Multienzyme One-Pot Cascade for the Stereoselective Hydroxyethyl Functionalization of Substituted Phenols

Stefan E. Payer, † Hannah Pollak, † Benjamin Schmidbauer, † Florian Hamm, † Filip Jurčić, † Kurt Faber, * † ‡ and Silvia M. Glueck * † ‡

† Institute of Chemistry, Organic and Bioorganic Chemistry, University of Graz, Heinrichstrasse 28/2, 8010 Graz, Austria
‡ Austrian Centre of Industrial Biotechnology (ACIB), Petersgasse 14, 8010 Graz, Austria

Supporting Information

ABSTRACT: The operability and substrate scope of a redesigned vinylphenol hydratase as a single biocatalyst or as part of multienzyme cascades using either substituted coumaric acids or phenols as stable, cheap, and readily available substrates are reported.

Various strategies are pursued in order to fulfill the requirement for a greener and more sustainable chemical production.¹ The ability of enzymes to work under ambient conditions in a highly selective manner evidences biocatalysis as a powerful concept for eco-friendly synthetic applications of valuable compounds, which enormously benefit from the rapid progress in molecular biology and biotechnology. The use of two or even more enzymes in a cascade fashion can considerably improve the efficiency of a multistage synthesis by circumventing the isolation of (unstable) intermediates, thus saving time, resources, and reagents while simultaneously diminishing the consumption of energy and the production of waste.²⁻⁴ Further aspects such as the overall cascade should run energetically downhill, and the introduction of an appropriate (internal) cofactor recycling in the case of cofactor-dependent enzymes and a preferably irreversible last step in order to increase the overall yield need to be taken into account. Limitations faced in one-pot setups, such as substrate/product/reagent inhibition or the incompatibility of reaction conditions required by one catalyst to the other(s), might be circumvented by a sequential (chronological separation) order.²

Herein, we present a redox-neutral, atom-efficient multienzyme system for the production of valuable (S)-1-((4-hydroxyphenyl)ethanols as an alternative to biocatalytic redox processes (Scheme 1).⁵⁻⁹ A promiscuous para-vinylphenol hydratase activity of ferulic acid decarboxylase from Enterobacter sp.⁶⁻¹² was significantly improved by a rational redesign approach (FDC* mutant),¹³ was merged with a prefixed decarboxylation step catalyzed by the wild-type enzyme (FDC).¹⁴ The cascade enables the utilization of cinnamic acid derivatives from renewable feedstocks¹⁵⁻¹⁸ as substrates or can be prolonged by two further enzymatic steps, which have been described in the literature,¹⁹ to exploit simple phenols as starting materials.

The replacement of a neutral valine by a carboxylate (Glu/Asp) residue as a catalytic base for the activation of water in the active site of FDC completely waived the requirement for bicarbonate as a proton relay cofactor and significantly enhanced the promiscuous hydration of 4-vinylphenols.¹³ In order to evaluate their biocatalytic potential, the substrate scope of the improved hydratase variants FDC_Es V46E and V46D was probed with a set of para-vinylphenols (4) bearing different substituents on the aromatic core or the vinyl side chain under previously optimized conditions¹³ (Scheme 2, Table 1).

A comparison of substrates 4a–e with previously reported results using wild-type decarboxylase FDC_Es in the presence of bicarbonate (3 M)¹⁰,¹¹ reveals a superior performance of the redesigned hydratase variants (Table 1). In all cases, conversion and stereoselectivity could be significantly increased compared to the wild-type enzyme, except for the stereoselectivity with 4d, which however was low in general. In addition to chlorinated vinylphenol (4b), also fluorine (4f) and bromine (4g) substituents were well tolerated in position 2. A strong electron-withdrawing nitro group in the same position (4h) was also accepted with high stereoselectivity, albeit in low conversion. It seems that electronic effects of the substituents ortho to the phenolic OH group play only a minor role.

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role, but their influence is mainly of steric nature; i.e., the results improve in the order of \( R_1 = \text{NO}_2 < \text{OEt} < \text{OMe} < \text{halogen} < \text{Me} < \text{H} \). Furthermore, the tolerance toward alkyl substituents on the styrene double bond was investigated since the hydration of such substrates would give rise to a quaternary stereocenter. However, only a methyl group on \( \text{C}_\alpha (4k) \) was accepted, yielding the \( \text{meso} \) tertiary benzylic alcohol with moderate success, whereas substitution on \( \text{C}_\beta (4l-n) \) was not tolerated at all. Overall, both variants performed fairly similar in terms of selectivity and reaction rates, with slightly better results using the glutamate variant (V46E) especially with halogens in position 3.

A major limitation for the preparation of chiral benzylic alcohols via the biocatalytic hydration of 4-vinylphenols is the preparation and storage of these compounds. A conventional protocol for the synthesis of hydroxystyrene derivatives exploits an atom-inefficient Wittig olefination of the corresponding hydroxybenzaldehydes with methyltriphenylphosphonium halides under basic conditions.\(^{20-22} \) The obtained hydroxystyrenes are prone to spontaneous cationic polymerization under neat conditions\(^ {23,24} \) and require stabilization in polar solvents for storage.\(^ {25} \) Alternatively, a preceding decarboxylation step catalyzed by phenolic and ferulic acid decarboxylases\(^ {26,27} \) would allow the design of an enzymatic cascade that converts stable coumaric acid derivatives into chiral benzylic alcohols avoiding the isolation of troublesome vinylphenols (Scheme 1A).

**Scheme 1. Elements of the Envisioned Multienzyme Decarboxylation/Hydration (A) and Hydroxyethylation (B) Cascade**

"TPL: Tyrosine phenol lyase; TAL: tyrosine ammonia lyase; FDC: ferulic acid decarboxylase; FDC*: FDC – hydratase variant.

**Scheme 2. Substrate Scope of FDC_Es V46E and V46D Hydratase Variants**

"For conversion and ee see Table 1.

**Table 1. Substrate Scope of FDC_Es V46E and V46D Hydratase Variants**

| substrate | product | \( R_1 \) | \( R_2 \) | \( R_3 \) | FDC_Es V46E conv (ee)\(^\text{a} \) [%] | FDC_Es V46E conv (ee)\(^\text{b} \) [%] | FDC_Es V46D conv (ee)\(^\text{c} \) [%] |
|-----------|---------|--------|--------|--------|-----------------|-----------------|-----------------|
| 4a | 5a | H | H | H | \( 94 (88 \) | \( 94 (89 \) | \( 77 (41 \) |
| 4b | 5b | 2-Cl | H | H | \( 81 (75 \) | \( 97 (76 \) | \( 74 (8 \) |
| 4c | 5c | 2-OMe | H | H | \( 43 (75 \) | \( 56 (55 \) | \( 27 (8 \) |
| 4d | 5d | 2-OEt | H | H | \( 43 (3 \) | \( 74 (29 \) | \( 17 (10 \) |
| 4e | 5e | 2-Me | H | H | \( 96 (84 \) | \( 96 (86 \) | \( 34 (71 \) |
| 4f | 5f | 2-F | H | H | \( 97 (66 \) | \( 97 (81 \) | n.d.\(^\text{d} \) |
| 4g | 5g | 2-Br | H | H | \( 98 (77 \) | \( 98 (76 \) | n.i.\(^\text{e} \) |
| 4h | 5h | 2-NO\(_2\) | H | H | \( 30 (90) \)\(^\text{f} \) | \( 29 (90) \)\(^\text{f} \) | n.i.\(^\text{f} \) |
| 4i | 5i | 3-F | H | H | \( 99 (53 \) | \( 99 (84 \) | n.i.\(^\text{g} \) |
| 4j | 5j | 3-Cl | H | H | \( 85 (18 \) | \( 92 (92 \) | n.i.\(^\text{h} \) |
| 4k | 5k | H | Me | H | n.d.\(^\text{i} \) | 34\(^\text{a} \) | n.i.\(^\text{j} \) |
| 4l | 5l | H | H | Me\(^\text{e} \) | <1 (n.d.) | <1 (n.d.) | n.i.\(^\text{k} \) |
| 4m | 5m | H | Me | Me\(^\text{e} \) | <1 (n.d.) | <1 (n.d.) | n.i.\(^\text{l} \) |
| 4n | 5n | H | Me | Me\(^\text{e} \) | <1 (n.d.) | <1 (n.d.) | n.i.\(^\text{m} \) |

\(^\text{a} \)Reaction conditions: purified FDC_Es variant (100 \( \mu \)M), substrates 4a–n (10 mM, as 10% w/w stock in propylene glycol) in potassium phosphate buffer (50 mM, pH 6.0), incubation for 24 h at 25 °C, and 700 rpm shaking (orbital shaker). \(^\text{b} \)Literature results with bicarbonate supplementation.\(^ {10,11} \) \(^\text{c} \)GC-MS conversion of the olefin 4k to a product with \( m/z \) of the alcohol 5k.\(^ {\text{d} \) \( n.d. \) = not determined due to low conversion.\(^ {\text{e} \) \( \text{GC-MS conversion of the olefin 4k to a product with } m/z \text{ of the alcohol 5k.} \)

"The \( E \)-configured olefin was used.\(^ {\text{f} \) The \( Z \)-configured olefin was used.\(^ {\text{g} \) The \( (S) \)-configured product was formed throughout unless otherwise stated.\(^ {\text{h} \) Absolute configuration was not determined. n.i. = not investigated in the literature.
A time study with 3-chlorocoumaric acid (3b) as a representative substrate showed rapid reaction progress with full consumption of the coumaric acid within 17 min and 94% conversion to the enantiomerically pure benzyl alcohol product 5b after 2 h (97% ee) (Figure 1a). Continued incubation under the reaction conditions is however accompanied by a linear decrease of the product ee, reaching 66% after 24 h. This phenomenon resembles previous observations and can be explained by a nonselective background hydration of 4 occurring either spontaneously or with FDC_Es wt in the absence of bicarbonate. Hence, careful monitoring of the reaction progress and to stop the biotransformation after an appropriate reaction time are required for optimal results.

The viability of the envisioned system was validated with coumaric acid derivatives 3a–j bearing analogous substituents to vinylphenols 4a–j (except for analogues of poorly accepted 4d and 4h) (Scheme 3, Table 2). To estimate the rate of racemization observed in the previous time study in the presence of different substituents, the reaction progress was evaluated after 3.5 and 24 h (Table 2, Scheme 3). All products were initially formed with a moderate to very good ee, which however decreases upon continued incubation for 24 h and a correlation between conversion, and rate of ee loss can be observed. Electron-withdrawing halogen substituents in position 2 (5b, 5f, 5g) seem to accelerate both the water addition and decline of ee in the order of Br > Cl > F due to deactivating polarization, whereas with an electron-donating group (5c, 5e) or no substitution in this position (5a) this effect is less pronounced. Halogens in position 3 support the formation of the quinone-methide form by inductive and mesomeric effects and hydration, and selectivity decline is more pronounced with a fluorine than a chlorine substituent (5j). Although stereoselectivity slightly suffered in the two-step setup, conversions comparable to the direct hydration of 4 were observed, highlighting the viability of this system.

The most straightforward way to prepare the benzyl alcohol products would be the direct hydroxyethyl functionalization of simple substituted phenols. In the present setup we envision telescoping a recently developed vinylation cascade by a fourth biocatalytic hydration step to gain direct access to chiral benzyl alcohols starting from phenols (Scheme 1B). An engineered PLP-dependent tyrosine phenol lyase (TPL) from Citrobacter freundii catalyzes the coupling of phenol with pyruvate and ammonia in the first step of the cascade to give the corresponding tyrosine derivative. The α-amino group of the tyrosine is eliminated (and thus formally recycled) by the action of a tyrosine ammonia lyase (TAL, from Rhodococcus sphaeroides) in the second step of the cascade, arriving at the substituted coumaric acid as the intermediate. The final decarboxylation drives the cascade toward complete conversion into hydroxystyrene derivatives, which in turn serve as substrates for enzymatic hydration. The redox-neutral net reaction of this system therefore represents a formal hydroxyethylation of phenols with pyruvate as cosubstrate and CO2 as sole side product, which does not require costly redox cofactors and associated recycling systems (Scheme 4). A reaction pH of 8.0 was shown to be crucial for the vinylation cascade to work efficiently, but the optimal pH of the hydration process was found at pH 6.0, above which the selectivity of the hydratase decreases. To address this compatibility issue, 2-chlorophenol (1b) was used as a

![Figure 1](image)

**Figure 1.** (a) Time study of the decarboxylation/hydration cascade with 3-chlorocoumaric acid (3b) as substrate at pH 6.0 (full conversion within 17 min). (b) Time profile of the four-enzyme vinylation/hydration cascade at pH 8 with 2-chlorophenol (1b) as substrate and FDC_Es V46E as hydration catalyst. The amount of coumaric acid 3b was ≤1% in all samples (not shown).

**Scheme 3. Two-Step Decarboxylation/Hydration Cascade**

```
  CO2  
 FDC_Es wt buffer pH 6 25 °C  |  H2O  
  OH  |
  3  |

CO2  
FDC_Es V46E buffer pH 6 25 °C  |  H2O  
  OH  |
  4  |

FDC_Es wt 3  5
  CO2  
  OH  |
  3  |

FDC_Es V46E 4  5
  CO2  
  OH  |
  4  |
```

For conversion and ee see Table 2.

| Substrate | Product | R | 3.5 h conv (ee) [%] | 24 h conv (ee) [%] |
|-----------|---------|---|-------------------|-------------------|
| 3a        | 5a      | H | 30 (91)           | 93 (84)           |
| 3b        | 5b      | 2-Cl| 91 (95)          | 96 (66)           |
| 3c        | 5c      | 2-OMe| 6 (54)           | 93 (42)           |
| 3e        | 5e      | 2-Me| 58 (91)          | 94 (78)           |
| 3f        | 5f      | 2-F | 61 (85)          | 96 (63)           |
| 3g        | 5g      | 2-Br| 94 (93)          | 98 (64)           |
| 3i        | 5i      | 3-F | 51 (93)          | 94 (75)           |
| 3j        | 5j      | 3-Cl| 14 (96)          | 86 (87)           |

"Reaction conditions: purified FDC_Es wt (10 μM), purified FDC_Es V46E variant (100 μM), substrates 3 (10 mM, supplied as 100 mM stock in PrOH, 10% v/v) in potassium phosphate buffer (50 mM, pH 6.0), incubation for 3.5 and 24 h at 25 °C, and 700 rpm shaking (orbital shaker). The (S)-enantiomer was formed throughout.

**Table 2. Results of the Substrate Screening for the Decarboxylation/Hydration Cascade**

"For conversion and ee see Table 2.
A steady conversion of phenol 1b to tyrosine 2b and further conversion of the latter to the corresponding coumaric acid 3b were observed. Due to its rapid decarboxylation, the amount of 3b was ≤ 1% over time (not shown in Figure 1b), and only formation of the hydroxystyrene 4b could be detected after 1 h, reaching a steady state at around 15% after 5 h. The benzylic alcohol 5b accumulated over time, reaching 75% conversion after 24 h. As in the two-step decarboxylation/hydration cascade, the ee of the chiral (S)-alcohol product drops linearly over time (87% after 24 h), albeit at a lower rate (Figure 1b). Even though the one-pot cascade was operated at pH 8.0 to optimize the performance of the vinylphenol cascade, a good stereoselectivity for the styrene hydration could be maintained, and the decline of ee was less pronounced. Attempts to improve the performance of the cascade by changing to a sequential mode (providing an option for pH adjustment) did not lead to significantly better results [see Table S5, Supporting Information (SI)].

In order to evaluate the biocatalytic scope of the multienzyme system, a representative set of substituted phenols (1) were applied as substrates (Table 3). All phenols were successfully converted into the corresponding benzylic alcohols (5) via the four-enzyme cascade, except for o-cresol (1e), whose conversion mainly stalled at the stage of the corresponding amino acid (2e). Slightly lower conversions to 5 compared to the two-step decarboxylation/hydration cascade (Table 2) can be explained by the presence of additives required for the preceding vinylphenol step (NH$_4$Cl, pyruvate, and PLP) and the nonoptimal reaction pH. However, stereoselectivity was generally improved with this system.

Finally, the one-pot cascade was performed on a 30–40 mg scale (0.2 mmol) with substrates 1f, 1g, 1i, and 1j (20 mM), followed by isolation and characterization of the products (for yields, see Table 3). Comparable results to the analytical scale reactions without significant erosion of the ee were achieved (see Table S4, SI).

In conclusion, we evaluated the substrate scope of two vinylphenol hydratases that were rationally designed from a ferulic acid decarboxylase and found them to perform the (S)-selective addition of water with high conversion and stereoselectivities although restricted to vinylphenols bearing various substituents on the aromatic core. These hydratases lack the dependency on bicarbonate required as the hydration cofactor by the wild-type decarboxylase, thus facilitating the implementation of this biotransformation into multienzyme cascades. Two redox-neutral systems aiming at circumventing the use of delicate vinylphenol substrates were investigated for the synthesis of (S)-benzylic alcohols starting from either substituted coumaric acids or simple phenols as substrates.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orlett.8b02058.

Experimental details and supplementary results, preparation of substrates and reference material, and compound characterization (PDF)

#### AUTHOR INFORMATION

**Corresponding Authors**

*E-mail: kurt.faber@uni-graz.at.*

*E-mail: si.glueck@uni-graz.at.*

**ORCID**

Kurt Faber: 0000-0003-0497-5430

Silvia M. Glueck: 0000-0003-2154-7585

**Notes**

The authors declare no competing financial interest.

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**Table 3. Results of the Phenol Hydroxyethylation Cascade**

| substrate | product | R      | conv$^{d}$ (ee) [%] | yield$^{d}$ (ee) [%] |
|-----------|---------|--------|---------------------|----------------------|
| 1a        | 5a      | H      | 73 (92)             | –                    |
| 1b        | 5b      | 2-Cl   | 85 (83)             | –                    |
| 1e        | 5e      | 2-Me   | 12’ (95)            | –                    |
| 1f        | 5f      | 2-F    | 91 (81)             | 84 (78)              |
| 1g        | 5g      | 2-Br   | 84 (87)             | 58 (88)              |
| 1i        | 5i      | 3-F    | 80 (87)             | 72 (85)              |
| 1j        | 5j      | 3-Cl   | 36 (95)             | 29 (92)              |

$^{a}$Reaction conditions analytical scale: Lyophilized *E. coli* whole cells containing the heterologously expressed TPL$_{-}$CF M379 V (10 mg mL$^{-1}$), TAL$_{-}$Rs (40 mg mL$^{-1}$), 35 mM), FDC$_{-}$Es wt (2 mg mL$^{-1}$), 32 U), and purified FDC$_{-}$Es V46E variant (100 μM, 1 mol %) in reaction buffer [potassium phosphate buffer (50 mM, pH 8.0), sodium pyruvate (92 mM), NH$_4$Cl (180 mM), and PLP (80 μM), pH adjusted to 8.0] with substrate phenol (10 mM, 50 μL of a 200 mM stock in PrOH, 5% v/v). Incubation at 30 °C and 850 rpm for 24 h.

$^{b}$HPLC conversion: the corresponding vinylphenol 4 was detected as the major remaining intermediate. *Phenol 1e and tyrosine 2e were detected as major constituents. *Isolated yield after column chromatography.
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