Green Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2019, **21**, 6246

Received 8th September 2019,
Accepted 29th October 2019

DOI: 10.1039/c9gc03161h

rsc.li/greenchem

Regio- and stereoselective multi-enzymatic aminohydroxylation of β-methylstyrene using dioxygen, ammonia and formate†

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We report an enzymatic route for the formal regio- and stereoselective aminohydroxylation of β-methylstyrene that consumes only dioxygen, ammonia and formate; carbonate is the by-product. The biocascade entails highly selective epoxidation, hydrolysis and hydrogen-borrowing alcohol amination. Thus, β-methylstyrene was converted into 1*R*,2*R* and 1*S*,2*R*-phenylpropanolamine in 59–63% isolated yields, and up to >99.5 : <0.5 dr and er.

Chiral 1,2-amino alcohol moieties are found in a plethora of natural products and active pharmaceutical ingredients (APIs), including antibiotics, anti-asthma drugs, hormones, alkaloids, enzyme inhibitors, and β-adrenergic blockers.[1–4] They also find application as ligands or auxiliaries in asymmetric organic synthesis.[5–7] In this context, phenylpropanolamines (PPAs, **5**) are particularly interesting as intermediates or final products due to their pharmaceutical properties. PPAs can be isolated as a mixture of diastereomers (1*S*,2*S*-**5** and 1*R*,2*S*-**5**) from the leaves of *Celastraceae* and *Ephedraceae* plant families.[8,9] Chemical synthesis of PPAs commonly consumes various reagents in suprastoichiometric amounts and leads to high yields yet modest optical purities or *vice versa*.[2,3,10–14] Moreover, most of these methods require several steps of isolation and purification of intermediates along the synthetic route, thus increasing significantly E-factors, solvent demands, and energy consumption (*e.g.*, for evaporation).[15,16] In some cases, catalytic steps involving the use of toxic transition metals are needed, thereby contributing to an unfavorable environmental footprint of the process. For instance, *trans*-β-methylstyrene (*trans*-**1**) was converted into 1*R*,2*R*-**5** through oxazoline intermediate in 75% overall yield, 99% de, but 86% ee.[17] The synthesis of the four PPA isomers **5** was accomplished *via* a multi-step route, which comprised an asymmetric reduction of α-functionalized ketones using chiral reducing agents. Although yields ranged from 40% to 98%, a mixture of stereoisomers was always isolated.[18] The PPA isomers **5** were also obtained in six steps in *ca.* 40% yield, 96% ee and dr starting from *rac*-2-phenyl-2-trimethylsilyloxyacetonitrile.[10] In a recent study, the direct 1,2-aminohydroxylation of *cis*- and *trans*-**1** using $PivONH_3OTf$ as aminating reagent was catalyzed by Fe(II)-phthalocyanine. Although the reaction proceeded with perfect regioselectivity, only moderate yields (up to 26%) of a mixture of diastereomers were obtained.[19] With the aim of finding viable alternatives to the use of toxic reagents and reducing the processes' generated waste to fulfill the criteria of green chemistry,[15,16,20] a number of biocatalytic routes towards PPAs synthesis have been reported. For instance, chemo-enzymatic approaches for the preparation of PPAs have combined either hydroxynitrile lyases (HNL) or Baker's yeasts with a chemical reduction step.[3] In the former case, 1*S*,2*R*-**5** and 1*R*,2*S*-**5** (35–47% yield) were obtained in high optical purities (99% ee, 90–92% de) through a five-step route.[21,22] In the latter case, 1*R*,2*R*-**5** and 1*R*,2*S*-**5** were obtained as a mixture of diastereomers in moderate yields.[23,24] Although fully enzymatic methods for the synthesis of 1,2-amino alcohols possessing one stereogenic center were recently developed,[25–27] only three routes are currently available for the stereoselective preparation of PPAs to thereby create two stereogenic centers.[3,4] The first route converts 1-phenyl-1,2-propanedione into 1*R*,2*S*-**5** or 1*S*,2*S*-**5** through a one-pot and sequential combination of an ω-transaminase (ωTA) with an alcohol dehydrogenase (ADH).[28] The second route comprises an enzymatic carboligation between benzaldehyde and pyruvate followed by a stereoselective transamination to yield 1*R*,2*S*-**5** and 1*R*,2*R*-**5** (up to >95% conversion; 98% de and >99% ee).[11] A similar route was lately reported for the enzymatic synthesis of 1*R*,2*S*-**5** (60% yield; ee and de >99.5%).[29] Conversely, the synthesis of 1*S*,2*R*-**5** using the two above-mentioned enzymatic approaches was reported with *ca.* 20% conversion and moderate levels of diastereomeric purities (60–80% de).[28] The third enzymatic method entails the enantioselective aminohydroxylation of styrene derivatives catalyzed by an engineered hemoprotein.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c9gc03161h

Starting from *trans*-anethole, the 1,2-amino alcohol product was obtained with 95% ee and 87 : 13 dr.[30]

In this work, we report a strategy for the synthesis of 1*S*,2*R*-**5** and 1*R*,2*R*-**5** in elevated optical purity by implementing a biocatalytic dual-enzyme hydrogen-borrowing (HB) amination.[31] Notably, HB-amination by pairing an alcohol dehydrogenase (ADH) with either an amine dehydrogenase (AmDH) or a reductive aminase (RedAm) was previously applied for the amination of molecules possessing only one hydroxyl moiety.[31–35] Herein, we investigated the potential of the biocatalytic HB-amination for a concomitant regio- and stereoselective amination of the synthetically relevant 1-phenylpropane-1,2-diol (**3**). Furthermore, the selective bioamination was integrated in a multi-enzymatic route that starts from the inexpensive and easily available substrate **1**.

All of the four diol isomers (**3**) were enzymatically synthesized from *cis*- or *trans*-**1** through a one-pot cascade that combined our fused styrene monooxygenase (Fus-SMO)[36] with either Sp(*S*)-EH or St(*R*)-EH as stereocomplementary epoxide hydrolases (Fig. 1A).[37] The enzymes were expressed and used as *E. coli* lyophilized cells. The stereoselectivity of combined epoxidation and hydrolysis was initially studied in a one-pot concurrent cascade on analytical scale (ESI section 4.1†), in which *trans*-**1** or *cis*-**1** (20 mM) were incubated in a biphasic mixture of KPi buffer (50 mM, pH 8.0, 0.5 mL) and heptane (0.5 mL), containing *E. coli*/Fus-SMO (10 mg), either *E. coli*/Sp(S)-EH or *E. coli*/St(*R*)-EH (10 mg), FAD (50 μM), NAD^+ (1 mM), and Cb-FDH (10 μM)/HCOONa (100 mM) for NADH recycling. The use of an aqueous/organic biphasic system limited the molecular toxicity of the epoxide intermediates to the enzymes, reduced the loss of volatile **1**, and enabled a practical isolation of the final diol products by simple phase separation. The four stereoisomers of diol **3** were obtained with elevated diastereomeric ratios (ESI, Table S2†). Thus, we performed the one-pot cascade slightly above three hundreds milligrams scale, which yielded diols **3** in quantitative conversion, high isolated yields (78–85%), and high optical purity (Table 1).

Table 1 Conversion [%] of **1** (*trans* or *cis*) to chiral **3** through a biocatalytic cascade combining *E. coli*/Fus-SMO/Cb-FDH and *E. coli*/EHs

Sub.	EH	Conv.[a] [%]	Isolated yield [%]	er[b] [%]	dr[b] [%]
trans-**1**	Sp(*S*)	>99	85	99 (1*S*,2*R*-**3**)	>99.5 : <0.5
trans-**1**	St(*R*)	>99	78	>99.5 (1*R*,2*S*-**3**)	>99.5 : <0.5
cis-**1**	Sp(*S*)	>99	83	95.5 (1*S*,2*S*-**3**)	>99.5 : <0.5
cis-**1**	St(*R*)	>99	79	>99.5 (1*R*,2*R*-**3**)	>99.5 : <0.5

[a] GC-FID analysis. [b] Normal phase-HPLC (chiral column).

Fus-SMO and Cb-FDH were co-expressed in the same host (ESI section 4.2†) in this latter set of experiments.[36]

Next, we focused on the second part of the multi-enzymatic process, which is the conversion of a diol enantiomer **3** into optically active PPA (**5**, Fig. 1B). Initially, we investigated the single oxidation of diol **3** (as a mixture of the four stereoisomers) by screening a panel of eleven stereocomplementary ADHs (six NAD^+ and five $NADP^+$ dependent; ESI section 5†). The ADHs were tested either as purified enzymes (*i.e.*, 50 μM Aa-ADH,[38] Lbv-ADH,[39] or Lb-ADH[40]) or lyophilized whole cells (*i.e.*, 20 mg mL^{-1} of *E. coli* cells expressing Sy-ADH,[41] Pp-ADH,[42] Bs-BDHA,[43] Ls-ADH,[44] Te-ADH variant 1, 2, or 3,[45] or Rs-ADH;[46] for details, see ESI, Tables S1 and S4†). The reactions were run for 24 h in Tris-HCl buffer (pH 7.5, 50 mM) at 30 °C, with the only exception being the oxidation catalyzed by Ls-ADH, which was conducted in KPi buffer (pH 6.5, 100 mM) at 40 °C. The reactions were supplemented with NAD^+ or $NADP^+$ (1 mM), which were recycled by a specific NAD(P)H oxidase—*i.e.*, NOX[47] 0.5 μM for NADH or YcnD[48] 5 μM for NADPH.

Only three NAD^+-dependent ADHs, namely Aa-ADH, Bs-BDHA, and Ls-ADH, proved to be sufficiently active towards diol **3** isomers. In these three cases, the desired 1-hydroxy-1-phenylpropan-2-one (**4**) was obtained as the main product (31%, 36%, and 15% conversions, respectively); however, 2-hydroxy-1-phenylpropan-1-one (**6**) (9–22%) and fully oxidized

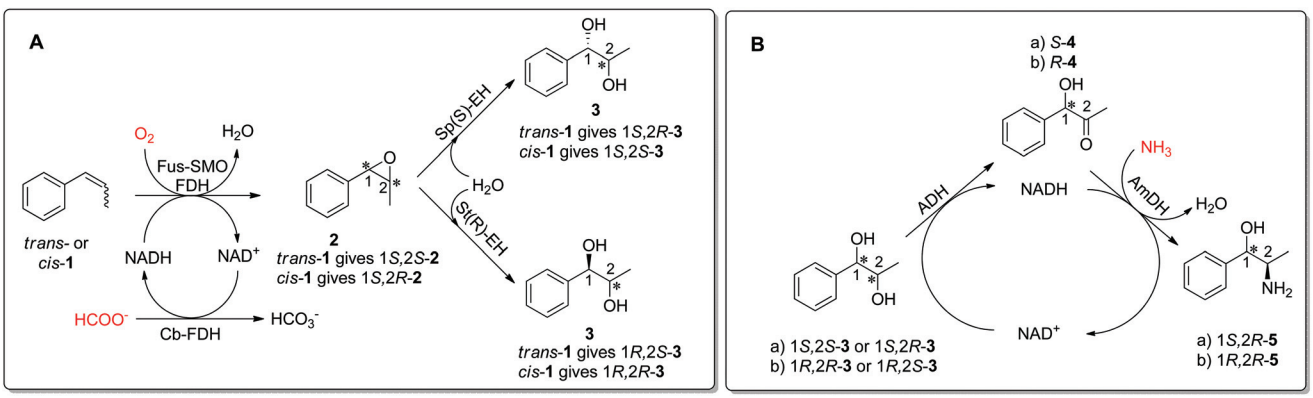

Fig. 1 (A) One-pot cascade for the stereoselective dihydroxylation of **1** (20–50 mM) in KPi buffer (pH 8.0, 50 mM)/heptane (1 : 1 v/v) using *E. coli*/Fus-SMO/FDH (5 mg mL^{-1}), *E. coli*/Sp(*S*)-EH or St(*R*)-EH (20 mg mL^{-1}), HCOONa (5 eq.), NAD^+ (1 mM), FAD (50 μM). (B) One-pot regio- and stereospecific HB-amination (ADH/AmDH) of **3** (5–20 mM) in $HCOONH_4$ buffer (pH 8.5, 1 M), NAD^+ (1 mM). Note: The names of all wild-type strains from which the enzymes used in this study were recombinantly expressed (and, in case, engineered) are reported in ESI, Table S1.†

di-ketone product (7) (2–5%) were also detected (ESI section 5†). Notably, the three ADHs exhibited varying stereoselectivity; whereas Bs-ADH oxidized 1*S*,2*R*-**3** and 1*R*,2*S*-**3**, Ls-ADH oxidized 1*S*,2*R*-**3** and 1*R*,2*R*-**3** and Aa-ADH oxidized 1*R*,2*R*-**3**, 1*S*,2*S*-**3** and 1*R*,2*S*-**3**. It is important to note that the composition of the reaction mixture might be partly determined by a possible spontaneous chemical isomerization between **4** and **6** (and their enantiomers) due to tautomeric equilibrium.

In the next step, we investigated the biocatalytic reductive amination of the hydroxy-ketone intermediate (*rac*-**4**, 20 mM) by screening three 'R-selective' amine dehydrogenases[49–51] (Ch1-AmDH, Rs-PhAmDH and Bb-AmDH; 100 μM) in $HCOONH_4$ buffer (pH 8.5, 1 M; 1 mL reaction volume) in the presence of NAD^+ (1 mM) and Cb-FDH (14.1 μM) at 30 °C for 24 h. Ch1-AmDH and Rs-PhAmDH showed conversion to **5** (24% and 79%, respectively) as a mixture of diastereomers (1*S*,2*R* and 1*R*,2*R*), whereas Bb-AmDH was inactive towards *rac*-**4** (data not shown). Therefore, we initially tested the HB-amination on analytical scale using 1*S*,2*S*-**3** (5 mM) as a substrate and combining Aa-ADH and AmDH (Ch1-AmDH or Rs-PhAmDH) in a 50 : 50 ratio (μM) in one pot. The reactions were conducted in $HCOONH_4$ buffer (pH 8.5, 1 M, 0.5 mL final volume) supplemented with NAD^+ (1 mM). Ch1-AmDH generally was the best performing AmDH for the HB-amination of 1*S*,2*S*-**3** in combination with Aa-ADH. Quantitative conversion and high product yield (89 ± 2%) were consistently obtained at 30 °C for 48 h (ESI, Table S5†); therefore, this temperature and reaction time were kept for further studies. Notably, the combination of ADH and AmDH in one pot prevented the formation of the byproducts **6** and **7**, which were previously detected in the single ADH-catalyzed oxidation of **3**. However, other by-products were observed in this non-optimized HB-amination, particularly 2-amino-1-phenylpropan-1-one (**8**, *ca.* 8%) (ESI, Table S5†).

Next, we proceeded with the optimization of the HB-amination of 1*S*,2*S*-**3** (5 mM) using varied molar ratios of Aa-ADH and either Ch1-AmDH or Rs-PhAmDH (ESI, Table S6†). Under these conditions, Aa-ADH (20 μM) and Ch1-AmDH (50 μM) were the best combination in terms of analytical yield into 1*S*,2*R*-**5** (87 ± 1%), chemoselectivity (*ca.* 2% of by-products), and optical purity (er >99.5 : <0.5 and dr 95 : 5). Notably, the intrinsic stereoselectivity of the HB-amination was perfect, as the dr of 95 : 5 reflects the level of optical purity of 1*S*,2*S*-**3** obtained in the previous cascade (Table 1). Interestingly, the application of a higher substrate concentration further improved the chemoselectivity of the HB-amination. For instance, at 10 mM concentration of 1*S*,2*S*-**3** substrate, 1*S*,2*R*-**5** was obtained in 69 ± 1% analytical yield with ≤1% of by-products, while er and dr remained unaltered (ESI, Table S7†). However, a further increase of substrate concentration while maintaining the same concentrations of Aa-ADH and Ch1-AmDH resulted in reduced yields. A fine tuning of the reaction conditions (ESI, Tables S8†) by varying the relative amount of dehydrogenases and substrate concentration led to optimal conditions—1*S*,2*S*-**3** (20 mM), Aa-ADH (70 μM), Ch1-AmDH (35 μM), under which 1*S*,2*R*-**5** was obtained in 98 ± 1% analytical yield and high optical purity (Table 2, entry 1). Finally, we monitored the progress of the HB-amination of 1*S*,2*S*-**3** (20 mM) over time under the optimized conditions. As depicted in Fig. 2, 42 hours are required for the reaction to reach completion.

Next, the biocatalytic HB-amination was investigated on the other three diol isomers (**3**). Bs-BDHA and Ls-ADH (50 μM each) operated almost equally well in combination with Ch1-AmDH for the amination of 1*S*,2*R*-**3** (5 mM) to give 1*S*,2*R*-**5** at 30 °C (ESI, Table S10†). Bs-BDHA was used for further studies, as it provided a slightly higher average yield (91 ± 3% *vs.* 89 ± 1%). Increasing the substrate concentration at constant enzyme concentrations afforded 95 ± 1%, 91 ± 1%, 87 ± 1%, and 80 ± 1% analytical yields at 15, 20, 25, and 30 mM concentrations of 1*S*,2*R*-**3**, respectively (ESI, Table S11†). Stereoselectivity was also high with >99.5 : <0.5 er and 98 : 2 dr

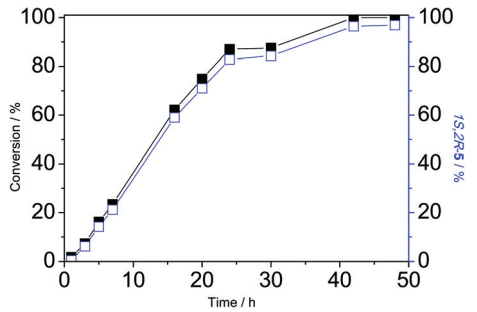

Fig. 2 Progress of the regio- and stereospecific HB-amination of 1*S*,2*S*-**3** (20 mM) to yield 1*S*,2*R*-**5** catalyzed by Aa-ADH (70 μM) and Ch1-AmDH (35 μM) in $HCOONH_4$ buffer (pH 8.5, 1 M, 0.5 mL) containing NAD^+ (1 mM).

Table 2 Regio- and stereospecific HB-amination of optically active **3** in $HCOONH_4$ buffer (pH 8.5, 1 M, 0.5 mL) containing NAD^+ (1 mM) at 30 °C and different enzyme concentrations (ADH/Ch1-AmDH) for 48 h

Entry	Sub.	Con. [mM]	ADH	ADH : Ch1-AmDH [μM]	Conv.[a] [%]	Product[a] [%]	er[b] [%]	dr [*SS* : *RR*/*RS* : *SR*][b]
1	1*S*,2*S*-**3**	20	Aa-ADH	70 : 35	>99	98 ± 1	>99.5 : <0.5	1 : 4/0 : 95[c]
2	1*S*,2*R*-**3**	15	Bs-BDHA	50 : 50	>99	95 ± 1	>99.5 : <0.5	0 : 2.4/0 : 97.6[c]
3	1*R*,2*R*-**3**	20	Ls-ADH	24 : 60	>99	98 ± 1	>99.5 : <0.5	n.d. : >99.5/n.d. : n.d.
4	1*R*,2*R*-**3**	20	Ls-ADH	35 : 70	>99	99 ± 1	>99.5 : <0.5	n.d. : >99.5/n.d. : n.d.
5	1*R*,2*S*-**3**	5	Aa-ADH	50 : 50	80 ± 5	75 ± 5	>99.5 : <0.5	0 : >99.5/0 : 0

[a] Measured by GC-FID; the error represents experimental deviation over two independent measurements and it does not directly refer to the intrinsic instrumental detection limit that is even more accurate. [b] Measured by RP-HPLC after derivatization with a chiral reagent. [c] dr due to initial optical purity of substrate.

Table 3 Overall yields for the multi-enzymatic conversion [%] of **1** (*trans* or *cis*) into 1*R*,2*R*-**5** or 1*S*,2*R*-**5**

Entry	Sub.	Step 1 Yield [%]	Step 2 Yield [%]	Combined Yield [%]	er [%]	dr [%]
1	*trans*-**1**	85	74	63 (1*S*,2*R*-**5**)	>99.5 : <0.5	98 : 2[a]
2	*cis*-**1**	79	74	59 (1*R*,2*R*-**5**)	>99.5 : <0.5	>99.5 : <0.5

[a] Dependent on stereoselectivity of Step 1.

(Table 2, entry 2). Also in this case, the dr reflects the enantiopurity of the diol substrate, whereas the HB-amination is stereospecific. Further tuning of the enzyme ratio did not provide any further improvement (ESI, Table S12†). Ls-ADH with Ch1-AmDH was found to be the best combination for the amination of 1*R*,2*R*-**3** at 30 °C, although Rs-PhAmDH also performed efficiently (ESI, Table S13†), yielding 1*R*,2*R*-**5** with perfect regio- and stereo-selectivity (er >99.5 : <0.5, dr >99.5 : <0.5). The Ls-ADH/Ch1-AmDH combination also tolerated higher substrate concentrations (87 ± 1% yield at 30 mM of 1*R*,2*R*-**3**; ESI, Table S14†). Under the optimized conditions (Ls-ADH 35 μM, Ch1-AmDH 70 μM, 20 mM 1*R*,2*R*-**3**), 1*R*,2*R*-**5** was obtained in 99 ± 1% analytical yield and perfect stereoselectivity (Table 2, entry 4; details of ESI, Table S15†). The last case was the amination of 1*R*,2*S*-**3** to yield 1*R*,2*R*-**5** (also obtained previously starting from 1*R*,2*R*-**3**). Aa-ADH was again the optimal ADH, whereas Ch1-AmDH performed slightly better than Rs-PhAmDH (ESI, Table S16† and Table 2, entry 5; 75 ± 5% *vs.* 63 ± 3% analytical yield, with 50 μM of each enzyme and at 5 mM of 1*R*,2*S*-**3**). Further optimization did not lead to any significant improvement, which is likely due to the insufficient activity of Aa-ADH on 1*R*,2*S*-**3**. In fact, the other case reported in Table 2 (entries 3 and 4) clearly demonstrated that the 1*R*-**4** intermediate is efficiently aminated by Ch1-AmDH.

In order to evaluate its applicability, the regio- and stereoselective dual enzyme HB-amination of 1,2-diols was performed slightly above one hundred milligrams scale for 1*R*,2*R*-**3** (20 mM, 105 mg, 0.690 mmol) and 1*S*,2*R*-**3** (15 mM, 102 mg, 0.670 mmol) to yield 1*R*,2*R*-**5** and 1*S*,2*R*-**5**, respectively. The reactions were performed in $HCOONH_4$ buffer (pH 8.5, 1 M) supplemented with NAD^+ (1 mM) at 30 °C for 48 h. Both amino alcohol products were quantitatively converted with high chemoselectivity (<2% by-products) as well as regio- and stereoselectivity. Upon extraction with MTBE, 1*R*,2*R*-**5** and 1*S*,2*R*-**5** could be isolated in elevated yield (74%), er (>99.5 : <0.5) and dr (>99.5 : <0.5 or 98 : 2, respectively). Therefore, considering the asymmetric dihydroxylation step (Table 1) along with the hydrogen-borrowing amination step, the overall yield for the conversion of **1** into optically active **5** were 59% and 63%, respectively (Table 3).

Conclusions

In conclusion, we developed a sequential multi-enzymatic process for the conversion of β-methylstyrene into phenylpropanolamines with high chemo-, regio-, and stereoselectivity. The use of multiple enzymes in one pot has several economic and environmental advantages as this eliminates the need for intermediate isolation steps, which generally lead to time-, solvent- and energy-consuming workups.[52–55] The present approach consists of four enzymatic reactions but required the sole and easy isolation of the diol intermediates **3**. The enzymatic route consumes only dioxygen and one equivalent of ammonia and formate and produces only one equivalent of carbonate as by-product.

With the aim of critically evaluating the greenness of our methodology to obtain optically active PPAs, we have estimated and compared the simple E-factors (*i.e.*, sEF, without solvents contribution) and the solvent demand for: (1) our process; (2) a representative multi-step chemical route involving metallorganic complexes;[17] (3) a recently reported direct and catalytic 1,2-aminohydroxylation of *cis*- and *trans*-**1**;[19] (4) and another highly atom-efficient one-pot two-step biocatalytic route starting from benzaldehyde (for details, see ESI section 10†).[11] The representative multi-step chemical route by Minakata *et al.*[17] results in a sEF above 110, mainly due to the intermediate purification step and the required excess of starting material. The direct and catalytic 1,2-aminohydroxylation by Legnani *et al.*[19] results in a sEF between *ca.* 50 and 80, depending on the reaction conditions; the main reason for this sEF value is the moderate conversion and the suprastoichiometric amount of a complex aminating agent. Notably, in these two chemical methods, the sEF associated to the preparation of the catalysts was not included as these data could not be accessed in a reliable manner; therefore, the actual sEF must be higher than estimated herein. Furthermore, as the final products are never obtained in optically pure form, an additional recrystallization step to upgrade er and dr would further increase the sEF of the process. In comparison, the biocatalytic route by Sehl *et al.*[11] results in the lowest sEF of *ca.* 4 due to the internal recycling of pyruvate between the two steps. However, the data used for the calculation of this sEF relate to a reaction on analytical scale, for which a conversion was measured but the product was not isolated. The new biocatalytic route described in this work results in a sEF of *ca.* 10. However, in our case, the reactions were conducted slightly above 300 mg (step 1) and 100 mg (step 2) scale, and the products were isolated. Moreover, comparing our methodology with the other biocatalytic route by Sehl *et al.*, the starting material is different (β-methylstyrene *vs.* benzaldehyde) and different biocatalyst's forms were used (*e.g.*, lyophilized cells, lyophilized crude cell extract, purified enzyme). By considering these factors, we deem the actual sEF values of the two biocatalytic processes to

be essentially equivalent. Additionally, the solvent demand of the two biocatalytic processes was also from two to six-fold lower compared with the values calculated for the chemical processes.

Finally, this work reports the first case in which the regioselectivity of the dual-enzyme HB-amination was investigated and exploited in preparative scale, thus further demonstrating the potential of this reaction in asymmetric synthesis. The currently attainable number and diversity of enantiomeric products are limited by the availability of complementary regio- and stereoselective ADHs and AmDHs. However, protein engineering and the discovery of novel AmDHs and ADHs are expected to enhance the applicability of this synthetic methodology towards the synthesis of a wide variety of enantiopure PPAs as well as other structurally diverse 1,2-amino alcohols.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financed by the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO), Grant ECHO Chemistry in Relation to Technology and Sustainability 2013 CW, project number 717.014.007. F. G. M. and T. K. received funding from the European Research Council (ERC) Starting Grant (H2020, grant agreement 638271, BioSusAmin).

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