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Reaction Cascade | Hot Paper

Lewis Base–Brønsted Acid–Enzyme Catalysis in Enantioselective Multistep One-Pot Syntheses

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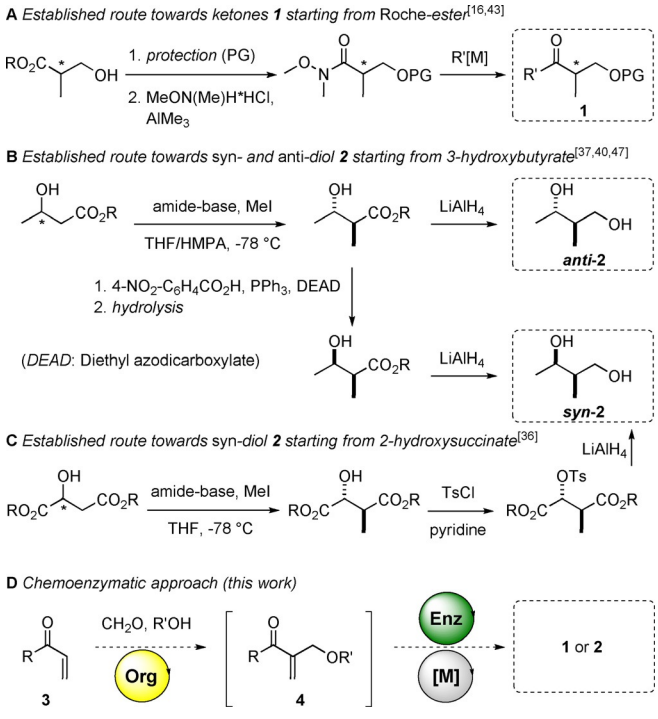
Abstract: *Establishing one-pot, multi-step protocols combining different types of catalysts is one important goal for increasing efficiency in modern organic synthesis. In particular, the high potential of biocatalysts still needs to be harvested. Based on an in-depth mechanistic investigation of a new organocatalytic protocol employing two catalysts {1,4-diazabicyclo[2.2.2]octane (DABCO); benzoic acid (BzOH)}, a sequence was established providing starting materials for enzymatic refinement (ene reductase; alcohol dehydrogenase): A gram-scale access to a variety of enantiopure key building blocks for natural product syntheses was enabled utilizing up to six catalytic steps within the same reaction vessel.*

Introduction

While natural product syntheses usually focus both on the target compound and on the key steps, reporting the production of starting material is often neglected or hidden in a footnote. This actually holds also true for many systematic endeavors. However, an efficient, scalable access to key building blocks is obviously of utmost importance for the success of a project, saving time, resources and financials. In this context, catalytic cascades can play an important role in target-oriented organic synthesis.[1–3] In recent advances it was demonstrated how elegant advantages of the individual catalytic steps can be exploited without the need for extensive purification, long hands-on times or large amounts of solvents. Sometimes combined approaches even turn out to be superior to individual steps by providing higher overall yields or avoiding the direct handling of certain troublesome materials. Naturally, however, those potentially fruitful endeavors bear challenges in orchestrating a suitable arrangement of reagents, catalysts and conditions to prevent not only undesired side reactions or decomposition of compounds, but also especially the inactivation of catalysts.[4–13]

The focus of the present study is on α-methylated ketones **1**[14–31] and diols **2**,[32–40] which are used extensively in natural product syntheses. Over decades, they not only proved indispensable for finding and examining new pharmacologically active agents, but also for elucidating the mode of action of established blockbusters ranking among the most important drugs by sale.[41,42]

Well-established routes towards ketone **1**[16,31,43] and diols **2**[36,37,44–47] apply stoichiometric amounts of reagents and enantiomerically pure starting materials (Scheme 1 A–C).[48]



Scheme 1. Key building blocks **1** and **2** for natural product syntheses. A–C) Established routes from enantiomerically pure starting materials; D) anticipated one-pot chemoenzymatic sequence from achiral enones **3** (**Org**: organocatalyst DABCO; **Enz**: biocatalyst; **M**: metal catalyst). Additional abbreviations not provided in the text or scheme: PG – protecting group; Ts – tosylate; THF – tetrahydrofuran.

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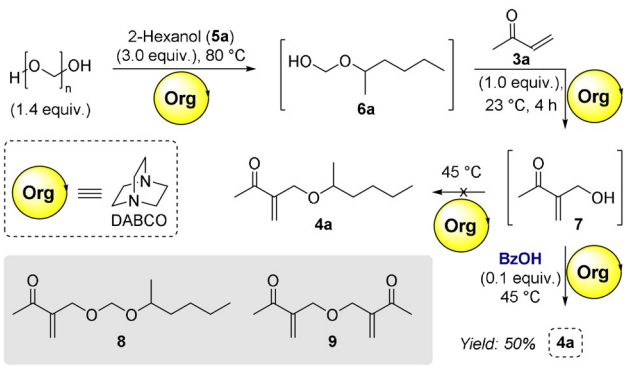
The methods have been utilized for decades until the recent past, proving productive and suitable for natural product syntheses. However, overcoming inconvenient work-up procedures as well as preventing the use of reagents such as trimethylaluminium, methyl iodide or hexamethylphosphoric triamide (HMPA) was the resource-economic goal of the present endeavor: Inexpensive starting materials **3** should be converted in a one-pot enantioselective catalytic procedure to the desired products, thereby drastically reducing the downstream processing operations. It was anticipated that a combination of an amine-based organocatalyst (yielding the intermediate **4** via a Morita–Baylis–Hillman-type[49–51] reaction sequence) with suitable biocatalysts would provide the target compounds (Scheme 1D).

Results and Discussion

Organocatalytic protocols. Based on our experience with reductases,[52–54] we were confident that the selective reductions of enone **4** should be feasible. However, finding compatible conditions for providing the required intermediate **4** might prove more difficult: While the one-pot Morita–Baylis–Hillman etherification sequence was feasible with primary alcohols,[55] the overall conversion would require improvement. Furthermore, upon applying the identical conditions for secondary alcohols, the transformation failed. As exemplified for 2-hexanol (**5a**), the corresponding intermediates **6a** and **7** were formed as expected, but the etherification leading to product **4a** did not occur upon heating to 45 °C (Scheme 2). Instead, side products **8** and **9** were formed indicating the comparable reduced nucleophilicity of the secondary alcohol **5a**. It was found (and later further optimized, see Supporting Information) that upon addition of benzoic acid (BzOH) the desired product **4a** could indeed be obtained for the first time. It is also interesting to note that the reaction conditions are not very sensitive to the relative DABCO:BzOH ratio (see Supporting Information). Before optimizing the reaction conditions as well as extending the scope and demonstrating the versatility of the approach



Scheme 2. Morita–Baylis–Hillman etherification sequence utilizing 0.05 equiv of DABCO as organocatalyst (added only once when premixing paraformaldehyde and alcohol **5a** before heating the mixture to 80 °C; all other components were added subsequently as shown). The formation of side products **8** and **9** was omitted upon addition of benzoic acid (BzOH).

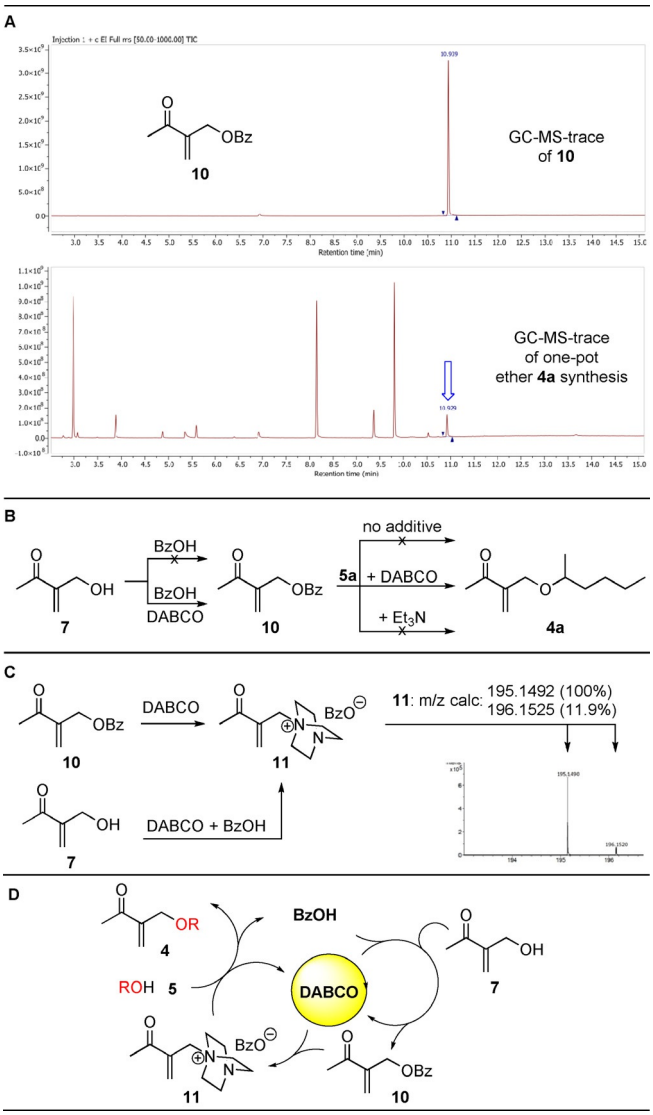
for the one-pot synthesis of the target compounds, we decided to shed some light on the role of the carboxylic acid for the etherification process.

Mechanistic insights. In order to elucidate the role of benzoic acid during the newly found etherification protocol, we first intended to rule out a process of general proton catalysis. Thus, we tested a series of non-carboxylic Brønsted acids being added to the one-pot etherification reaction. Several additives with p*K*a-values matching or not matching those of the carboxylic acids did not provide equally good results under otherwise identical conditions (for details see Supporting Information).

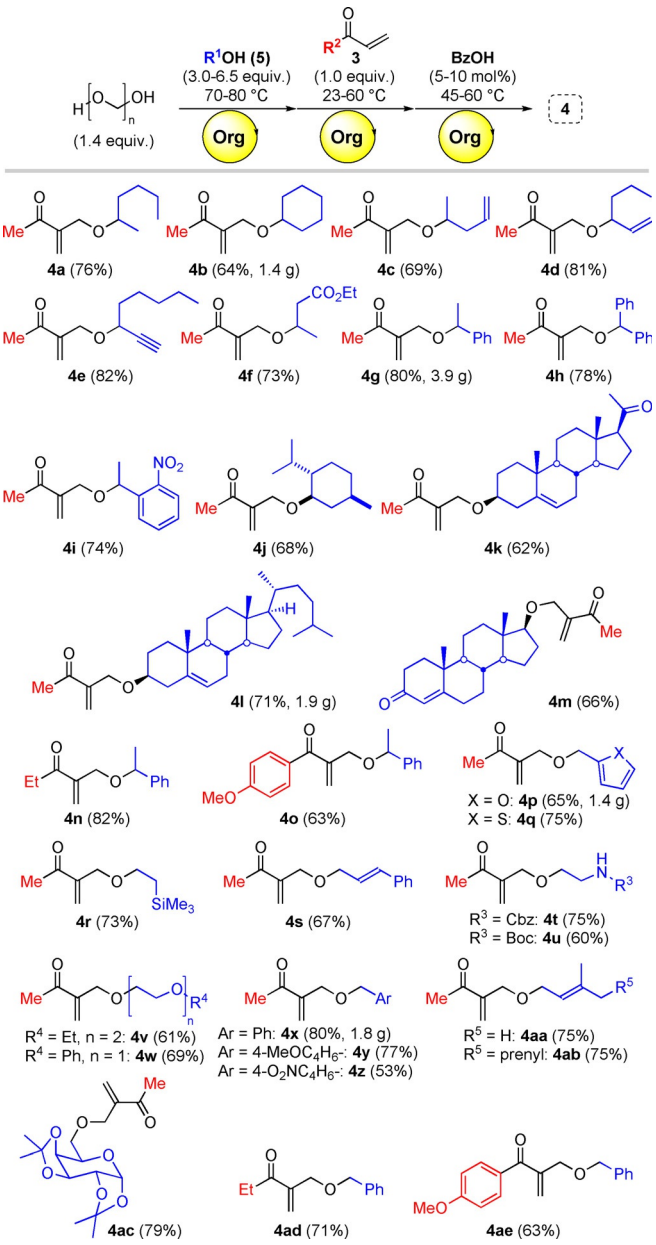
Next, the benzoate **10** of the corresponding Morita–Baylis–Hillman product **7** was prepared as a reference compound to evaluate its role in the overall process. Interestingly, GC–MS analysis revealed that benzoate **10** is indeed also formed during one-pot ether **4a** synthesis (Scheme 3A). Furthermore, isolated intermediate **7** was not converted yielding ester **10** under reaction conditions in the absence of DABCO. The organocatalyst is also essential for the following etherification: Ether **4a** is neither formed in the absence of the additive nor in the presence of a Brønsted base[56,57] such as triethylamine (Scheme 3B; see also Supporting Information). Alternatively, we considered the involvement of a highly electrophilic ammonium species **11**.[58] Its presence could be confirmed by high resolution mass spectrometry when treating ester **10** with DABCO as well as upon converting alcohol **7** in the presence of benzoic acid (Scheme 3C and Supporting Information).

From the results obtained, a plausible central role of DABCO in the reaction mechanism can be deduced as its involvement in the formation of the key intermediates **10** and **11** could be verified. Furthermore, benzoic acid can be considered as a non-proton co-catalyst ultimately required for the formation of the electrophilic intermediate **11**, boosting the formation of ethers also derived from secondary alcohols **5** (Scheme 3D).

Scope. Based on the mechanistic insights, a general protocol for a one-pot procedure towards enones **4** could be established after some optimization in detail (see Supporting Information: In particular, the synthesis of steroid-derived derivatives **4k–m** requires special attention due to low solubility). The versatility was tested with a series of primary and secondary alcohols **5** (Scheme 4). It was demonstrated that not only simple alkyl- and aryl-substituted derivatives **4a–g** could be accessed in good to excellent yield, but also sterically demanding compounds such as **4h–m**. Furthermore, the acceptor **3** is not limited to methyl vinyl ketone (**3a**, R^2 = Me), but also substituent R^2 can be altered as was shown in the synthesis of ethyl- and aryl ketones **4n + o**. Also, primary alcohols were introduced with a wide range of ethers **4p–4ae** bearing various functional groups that were compatible with the reaction conditions. Overall, 31 examples with an average yield of 71 % over three steps could be provided from mostly commercially available materials by the established protocol in scale with reagent grade purity determined by quantitative NMR spectroscopy (qNMR) or elemental analysis. It should be noted that ethers of tertiary alcohols could also be accessed by evaporating the sacrificial secondary alcohol (e.g. hexa-



Scheme 3. Mechanistic investigations: A) GC–MS confirmation of formation of benzoate **10** during ether synthesis; B) DABCO as essential catalyst for the formation of **10** as well as **4a**. For the conversion of alcohol **7** to ester **10** 0.10 equiv DABCO was used (with 0.2 equiv BzOH in THF). The same amount of DABCO with 8 equiv of **5a** was applied in the second set of experiments when transforming the ester **10** to ether **4a**; C) detection of ammonium salt **11** via high resolution mass spectrometry (1 equiv of DABCO used); D) proposed central role of DABCO during the one-pot etherification process.

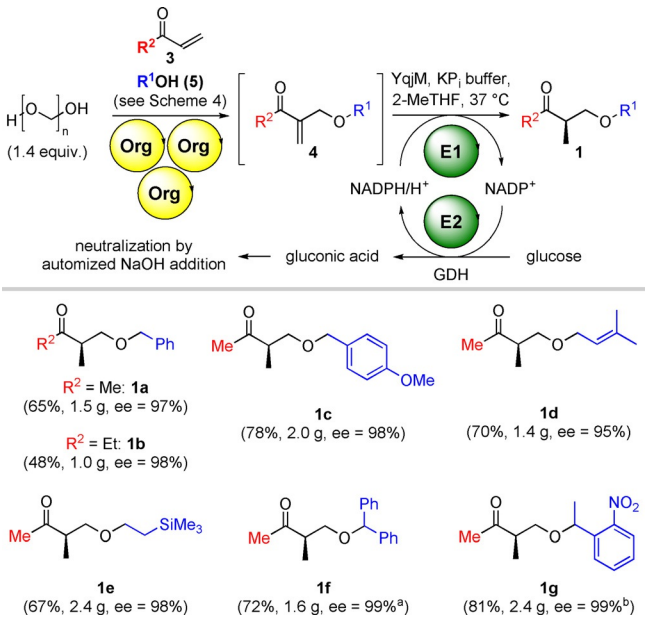


Scheme 4. Scope of one-pot Morita–Baylis–Hillman etherification protocol (**Org** = DABCO). For solid alcohols not melting under the given conditions: addition of minimum amounts of suitable solvents; occasional low loadings of alcohol due to restricted solubility (please see Supporting Information for individual procedures).

fluoro-2-propanol or 2-propanol) of the first step, before adding the alcohol of choice and the benzoic acid (see Supporting Information for details).

Chemoenzymatic one-pot syntheses. With a short, mild, and productive procedure for the synthesis of starting materials **4** in hand, we turned our attention to their utilization. We demonstrated that 1,4-additons of benzyl mercaptan were feasible in one-pot fashion and that the unsaturated ketones are suitable as monomers for standard free radical polymerization (see Supporting Information for procedures and characterization of the corresponding homo- and copolymers as well as some preliminary results on enantioselective 1,4-additions of benzyl mercaptan). We next focused on the one-pot synthesis of building blocks **1**. For the only additional enantioselective reduction step required, the versatile YqjM-wildtype ene reductase from *Bacillus subtilis* (EC: 1.6.99.1) was our biocatalyst of choice.[53,59–63] To our delight, straightforward addition of the biocatalytic system including a glucose dehydrogenase-based co-factor recycling (NADPH – nicotinamide adenine dinucleotide phosphate) and low amounts of 2-MeTHF as a co-solvent to the very same flask of an organocatalytic batch yielded full conversion of benzylated model substrate **4x** into the corresponding α-methylated ketone **1a** at 37 °C within 6 h. In order to translate the findings into a useful organic synthetic application, we

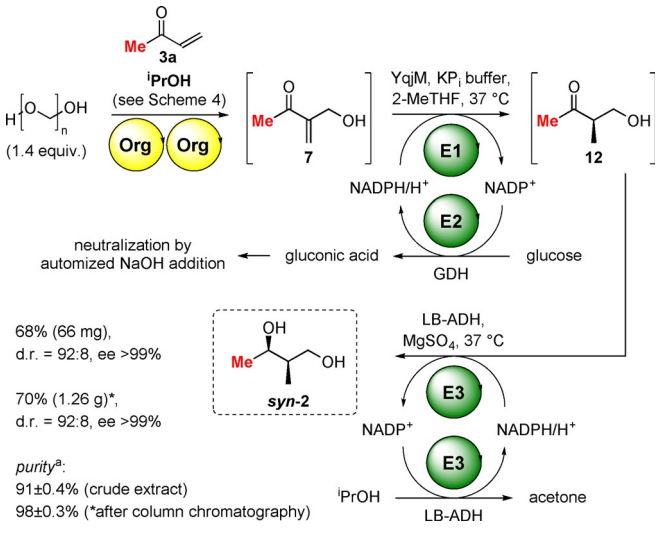
first of all scaled the preparation of building block **1a** to the gram-level revealing easy feasibility in excellent enantiomeric excesses of >98%, very good yields of 65% over four consecutive catalytic steps (90% per step) and high purity of the isolated product (Scheme 5). Spurred by the positive



Scheme 5. Gram-scale enantioselective synthesis of building blocks **1a–g** via an organo- and biocatatalytic four-step one-pot sequence from commercially available vinyl ketones [**E1**: ene reductase YqjM (57–221 U mmol^{-1}); **E2**: glucose dehydrogenase (GDH; 34–69 U mmol^{-1}); KP_i-buffer – potassium phosphate buffer]. a) For both diastereoisomers, d.r. 50:50. b) 2-MeTHF (0–2.5% v/v) was already introduced for the coupled organocatalysis.

results, we sought for reasonable diversity of the compounds being produced, which is an often challenging aspect when dealing with enzyme-catalyzed processes known for certain substrate specificities. However, utilization of ethyl derivative **1b** (48%, 98% *ee*) as a substrate still proved to be feasible. Further alteration by introduction of structurally diverse ethers commonly used as organic protecting groups also turned out to be possible by the modular exchange of the employed alcohol. In addition to the *p*-methoxybenzyl derivative **1c** (PMB; 78%, 98% *ee*), prenylic system **1d** (70%, 95% *ee*) and silicon-based compound **1e** (67%, 98% *ee*) could be provided readily, the latter two even without the need for any additional co-solvents. Remarkably, the enzyme appears to be quite tolerant to steric demand on the "non-ketone side" of the substrates as bulky benzhydryl derivative **1f** (72%, 99% *ee*) could be accessed under increased biocatalyst loadings. Also, transformation into nitro-containing compounds **1g** (81%, 99% *ee*) proceeded smoothly without undesired nitroreductase activity being detected.[62] Again, the "non-ketone side" of the substrate seems to be greatly unaffected by the active site of the enzyme, as evidenced in no observable discrimination between vinyl ketones' **4i** enantiomers. On average, the sequence towards building blocks allowing versatile deprotection strategies in subsequent applications could be performed on a gram-scale for all derivatives with excellent enantioselectivities of Ø = 98% and very good yields of Ø = 69% over four steps (91% per step) in high purities of Ø = 97% (by qNMR). If desired, excesses of alcohols being used for the preparation of ethers **4** could be re-isolated easily in excellent yields and high purities (see Supporting Information).

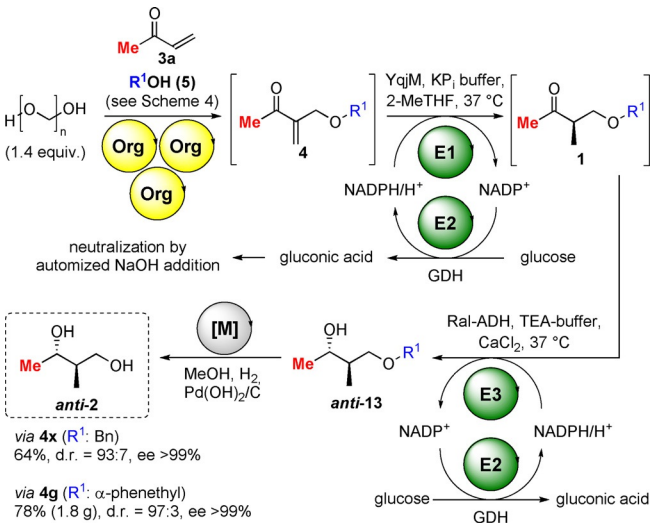
Next we turned towards the one-pot preparation of 2-methylbutane-1,3-diol (**2**). Intermediate **7** appears to be the ideal precursor: By combining two biocatalytic steps, namely the ene reductase-catalyzed reduction of the C=C double bond and the alcohol dehydrogenase (ADH)-catalyzed reduction of the carbonyl group, the diol **2** should be accessible. While the YqjM was again the ene reductase of choice, the utilization of stereocomplementary ADHs[52–54,64–68] was envisaged to provide enantiopure *syn*- and *anti*-products **2**. Initial screening revealed that the Prelog-type LB-ADH from *Lactobacillus brevis* enabled full conversion of isolated substrate **7** giving the (*R*,*R*)-configurated *syn*-diol ***syn*-2** in good diastereoselectivity (d.r. 91:9). *Anti*-Prelog-type T-ADH from *Thermoanaerobacter* sp. and Ral-ADH from *Ralstonia* sp. also provided full conversion of the starting material now towards (*R*,*S*)-diol ***anti*-2**. However, the diastereoselectivity remained unsatisfactory (d.r. < 84:16; see Supporting Information). Consequently, we first focused on the one-pot procedure towards the *syn*-compound ***syn*-2**. After testing the compatibility of all individual catalytic steps, full conversion after each step could be detected translating into very good yields of isolated product ***syn*-2** in the consecutive one-pot procedure (68%, d.r. 92:8, >99% *ee*; Scheme 6). Scaling the reaction proved to be unproblematic: In gram-scale the yields were almost identical (70%, same selectivity, purity 98%) and it should be noted that the crude



Scheme 6. Gram-scale enantioselective synthesis of building block ***syn*-2** via an organo- and biocatalytic four-step one-pot sequence from commercially available vinyl ketones **3a** [**E1**: ene reductase YqjM (24 U mmol^{-1}); **E2**: glucose dehydrogenase (GDH; 24 U mmol^{-1}); **E3**: LB-ADH (860 U mmol^{-1})]. a) Determined via qNMR.

product already exhibited a high degree of purity (91% according to qNMR).

Lastly, we decided to adjust strategies and employ substrate design to overcome the so far insufficient diastereoselectivity for the preparation of the remaining diastereoisomer of (*R*,*S*)-diol ***anti*-2**. Therefore, we resorted to our established four-step one-pot synthesis of benzyl ether **4x** and tested the elongation of the sequence by the addition of the Prelog-type T-ADH or Ral-ADH directly to the reaction mixture. While the T-ADH's performance seemed to be highly suffering from the given reaction conditions (see Supporting Information), utilization of the Ral-ADH loaded with 1 mm Ca^{2+} in triethanolamine/HCl buffer (TEA buffer, 100 mm, pH 7.5) turned out to be well feasible.[68] After achieving full conversion using a reductive glucose-based cofactor recycling system, simple hydrogenolysis of the crude product ***anti*-13** revealed the corresponding (*R*,*S*)-diol ***anti*-2** to be formed in good diastereoselectivity of 93:7 and excellent enantioselectivity of >99% *ee* (Scheme 7). After six steps, the product was isolated in very good yield of 64% (93% per step). It was anticipated that increasing the steric bulk of the ether would lead to improved diastereoselectivity. When employing the sequence with the nitro-substituted phenethyl alcohol via **4i** and **1g**, the selectivity was indeed improved (d.r. 95:5, >99% *ee*). Furthermore, the protecting group allowed convenient photolytic release of diol ***anti*-2** (irradiation at 340 nm in Et_2O; see Supporting Information). Unfortunately, a number of impurities rendered the purification, and thus the procedure, impractical since the purity of the final product was <80% (qNMR). However, the observed increase in diastereoselectivity made us wonder whether a causality between the observed effects and derivatives **4i** additional methyl group in comparison to benzylated material **4x** existed. Thus, we repeated the whole sequence implementing racemic 1-phenylethanol-based intermediate **4g** observing overall excellent stereoselectivity (d.r. 97:3, >99% *ee*). The six-step sequence utilizing six catalysts (two organocatalysts, three enzymes and one metal) was also readily scalable from semi-preparative (84 mg, 70%) to gram-scale (1.8 g, 78% = 96% per step!) without any purification in between.



Scheme 7. Gram-scale enantioselective synthesis of building block ***anti*-2** via an organo-, bio-, and metal-catalyzed six-step pot sequence from commercially available vinyl ketone **3a** [**E1**: ene reductase YqjM (86–140 U mmol^{-1}); **E2**: glucose dehydrogenase (GDH; 56–76 U mmol^{-1}); **E3**: Ral-ADH (127–250 U mmol^{-1})]; $CaCl_2$ was added for stabilization of the biocatalyst].

Conclusion

In summary, we have developed a novel organocatalyzed multicomponent one-pot procedure enabling low-solvent to solvent-free access to primary, secondary and tertiary alcohol ethers **4** of allylic alcohols **7** directly starting from *para*-formaldehyde, vinyl ketones **3**, and alcohols **5**. In doing so, only low loadings of affordable, non-toxic and easy-to-handle DABCO and benzoic acid catalyze the formation of 31 diversely complex primary and secondary ethers with broad group tolerance in very good yields over three steps not shown to be accessible by current methods in such ease or at all. The plausible involvement of the catalysts in coupled catalytic cycles with DABCO playing the central role having multiple functions was proposed based on experimental data. Due to the mild conditions, the method was then proven well compatible with biocatalytic transformations in one-pot-fashions containing in total four to six catalytic steps within the very same vessel. As a result, gram-scale access to very prominent key building blocks in total synthesis and novel derivatives thereof was enabled in excellent yields, stereoselectivities, and purities going head to head with the outcome of conventional methods. However, the established sequences feature a decreased need for stoichiometric reagents, begin with achiral and economically reasonable starting materials, and generally reduce the amount of hazardous reagents in comparison to known methods drastically. Further applications underlying the off-topic add-on utility of ethers **4**, for example, for applications in polymer chemistry, lastly reasoned the established organocatalytic method to be valuable in light of an even broader synthetic context.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · biocatalysis · building blocks · one-pot reaction cascade · organocatalysis

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