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Guerbet Alcohols: From Processes under Harsh Conditions to Synthesis at Room Temperature under Ambient Pressure

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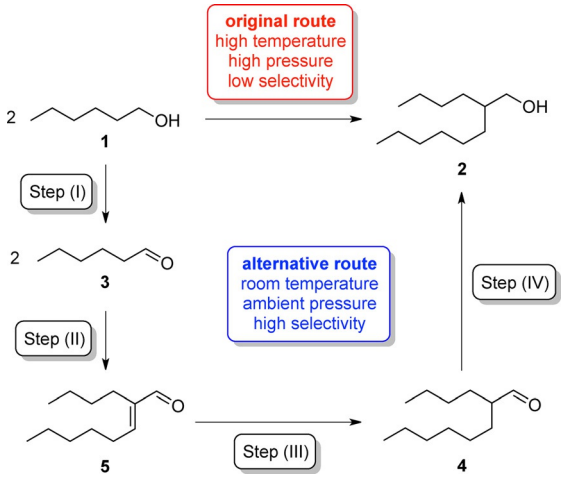
Dedicated to Professor Dr. Albrecht Berkessel on the occasion of his 60th birthday

A novel synthetic approach towards Guerbet alcohols, which are important intermediates in the production of plasticizers, lubricants, and surfactants, was developed. In contrast to the harsh reaction conditions of Guerbet alcohols produced today, which include high temperatures, the new developed process runs at room temperature. The key feature of this alternative process is the combination of organocatalytic and enzymatic steps towards a chemoenzymatic synthesis. In detail, the piperidinyloxyl-catalyzed oxidation of 1-hexanol by using hypochlorite and the lysine-catalyzed homoaldol condensation of the resulting aldehyde were combined with two subsequent enzymatic reductions of the C=C and C=O bonds of the in situ formed 2-branched α,β-unsaturated aldehyde by means of an ene reductase from *Gluconobacter oxydans* and an alcohol dehydrogenase from *Rhodococcus* sp. under in situ cofactor regeneration. The desired 2-branched aliphatic primary alcohol was obtained with high conversion and selectivity and without the need for intermediate purifications.



Scheme 1. Original and alternative routes for the Guerbet reaction of 1-hexanol (**1**) to 2-butyl-1-octanol (**2**).

Guerbet alcohols, the first synthesis of which dates back to 1899, are 2-branched primary aliphatic alcohols[1,2] that have a distinctly lower melting point than their straight-chain homologues owing to their sterically demanding structures. This property and their amphiphilic character make them attractive intermediates, for example, for plasticizers, lubricants, and surfactants.[3] The original Guerbet reaction is particularly used for the production of higher homologues of 2-branched aliphatic alcohols on the industrial scale[4] and formally represents a "self-condensation reaction" of primary aliphatic alcohols (Scheme 1). A selected example (and a model reaction for our studies) is the conversion of 1-hexanol (**1**) into 2-butyl-1-octanol (**2**).

In spite of the broad industrial application range of Guerbet alcohols, their preparation still has drawbacks, including elevated reaction temperatures and high-pressure conditions, both of which are required even if alkali hydroxides and Raney-Ni are used as catalysts.[1,5] Such harsh reaction conditions also cause selectivity concerns and the formation of undesired by-products. Modern improvements of the "classic" Guerbet reaction include the application of transition-metal-based hydrogenation catalysts[6] such as Rh,[7] Ir,[8] Pd,[9] and Cu[10] as well as metal oxides[11] to work at lower temperatures and atmospheric pressure. However, owing to various limitations for their use at the industrial scale, the "classic" process at high temperature and pressure is still used. Thus, the development of sustainable alternatives enabling the synthesis of Guerbet alcohols under smooth reaction conditions and avoiding the Cannizzaro[12] and Tishchenko[13] reactions as two major side reactions based on disproportionation of the aldehyde is a current challenge in organic chemistry.

In continuation of our studies on chemoenzymatic one-pot processes,[14] we became interested in integrating biocatalytic reactions in multistep syntheses of bulk chemicals. Biocatalysis already plays an important role in today's industrial production of fine chemicals, for which stereoselectivity is often required. However, only a few industrial processes for bulk chemicals involve enzymatic steps.[15,16] On the other hand, biocatalysts provide unique advantages such as high selectivity and mild reaction conditions, which thus also makes them attractive for the field of bulk chemicals. Addressing this issue, in the following, a biointegrated cascade synthesis of Guerbet alcohols is reported.

In detail, our concept follows the mechanism of the "classic" Guerbet reaction (Scheme 1) but at the same time allows these reaction steps to be conducted at room temperature under

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ambient pressure conditions instead of under harsh reaction conditions. Extensive studies have provided insight into the mechanism of the Guerbet reaction,[17] which can be divided into four sequential steps: one, oxidation of **1** to hexanal (**3**); two, aldol condensation to 2-butyl-2-octenal (**5**); three, C=C bond reduction to 2-butyloctanal (**4**); four, aldehyde reduction to **2**. Our goal was to develop highly efficient reaction steps catalyzed by chemo- or biocatalysts that run at room temperature and ambient pressure and that are compatible with each other so that they can be integrated within a one-pot-like cascade sequence without the need to isolate any intermediate.

Starting with the initial step of the process, namely, the oxidation of the primary alcohol to the aldehyde, extensive studies were made by using model substrate **1** by evaluating different "green" oxidation catalysts. One of the challenges in working with aldehydes, especially in an aqueous environment, is their oxidation sensitivity, as documented by Shapiro and Vigalok.[18] In agreement with their results, we found aldehyde **3** (as well as the other aldehydes studied) to be rapidly oxidized in air. To overcome this undesired oxidation, all steps with aldehydes as substrates and/or products were performed under an argon atmosphere and by using degassed solvents for the reactions. Upon evaluating an enzymatic oxidation by screening several alcohol dehydrogenases, only poor oxidation properties were identified, which thus made an efficient oxidation process difficult (data not shown). In addition, oxygen-consuming alcohol oxidases were tested and showed moderate activity, but unfortunately, **3** was further oxidized to the corresponding acid (data not shown). Next, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and related polymer-immobilized piperidinyloxyl (PIPO)[19] jointly with bromide as a catalytic system was used for the oxidation of **1** owing to the known[20] prevention of overoxidation of aldehydes in air in the case of TEMPO. In this process, cheap hypochlorite serves as a stoichiometric oxidant in an aqueous/organic biphasic solvent mixture. With both TEMPO and PIPO, high conversions were obtained after only 90 min at a low catalyst loading of 1 mol% (Figure 1). Under optimized conditions (i.e., PIPO, dosage of hypochlorite), an excellent conversion of >99% and selectivity of 98% were obtained for the formation of aldehyde **3**. Notably, only a minor amount of hexyl hexanoate (2%) was found, which thus indicates that byproduct formation was nearly prevented. In addition, no overoxidation to the corresponding acid was found with PIPO despite the fact that an excess amount of hypochlorite (1.5 equiv.) was used.

The second step consists of a self-aldol condensation of aldehyde **3**. A screening of potential catalysts for this reaction revealed L-lysine to be the most suitable candidate upon conducting this aldol condensation in an organic solvent. In the presence of L-lysine (20 mol%), quantitative conversion to desired product **5** was obtained after 6 h (Figure 2). The use of an organic solvent offers the advantage of the direct use of the organic phase from step 1 containing aldehyde **3**, which avoids workup of aldehyde **3** prior to step 2. Furthermore, the amino acid L-lysine represents an attractive catalyst for various reasons: first, it is produced on >1 000 000 metric-ton scale and thus is commercially available on large scale; second,

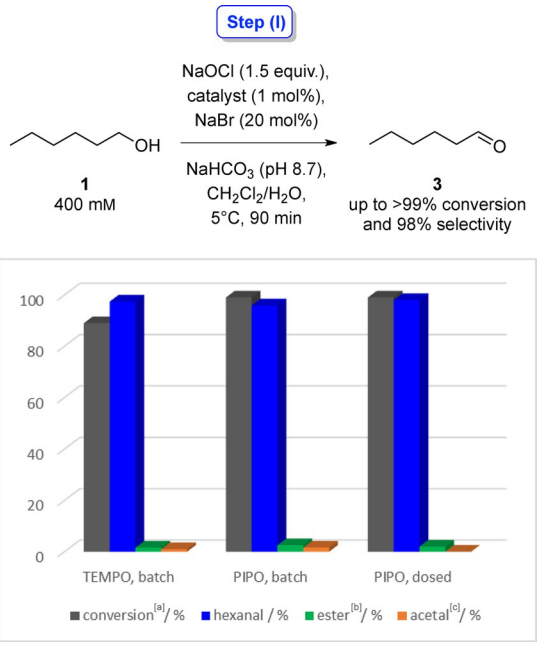


Figure 1. Comparison of TEMPO and PIPO as catalysts for the oxidation of **1** in batch and under dosage of hypochlorite. Products are given as percentage of the sum of all products. [a] Overall consumption of substrate. [b] Hexyl hexanoate. [c] Hexanal dihexyl acetal.

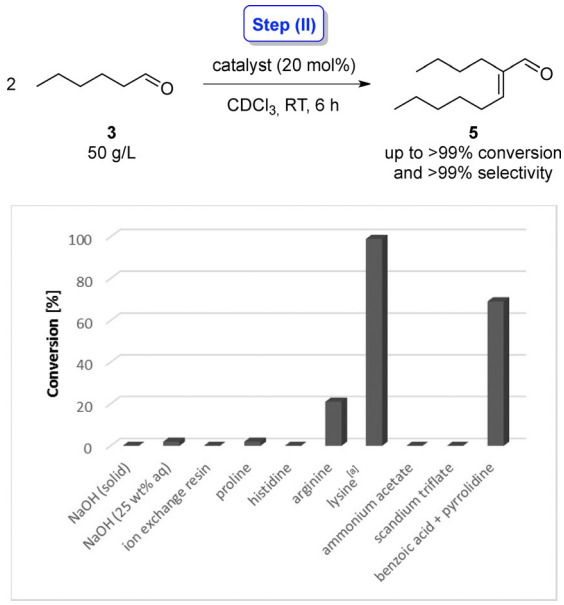


Figure 2. Screening of catalysts for the homoaldol condensation of hexanal (**3**). [a] Confirmed in CH_2Cl_2 at 50 g L^{-1} by GC analysis.

L-lysine is insoluble under the reaction conditions, which thus enables simple catalyst separation from the reaction mixture and provides an opportunity for catalyst recycling.

The third and fourth steps consist of reduction of the C=C bond in **5** by means of an ene reductase (ER), followed by reduction of formed aldehyde **4** catalyzed by an alcohol dehydrogenase (ADH). Both the ER and ADH are NAD(P)H dependent and therefore require an in situ cofactor for regeneration. For these enzymatic ene and aldehyde reductions, 12 ERs and

11 ADHs were tested with respect to their activity by means of spectrophotometric screening; this revealed an ER from *Gluconobacter oxydans* (GOx-ER)[21] and an ADH from *Rhodococcus* sp. (Rsp-ADH)[22] to be suitable and the most promising candidates (for data of this screening, see the Supporting Information). Both enzymes show complementary cofactor specificities, as GOx-ER prefers NADPH and Rsp-ADH prefers NADH. Hence, for in situ cofactor regeneration, a glucose dehydrogenase (GDH) accepting both cofactors and D-glucose were chosen, which thus enabled efficient in situ recycling of both cofactors although with the use of only one glucose dehydrogenase (which would be beneficial for subsequent combination of steps 3 and 4).

With these two efficient biocatalysts in hand, we next conducted biotransformations on a preparative scale (Figure 3). First, enzymatic reduction of the C=C and C=O bonds was performed separately in pure aqueous buffer as the solvent; moderate conversions of 70 and 78% were obtained, respectively, with high selectivities of >99%. However, during downstream processing and product-isolation steps, a significant amount of material was lost (substrate **5** and intermediate **4**) and precipitation of the protein was found. As both compounds bear aldehyde groups and aldehydes are likely to react with surface lysine residues, we assume that this loss is caused by adduct formation through Schiff base formation with enzymes, as previously described.[23] A well-known option to address this issue is to keep the apparent concentration of the aldehyde low by dosing the substrate and by applying a fast aldehyde-consuming reaction. Thus, from this perspective we also considered an increase in the efficiency and conversion of step 3 and in particular step 4 in buffer as a task of highest priority. Towards this end, an organic cosolvent was added to increase the solubility of the substrates. In this study, water-immiscible and water-miscible solvents were used; 2-methyltetrahydrofuran (2-MeTHF) and methanol (MeOH) were chosen as representatives because of their preferred use in terms of sustainability (Figure 3).

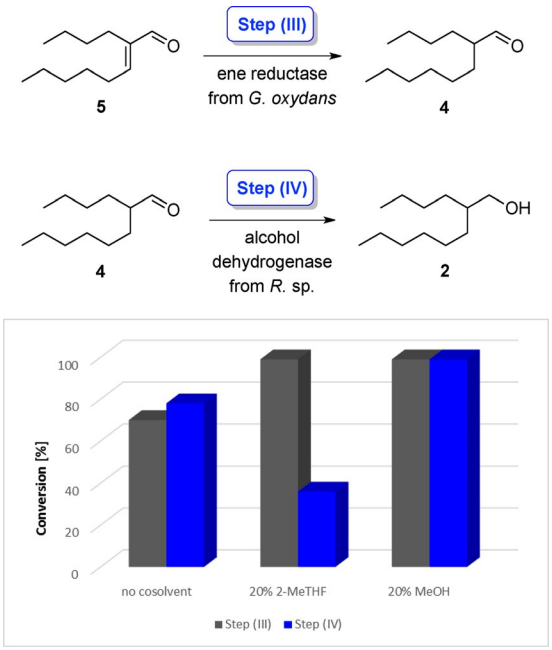


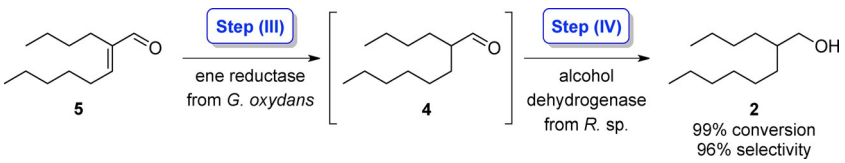
Figure 3. Preparative-scale enzymatic reactions in different solvent systems. Reaction conditions: GOx-ER or Rsp-ADH, $NAD(P)^+$, GDH, D-glucose, potassium phosphate buffer (200 mM, pH 7), 20% v/v organic cosolvent, RT, 24 h.

In the presence of 20% v/v 2-MeTHF, quantitative conversion for the reduction of enal **5** was obtained (step 3), but a low conversion (36%) was found for the ADH-catalyzed reduction of aldehyde **4** in step 4. However, upon changing the organic cosolvent to a water-miscible one, we were pleased to find excellent conversions (>99%) and selectivities (99%) for both steps 3 and 4 in the presence of 20% v/v MeOH. Notably, recycling of the in situ cofactor proceeded fully through the GDH-catalyzed transformation of D-glucose into D-gluconolactone. Alternative consumption of MeOH through the ADH and its possible oxidation to formaldehyde was not an issue, because the activity of Rsp-ADH for MeOH oxidation is very low ($<0.1\ U\ mg^{-1}$).

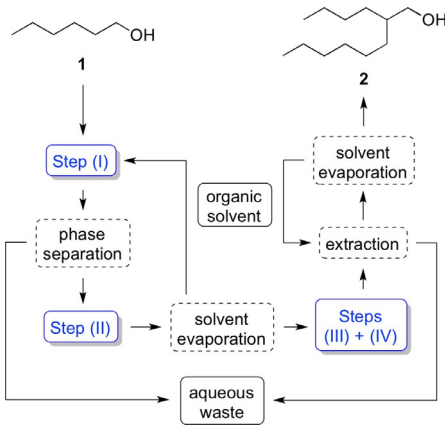
We next focused on the combination of steps 3 and 4 towards a tandem process; this was challenging, as **5** is also a potential substrate for the ADH, which would then lead to an undesired side reaction. Resulting 2-butyl-2-octenol in turn is not a substrate for the GOx-ER. However, we were pleased to find that upon combining reactions steps 3 and 4 in a tandem-type one-pot process, quantitative conversion and a high selectivity of 94% (showing only 6% of 2-butyl-2-octenol as a byproduct) were obtained (Scheme 2).

After establishing the individual reactions in steps 1 to 4 successfully and already obtaining a tandem-type combination of steps 3 and 4, a "proof of concept" for a combined process of all steps with minimized required workup steps was demonstrated (Scheme 3).

In such a process, initial PIPO-catalyzed oxidation of **1** (step 1) led to >99% conversion and 98% selectivity for aldehyde **3**. After simple, but careful, phase separation (to ensure complete absence of water) and without further workup, L-lysine (in total 40 mol%, added in two portions) was added to catalyze the desired aldol condensation to **5** (step 2). Both high conversion (92%) and high selectivity (>99%) were

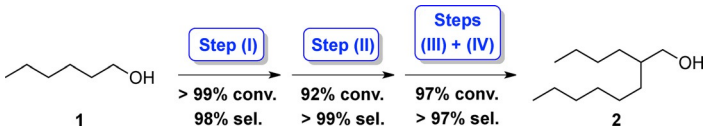


Scheme 2. Preparative-scale tandem-type one-pot process. Reaction conditions: GOx-ER and Rsp-ADH, $NAD(P)^+$, GDH, D-glucose, potassium phosphate buffer (200 mM, pH 7), 20% v/v MeOH, RT, 24 h.



Scheme 3. Workup illustrating the flow chart of the process unit-operation steps to 2-butyl-1-octanol (**2**) starting from 1-hexanol (**1**).

obtained in this step. The reaction mixture was washed with dilute aqueous hydrochloric acid, dried with magnesium sulfate, and concentrated under reduced pressure to yield 80% crude **5** over both steps. Using crude product **5** for the subsequent two-step enzymatic reduction process (steps 3 and 4) then gave the desired target product, 2-butyl-1-octanol (**2**), with 97% conversion and 97% selectivity, which thus indicated that residual components of the previous steps (such as PIPO and dichloromethane) had no significant negative impact on the two-step tandem biotransformation (steps 3 and 4). A yield of 78% was achieved for the last two steps, which led to a combined overall yield of 62% (Scheme 4).



Scheme 4. Biointegrated four-step cascade to synthesize 2-butyl-1-octanol (**2**) starting from 1-hexanol (**1**).

In conclusion, a "proof of concept" for the synthesis of Guerbet alcohols at room temperature under ambient pressure conditions was established (in contrast to today's industrial production for which harsh reaction conditions, e.g., high temperature, are needed). The process concept was based on a chemoenzymatic synthesis and consisted of a combination of two organocatalytic steps with a biocatalytic two-step tandem process. In detail, this biointegrated cascade to Guerbet alcohols started from 1-hexanol as a readily available aliphatic primary alcohol and led to both high conversions and selectivities for all four steps. The combination of the four reaction steps towards a cascade process was done with minimized required workup steps for the intermediates and gave conversions of 92 to >99% and selectivities of 97 to >99% for steps 1 to 4. Among the challenges for future work are further optimization of the reaction and workup steps as well as an increase in the substrate loading and overall yield of the desired Guerbet alcohol product.

Experimental Section

Combined chemoenzymatic cascade for the synthesis of Guerbet alcohol 2 (according to Scheme 4)

After dissolving 1-hexanol (**1**; 1 mL, 8 mmol) in CH_2Cl_2 (20 mL), NaBr (82.3 mg, 0.8 mmol, 10 mol%) and PIPO (25 mg, 0.08 mmol aminoxyl, 1 mol%) were added, and the resulting mixture was cooled to 5 °C. Then, a precooled solution of 0.35 M NaOCl (12 mmol, 1.5 equiv.) and $NaHCO_3$ (0.53 M, 17.7 mmol, 2.2 equiv.) in H_2O (33.7 mL) was added over 60 min, and the mixture was stirred for another 30 min at 5 °C. The organic phase, showing >99% conversion and 98% selectivity, was passed through a phase-separating filter. Subsequently, L-lysine (229 mg, 1.6 mmol, 20 mol%) was added, and the mixture was stirred for 16 h at room temperature prior to the addition of an additional portion of L-lysine (229 mg, 1.6 mmol, 20 mol%). After a total reaction time of 48 h, 92% conversion and >99% selectivity were obtained for aldol condensation product **5**. The mixture was washed with 0.5 M HCl (3×20 mL) and dried ($MgSO_4$) prior to evaporation of the solvent under reduced pressure to obtain **5** as a crude product (80% yield). The enzymes GOx-ER (10 U, 6.6 mg purified by *N*-terminal His-tag, 1.5 U mg^{-1}, 100 U $mmol^{-1}$) and Rsp-ADH (20 U, 2.73 mL crude extract, 7.3 U mL^{-1}, 200 U $mmol^{-1}$), GDH2 (Amano, 100 U, 1000 U $mmol^{-1}$), cofactor $NADP^+$ sodium salt (2.3 mg, 3 μmol, 3 mol%), cofactor NAD^+ (2.0 mg, 3 μmol, 3 mol%), and D-glucose (0.6 mmol, 108.1 mg, 6 equiv.) were dissolved in degassed potassium phosphate buffer (pH 7, 200 mM) to a total volume of 4 mL. Crude product **5** (18.1 mg, 0.1 mmol) obtained as described above was dissolved in MeOH (1 mL) and was added to the solution. The mixture was stirred at room temperature for 24 h, acidified with 0.5 M HCl (1 mL), and extracted with methyl *tert*-butyl ether (3×5 mL), thus as a step in which water-soluble glucose was also separated. A conversion of 97%, a selectivity of 97%, and an overall yield of 62% were obtained after evaporation of the organic solvent under reduced pressure.

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Keywords: biocatalysis · chemoenzymatic synthesis · domino reactions · Guerbet alcohols · organocatalysis

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