]

Aliphatic alcohol	Product	Conversion[b] [%]	*ee*[c] [%]	Benzoin conversion[b] [%]
CH_3OH		>99[d]	–	–
		>99	99	–
		15[e]	98	81
		91[e]	98	–
	–	–	–	99
	–	–	–	99
	–	–	–	99
	–	–	–	99

[a] Reaction conditions: benzaldehyde (6 mM), aliphatic alcohol (53.5 mM), BAL (1 mg mL^{-1}, 20 U), ThDP (0.15 mM), alcohol oxidase from *Hansenula* sp. (0.25 mg mL^{-1}, 8 U), catalase from bovine liver (12 U, 0.35 mg mL^{-1}), FAD (0.1 mM), phosphate buffer pH 8.0 (50 mM), 2-MeTHF (5 vol.%), $MgSO_4$ (2.5 mM). Absolute configuration assigned to (*R*) for BAL-catalyzed carboligations.[8,11,12] [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC (see Experimental Section). [d] In agreement with previous literature.[6d] [e] Traces (5–10%) of the other crossed product (benzaldehyde as acceptor and the formed aliphatic aldehyde as donor) were observed by ^{1}H NMR (see also below, Figure 1).

design of improved enzymes,[1] it may be expected that novel biocatalysts can be found for the oxidation of more challenging aliphatic alcohols. In addition, apart from oxidases, other oxidative enzymes (e.g., oxidoreductases) could be envisaged for the analogous processes of alcohol-to-aldehydes as well.[7]

In a second set of experiments, the reaction conditions for the one-pot multistep strategy were further studied. To this end, the BAL-catalyzed carboligation of benzaldehyde with butyraldehyde, using butanol as the substrate, was chosen as a model reaction. The results are depicted in Figure 1.

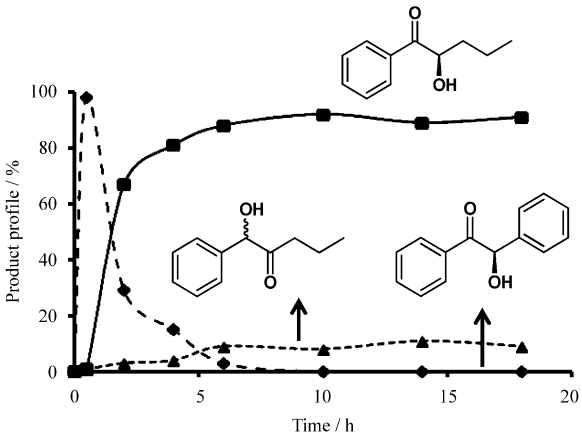


Figure 1. Kinetic profile obtained for the oxidase–lyase one-pot reaction using benzaldehyde and butanol as substrates. Reactions conditions: benzaldehyde (6 mM), butanol (53.5 mM), BAL (20 U, 1 mg mL^{-1}), ThDP (0.15 mM), alcohol oxidase from *Hansenula* sp. (8 U, 0.25 mg mL^{-1}), catalase from bovine liver (12 U, 0.358 mg mL^{-1}), FAD (0.1 mM), phosphate buffer (50 mM, pH 8.0), 2-MeTHF (5 vol.%), $MgSO_4$ (2.5 mM). Product profile determined by ^{1}H NMR.

As observed (Figure 1), the production of benzoin proceeded extremely fast and selectively in the first minutes of the reaction, consistent with previous literature reporting BAL-catalyzed benzoin condensations.[8,11–14] Subsequently, upon enzymatic oxidation of butanol to form butyraldehyde, the crossed carboligation product was formed, reaching approximately 90% conversion in 5–6 h. Interestingly, the other crossed carboligation product—with benzaldehyde as the acceptor and butyraldehyde as the donor—was observed in low concentrations as well. To improve the biocatalytic selectivity over the desired cross-condensation product, the setup of directed evolution rounds[1a] might lead to improved variants of lyases, displaying higher bias for using benzaldehyde as donor substrate. As another option, reaction kinetics could be controlled. For instance, by stopping the reaction at short reaction times (≈2 h), a mixture of the desired crossed product with benzoin was obtained. As both compounds could be easily separated—benzoin precipitates as a solid in aqueous solutions—and (*R*)-benzoin was actually a substrate for BAL as well (Scheme 1), after separation of the crossed aromatic–aliphatic compounds, the remnant benzoin could be recycled again in the reaction to afford more of the desired product.

Finally, the influence of the benzaldehyde loadings in the reaction was assessed by using an excess of aliphatic alcohol in all reactions. Likewise, apart from using 2-MeTHF as a cosolvent for the reaction (to fully dissolve the substrates in the aqueous media), in another set of experiments, butanol was directly used as both cosolvent and substrate for the reaction. Other aliphatic alcohols (e.g., isopropanol) have also been used as cosolvents for lyases[11d] and for other biocatalytic reactions in general.[18] The results of our experimental setup are depicted in Figure 2.

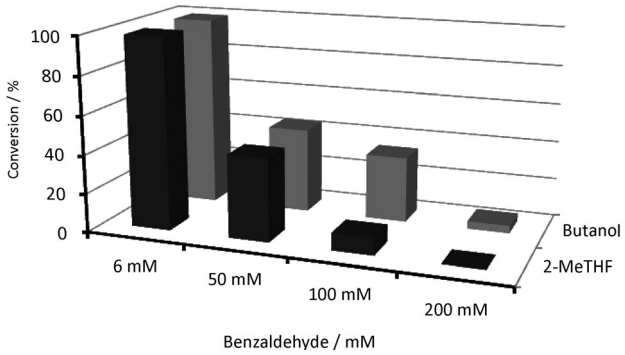


Figure 2. Influence of the benzaldehyde loading in the conceptual one-pot oxidase–lyase setup. Reaction conditions: 1:5 ratio benzaldehyde/butanol in the set of 2-MeTHF as cosolvent; BAL (20 U, 1 mg mL^{-1}), ThDP (0.15 mM), alcohol oxidase from *Hansenula* sp. (8 U, 0.25 mg mL^{-1}), catalase from bovine liver (12 U, 0.358 mg mL^{-1}), FAD (0.1 mM), phosphate buffer (50 mM, pH 8.0), cosolvent (5 vol.%, 2-MeTHF or butanol,), $MgSO_4$ (2.5 mM).

Remarkably, the oxidase–lyase system remained active at higher benzaldehyde loadings (even up to 200 mM benzaldehyde in the case of butanol as the cosolvent), yet at the cost of significantly decreasing the conversion in the crossed aromatic–aliphatic product. The lower conversion may be partly explained by the influence of the butanol concentration. Compared to the use of cosolvent 2-MeTHF with a lower excess of aliphatic alcohol, if butanol was used as the cosolvent and was, thus, present in a higher excess, higher conversions to the crossed α-hydroxyketone were observed at a benzaldehyde concentration of 100 mM. Although the combined one-pot two-step approach was assumed to be feasible and promising at first sight, the observed results clearly pointed out the need for further optimization both at the enzyme level, as well as from the process development point of view (e.g., optimal loading of enzymes, stepwise addition of different substrates). Once these further improvements are installed, it may be expected that higher conversions of a valuable building block can be achieved.

Conclusions

Herein, we explored the possibility of using (biobased) aliphatic alcohols for the in situ enzymatic production of aldehydes and the subsequent lyase-catalyzed carboligation to afford valuable α-hydroxyketones typically with high conversions and always with excellent enantioselectivity. The system allows the use of either biobased cosolvents such as 2-MeTHF or directly alcohols (e.g., butanol) as both substrate and cosolvent for the

production of the crossed α-hydroxyketones. Moreover, the possibilities of affording important optically active building blocks from biorenewable resources represent an important option for future synthetic processes, in which the replacement of petroleum-based resources will be more important. For industrial application, however, extensive process optimization is needed to enable higher productivities and substrate loadings. A possibility for such further improvements would be the genetic design of oxidase and lyase variants that could catalyze the oxidation–carboligation steps in a faster and proper way, or the construction of a designer bug (whole cell) overexpressing all the enzymes for a simplified and even further integrated process. Apart from these genetic considerations, other kinetic aspects related to the reaction setup might also be modified, such as optimal enzyme loadings, step-wise addition of substrates, operation at low reaction times and in repetitive batches. We hope that this work will trigger other research groups to undertake more studies on the setup of enzymatic processes with a focus on biobased substrates.

Experimental Section

Chemicals

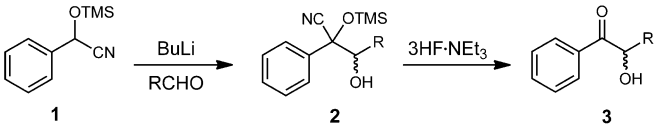
All compounds were purchased from Sigma–Aldrich and were used directly. Benzaldehyde lyase form *Pseudomonas fluorescens* was cloned and overexpressed in *Escherichia coli* cells, and produced by fermentation.[13] After fermentation, BAL was lyophilized and stored at −20 °C until use. BAL characterization was performed by using benzaldehyde as the substrate and benzoin formation was monitored as a control reaction, as reported elsewhere.[13] Alcohol oxidase from *Hansenula* sp. and catalase from bovine liver were purchased from Sigma–Aldrich.

Standard oxidase–lyase protocol

Benzaldehyde (6.36 mg, 0.6 mmol) was dissolved in a 10 mL mixture of 5 vol.% 2-MeTHF, phosphate buffer (50 mM, pH 8.0) containing $MgSO_4$ (2.5 mM), FAD (0.1 mM), ThDP (0.15 mM), and aliphatic alcohol (53.5 mM). After addition of BAL (10 mg, 20 U), alcohol oxidase from *Hansenula* sp. (3.5 mg, 8 U) and catalase from bovine liver (3.5 mg, 12 U), the reaction system was covered with an air-filled balloon and the mixture was gently stirred for 16 h. The reaction mixture was extracted with ethyl acetate (3×20 mL), and the organic layer washed with water (3×20 mL) and brine (1×20 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuum. Reactions were followed by ^{1}H NMR and the enantiomeric excesses were determined by chiral-phase HPLC (Chiralpak IA column, UV detection at 210 nm).

Synthesis of racemates

The reaction scheme is shown in Scheme 2.



Scheme 2. Synthesis of racemates **3**.

Synthesis of **2**: Isopropylamine (3.1 g, 31.4 mmol) and dry THF (60 mL) were added into a flask under argon atmosphere at −78 °C. Butyl lithium (32.8 mmol, 1.15 equiv.) was added dropwise and the reaction mixture was allowed to reach RT within 15 min. The flask was cooled down again to −78 °C and α-(trimethylsilyloxy)phenylacetonitrile **1** (5.8 g, 28.6 mmol) was added dropwise. The reaction mixture was stirred for 15 min until the aldehyde (30.0 mmol, 1.05 equiv.) was added slowly within 30 min into the flask. After 1.5 h the reaction was allowed to reach RT. After stirring for another hour the reaction was quenched by adding 60 mL saturated NH_4Cl solution. After neutralization of the reaction mixture with 10% aqueous HCl solution, the aqueous phase was extracted with EtOAc (3×60 mL) and subsequently washed with water (1×60 mL) and brine (1×60 mL). The combined organic layers were dried over Na_2SO_4. After the removal of the drying agent and solvent, the raw product was purified by flash chromatography (ethyl acetate/petroleum ether 1:20).

Synthesis of **3**:[19] **2** (7.85 mmol) in dry diethylether (10 mL) was charged to a flask under an argon atmosphere. $3HF{\cdot}NEt_3$ (17.28 mmol, 2.2 equiv.) was added and the reaction mixture was stirred for 2 h at RT. Then, saturated $NaHCO_3$ solution was added until neutralization. The aqueous phase was extracted with diethylether (3×20 mL) and washed with water (2×20 mL) and brine (1×20 mL). The organic layer was dried over $MgSO_4$. After the removal of drying agent and solvent, the raw product was purified by flash chromatography (ethyl acetate/petroleum ether 1:20).

Determination of enantiomeric excess

Enantiomeric excesses were determined by HPLC, using a Chiralcel OD-H column (*n*-heptane/isopropanol 99:1, $\lambda = 250$ nm), flow 0.5 mL min^{-1}. Major enantiomer $t_R = 31.4$ min, minor enantiomer $t_S = 22.6$ min (Figure 3).

NMR data of products

NMR spectra were recorded on a Bruker DPX400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: $\delta = 7.27$) and $CDCl_3$ (^{13}C: $\delta = 77.0$) as an internal standard.

2-hydroxy-1-phenylpropan-1-one: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.86 (d, $J = 7.6$ Hz, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 2H), 5.10 (q, $J = 7.0$ Hz, 1H), 1.38 ppm (d, $J = 7.0$ Hz, 3H);

2-hydroxy-1-phenylbutan-1-one: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (d, $J = 7.9$ Hz, 2H), 7.60 (d, $J = 7.5$ Hz, 1H), 7.49 (d, $J = 7.5$ Hz, 2H), 5.05 (q, $J = 3.86$ Hz, 1H), 1.99–1.91 (m, 1H), 1.65–1.56 (m, 1H), 0.93 ppm (t, $J = 7.4$ Hz, 3H); ^{13}C NMR(300 MHz, $CDCl_3$): $\delta = 202.1$, 133.9, 128.8, 128.5, 174.0, 28.78, 8.9 ppm.

2-hydroxy-1-phenylpentan-1-one: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.91 (d, $J = 7.2$ Hz, 2H), 7.61 (d, $J = 7.3$ Hz, 1H), 7.50 (d, $J = 7.4$ Hz, 2H), 5.09 (m, 1H), 1.85–1.39 (m, 4H), 0.91 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR(300 MHz, $CDCl_3$): $\delta = 202.2$, 130.2, 128.8, 128.5, 72.9, 37.9, 18.3, 13.8 ppm.

Benzoin: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.85$–7.19 (m, 10H), 5.88 (d, $J = 6.1$ Hz, 1H), 4.48 ppm (d, $J = 6.1$ Hz, 1H); ^{13}C NMR(300 MHz, $CDCl_3$): $\delta = 198.9$, 139.0, 133.9, 129.2, 129.1, 187.7, 128.6, 127.7 ppm.

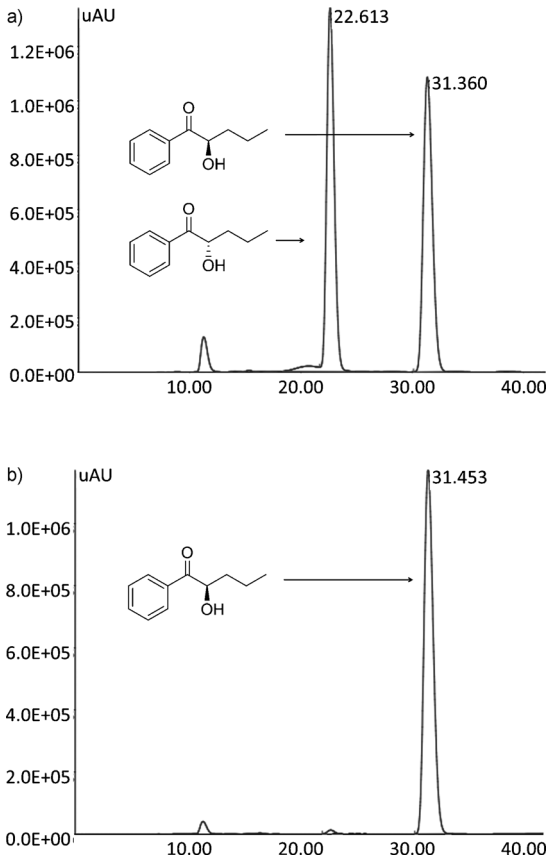


Figure 3. HPLC chromatogram of a) (*R*,*S*)-2-hydroxy-1-phenylpentan-1-one; b) (*R*)-2-hydroxy-1-phenylpentan-1-one obtained by oxidase–lyase carboligation.

Keywords: alcohols · aldehydes · asymmetric synthesis · enzyme catalysis · green chemistry

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