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ORIGINAL PAPER

Regioselective Biocatalytic Transformations Employing Transaminases and Tyrosine Phenol Lyases

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Abstract
Regioselective reactions allow the differentiation between two or more chemically identical reactive centers within the same molecule. They are highly desirable transformations in organic synthesis, as they avoid additional chemical operations and sophisticated protection/deprotection strategies. In this context, enzymes, which present exquisite selectivity and reactivity, have been widely employed as catalysts in numerous regioselective transformations. This review focuses on two recently developed biocatalytic processes that present outstanding regioselectity: the transaminase-catalyzed asymmetric amination of di- and triketo compounds, and the stereoselective C–C coupling between phenol derivatives, ammonia and pyruvate for the synthesis of tyrosine analogues, catalyzed by tyrosine phenol lyases. Additionally, elegant and straightforward cascades that have combined the aforementioned biotransformations with other enzymatic and/or chemocatalytic processes are compiled in this contribution. Overall, this review aims to provide a general view of the synthetic possibilities that two relatively recently described regio- and stereoselective biotransformations can provide.

Keywords Biocatalysis · Regioselectivity · Identical functional group differentiation · Transaminase · Tyrosine phenol lyase · Protecting-group-free

1 Introduction

Over the last 15 years, biocatalysis has emerged as a valuable tool in organic chemistry that provides straightforward and efficient alternatives to the traditional chemical and chemocatalytic approaches used in synthesis. Among the various advantages of the use of enzymes for synthetic purposes, the most important is probably their inherent selectivity [1]. When enzymes catalyze the transformation of a substrate, they can distinguish between different stereoisomers or different orientations of prochiral/meso compounds (stereoselectivity), between different functional groups (chemoselectivity), or between functional groups that are chemically identical but situated in different positions within the same molecule (regioselectivity) [2].

Regioselective transformations are highly desirable in organic synthesis as they avoid additional reaction steps and sophisticated protection/deprotection strategies [3, 4], thus resulting in simpler, higher-yielding and more cost-effective synthesis routes. Consequently, protecting-group-free strategies are considered superior to traditional protection-based routes and have received well-deserved recognition [5, 6]. In the field of biocatalysis, regioselective reactions have been described for numerous enzyme classes, whereby hydrolytic enzymes have been studied in most detail [7, 8]. For instance, in carbohydrate chemistry, lipases can catalyze the selective acylation of a single primary [9] or secondary alcohol [10] in the presence of several other primary or secondary hydroxyl groups, respectively. Among other selective transformations, lipases also catalyze the monoamidation of glutamic acid diesters [11], the monodeacetylation of di- or triacetoxyacetophenones by transesterification [12], and the monoacetylation of dihydroxybenzene derivatives with vinyl acetate [13]. Likewise, dinitriles have been hydrolyzed to the corresponding monocarboxylic acids by nitrilases [14] or to monoamides by nitrile hydratases [15] with moderate to excellent regioselectivity. Epoxide hydrolases showing opposite regioselectivity on the (*S*)- and (*R*)-enantiomer of the same substrate have been used for the enantioconvergent hydrolysis of racemic mixtures of oxiranes [16–28] into

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vicinal diols. Methyl transferases perform highly regioselective methylations in vivo and have also been successfully employed in biocatalysis for regioselective alkyl transfer, in some cases using non-natural derivatives of the *S*-adenosyl methionine (SAM) cofactor as alkyl donors [29–33]. Oxidoreductases are also capable of differentiating between identical functional groups: Alcohol dehydrogenases have been found to reduce one carbonyl group of diketo compounds with very high regio- and enantioselectivity [34, 35], and both native and evolved P450 monooxygenases have successfully been applied in the regio- and stereoselective hydroxylation of arenes, linear alkanes, terpenes, and steroids [36–45]. Also worth mentioning is the oxidative monocleavage of dialkenes at the expense of molecular oxygen that has been achieved using an enzyme preparation from the fungus *Trametes hirsuta* [46].

Among the different regioselective enzymatic reactions existing in literature, in this contribution we will focus on two biotransformations that have gained particular relevance in the last few years. These are the monoamination of multiketo compounds catalyzed by transaminases, and the *para*-selective C–C bond formation reaction mediated by tyrosine phenol lyases on *para*-unsubstituted phenols. In addition, examples of cascades that have employed either of these biotransformations in combination with further biocatalytic processes for the regio- and stereoselective synthesis of nitrogen heterocycles and tyrosine derivatives will be discussed in this review.

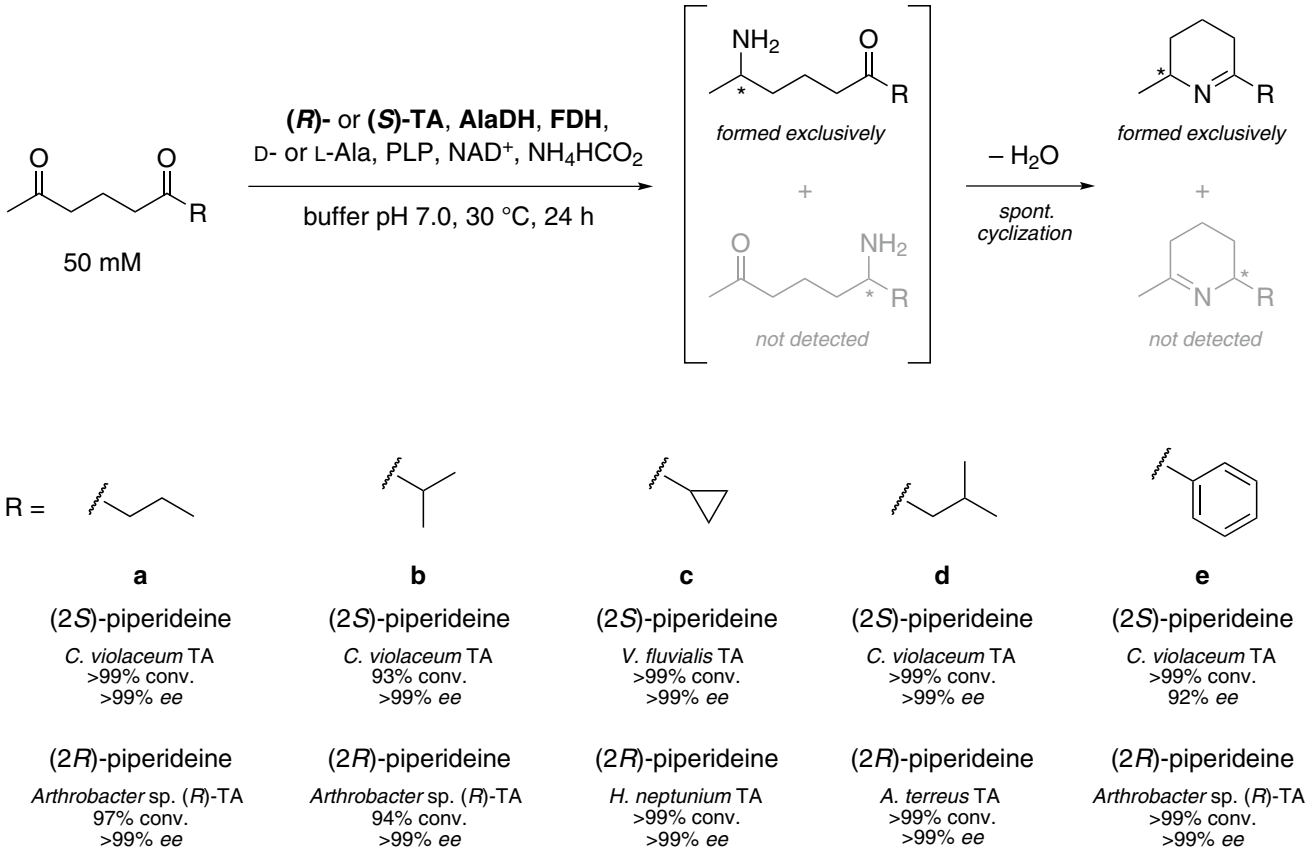
2 Regioselective Transformations Catalyzed by Transaminases

Optically pure amines are valuable building blocks in the synthesis of pharmaceuticals and agrochemicals. In addition, versatile applications as resolving agents, chiral auxiliaries and organocatalytic reagents have been reported for this compound class [47]. Therefore, synthetic organic chemists have historically devoted great effort to the development of efficient and versatile strategies for the stereoselective synthesis of chiral amines. These efforts have also led to the development of several biocatalytic methods for chiral amine synthesis, which rely on enzymes such as lipases, amine oxidases, imine reductases, and transaminases, among others [48–51]. Transaminases (TAs, EC 2.6.1.X) are pyridoxal 5′-phosphate (PLP)-dependent enzymes that mediate the stereoselective transfer of an amino group from an amine donor to a carbonyl acceptor. Depending on the stereopreference of the selected enzyme, (*S*)- or (*R*)-amines can be accessed in high optical purity starting from the prochiral ketones [52–56]. Taking advantage of their potential, these biocatalysts have been implemented in pharmaceutical synthesis during the last decade. An outstanding example is the TA-catalyzed stereoselective amination that has replaced a rhodium(I)-mediated asymmetric enamine hydrogenation as the key step in the manufacture of the antidiabetic drug Sitagliptin [57].

Focusing on the scope of this contribution, TAs have been successfully applied to regioselective transformations. In particular, the asymmetric monoamination of di- and triketones has been achieved. Most wild-type TAs present a high selectivity for the sterically less demanding ketone moiety, in particular methyl ketones, while carbonyl groups with more bulky substituents remain untouched. This selectivity was exploited for the regio- and stereoselective monoamination of diketones without the use of protecting groups [58]. 1,5-Diketo compounds were exclusively converted into one out of the two possible regioisomeric aminoketone intermediates. These species spontaneously cyclized, yielding the corresponding Δ^1-piperideines in optically pure form (Scheme 1). By choosing TAs with suitable stereopreference, both enantiomers of the piperideines could be accessed in up to > 99% conversion and *ee*.

Diastereoselective reduction of the cyclic imines thus formed gave access to the corresponding 2,6-disubstituted piperidines. For instance, the two enantiomers of the alkaloids dihydropinidine [59] and isosolenopsin [60] were synthesized in three steps from the commercially available 6-methyl-3,4-dihydropyran-2-one with overall yields of 61–72% over three steps (Scheme 2a). Grignard reactions gave access to the corresponding 1,5-diketone compounds, which were regio- and stereoselectively transformed into the Δ^1-piperideines through transaminase-catalyzed reactions. The cyclic imines were readily reduced by hydrogenation with palladium on charcoal (Pd/C) as catalyst, affording the *cis*-disubstituted piperidines with excellent diastereoselectivity (> 98% *de*). In a similar fashion, both enantiomers of the alkaloid *epi*-dihydropinidine (Scheme 2b) were accessed in high yield (up to 91% over two steps) and moderate diastereoselectivity when the enantiopure imine intermediate was treated with $LiAlH_4$ in the presence of Et_3Al [59]. This reduction reaction, in contrast to the Pd/C-catalyzed hydrogenation, affords predominantly the *anti*-diastereoisomers.

An extension of this concept was recently used in the chemo-enzymatic asymmetric synthesis of both enantiomers of the ant venom alkaloid xenovenine [61]. A key step in this process is the biocatalytic amination of a triketone intermediate, which was prepared in two steps starting from commercially available 2-(*n*-heptyl)furan (Scheme 3). Two enantiocomplementary TAs from *Arthrobacter* sp. mediated the regio- and stereoselective amination of the least sterically demanding carbonyl group, followed by the spontaneous cyclization of the resulting intermediate. The five-membered cyclic amine obtained was aromatized to the corresponding pyrrolizidine by subjecting the crude product of the biotransformation to a 0.1% v/v solution of acetic acid

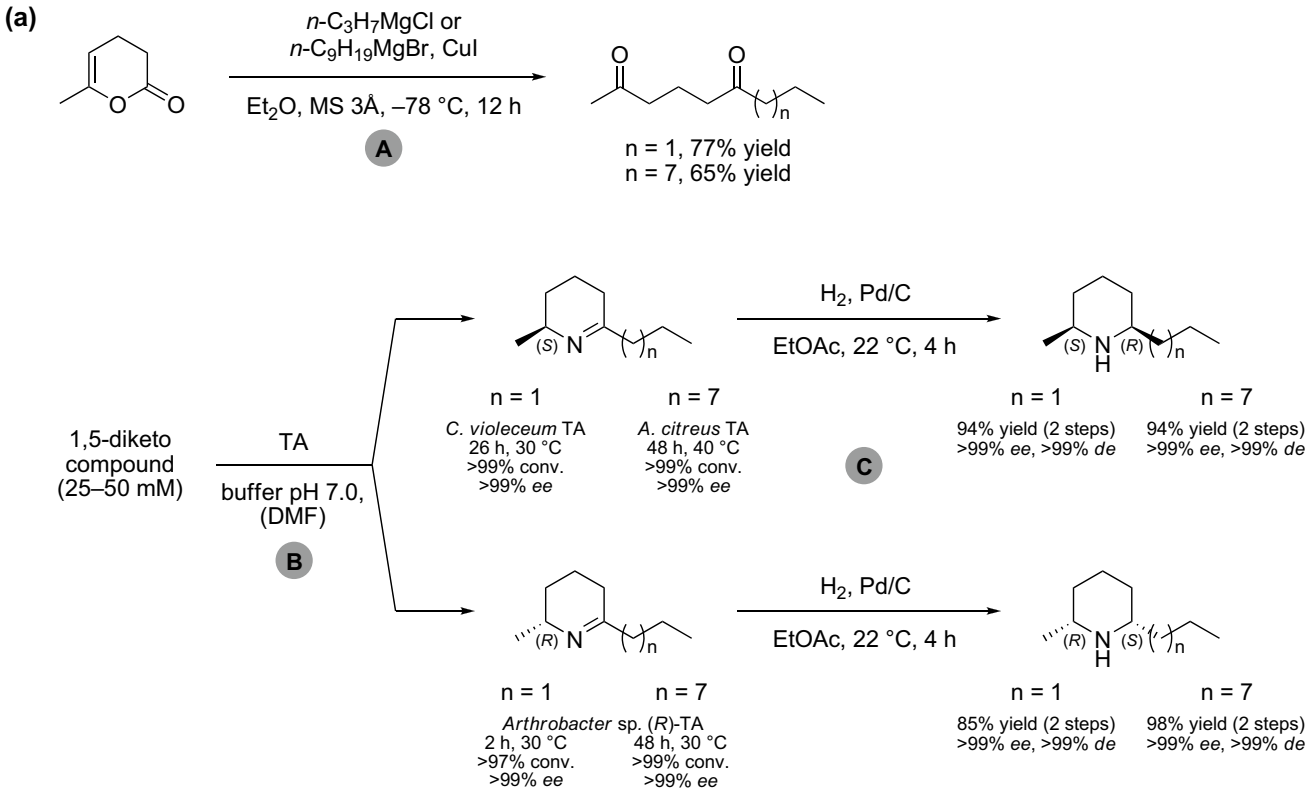


Scheme 1 Regioselective amination of various 1,5-diketones. *AlaDH* alanine dehydrogenase, *FDH* formate dehydrogenase

in methanol. Finally, the hydrogenation of this compound catalyzed by Pd/C in the presence of camphorsulphonic acid (CSA) led to the desired (5*Z*, 8*E*)-diastereoisomer, independently of the substrate enantiomer. Thus, the naturally occurring (+)-enantiomer was obtained in 30% isolated yield over the three steps by treating the triketone with the (*R*)-TA from *Arthrobacter* sp., whereas the (*S*)-TA from *Arthrobacter* sp. led to the formation of (–)-xenovenine in 48% yield. Both antipodes were isolated in enantio- and diastereomerically pure form.

Taking further advantage of this methodology, an elegant multienzymatic approach combining TAs and mononoamine oxidases (MAOs) has been described for the asymmetric synthesis of 2,5-disubstituted pyrrolidines [62, 63]. The authors employed two commercially available transaminases with opposite stereopreference, ATA-113 and ATA-117, for the regio- and stereoselective synthesis of (*S*)- and (*R*)-Δ^1-pyrrolines, respectively. In this case, hydrogenation of the cyclic imines over Pd/C proceeded with poor diastereoselectivity and was hence not a suitable method for obtaining the corresponding disubstituted pyrrolidines as pure stereoisomers. Instead, the authors implemented a 'cyclic deracemisation' system using monoamine oxidase and ammonia–borane to obtain the desired chiral pyrrolidines in excellent optical purity (Scheme 4). The non-selective reducing agent $NH_3{\cdot}BH_3$ reduces the cyclic imine to a mixture of diasteroisomers of the desired amine. Engineered variants of monoamine oxidase from *Aspergillus niger* (MAO-N) catalyze the selective oxidation of the (5*S*)-diastereomer back to the imine. Successive rounds of reduction and oxidation, which take place concurrently in the same reaction vessel, lead to accumulation of the (5*R*)-configured pyrrolidine in > 99% *de*. Due to the complementary regioselectivity displayed by the TAs and the MAO-N variants, the stereochemistry of C2 (established by the TA) was not affected by MAO-N. Consequently, the cascade proceeded with excellent enantio- and diasteroselectivity (up to > 99% *ee* and > 99% *de*) for almost all cases studied.

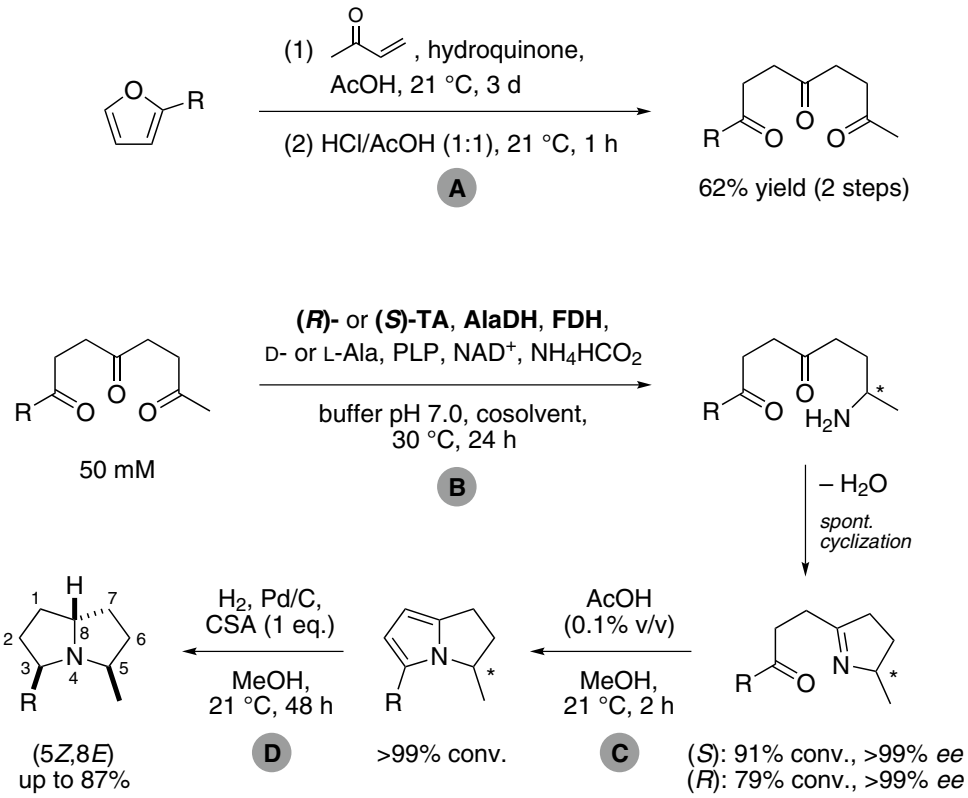
Due to the fact that this contribution focuses only on regioselective processes, TA-catalyzed conversion of ketones in the presence of ester groups within the same molecule [64–66], or the differentiation between aldehyde and ketone groups are out of the scope of this review [67, 68].

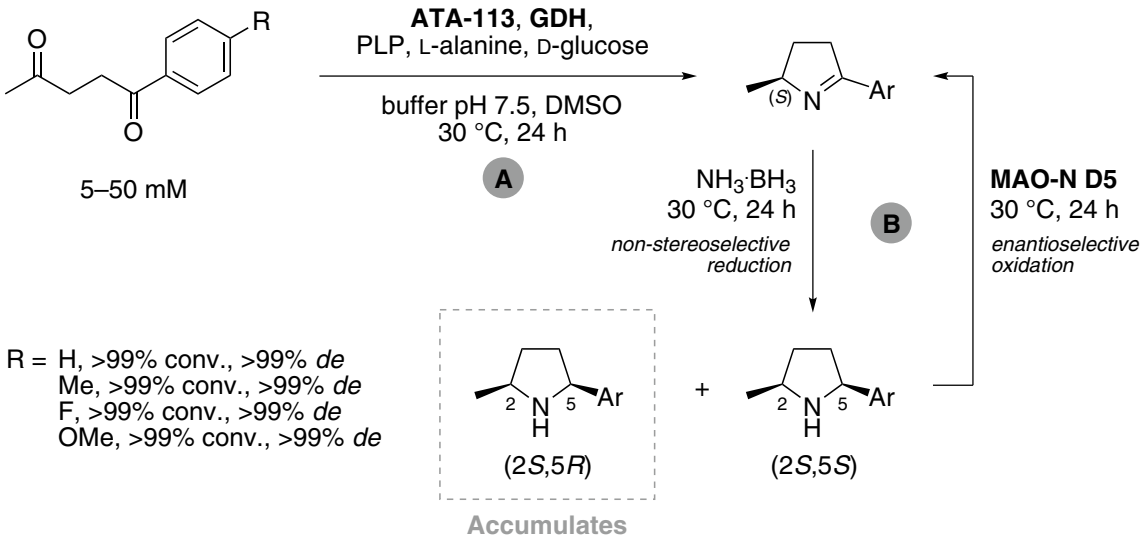


Scheme 2 **a** Total synthesis of the two enantiomers of dihydropinidine (n = 1) and isosolenopsin (n = 7). The chemoenzymatic approach combines a Grignard reaction [A], a TA-catalyzed regioselective monoamination [B], and a diastereoselective *syn*-hydrogenation catalyzed by Pd/C [C]. **b** Synthesis of (2*S*, 6*S*)- and (2*R*, 6*R*)-*epi*-dihydropinidine. Imine intermediates were synthesized as shown in **a**, and then reduced by $LiAlH_4$ in the presence of Et_3Al affording the *anti*-diastereoisomers

3 Regioselective Transformations Catalyzed by Tyrosine Phenol Lyases

The formation of carbon–carbon (C–C) bonds is the key reaction in organic synthesis that builds the carbon framework of every organic molecule by connecting smaller and simpler substructures. The development and identification of new biocatalysts able to mediate C–C couplings with high control of chemo-, regio- and stereoselectivity has undoubtedly expanded the chemist's toolbox for the synthesis of multifunctional products [69]. For instance, the chemical synthesis of tyrosine derivatives, which are valuable building blocks in the synthesis of several anti-cancer therapeutics [70, 71], comprises several laborious and time-consuming steps. In contrast, PLP-dependent tyrosine phenol lyases (TPLs, EC 4.1.99.2) can catalyze the regio- and stereoselective reversible formation of tyrosine from pyruvate, phenols and ammonia in a single and "green" reaction [72–74]. TPLs are not limited to phenol as substrate, however: For instance, the TPL from *Erwinia herbicola* has been used to convert catechol into L-dihydroxyphenylalanine (L-DOPA) [75, 76], and this reaction

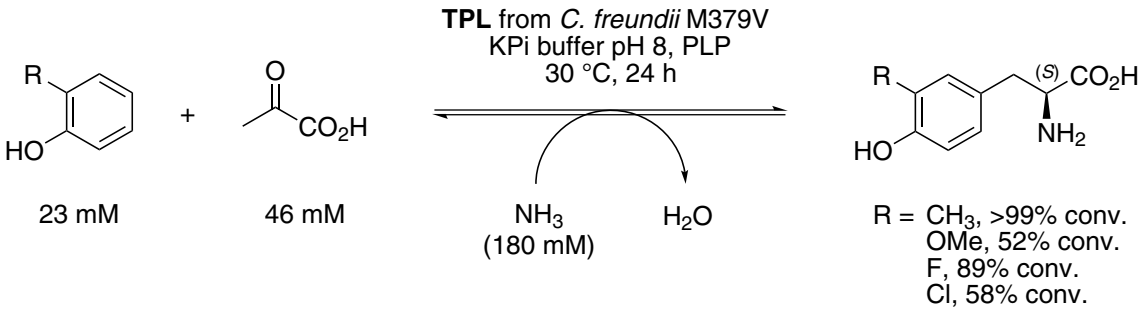




Scheme 3 Total synthesis of the two enantiomers of (5*Z*, 8*E*)-xenovenine. The chemoenzymatic approach combines a retro-Paal–Knorr reaction [A], a TA-catalyzed regioselective monoamination [B], an aromatization reaction [C], and a diastereoselective hydrogenation catalyzed by Pd/C in the presence of CSA [D]. R = *n*-C_7H_{15} CSA = camphorsulfonic acid

Scheme 4 ATA-113/MAO-N one-pot sequential process for the synthesis of (2*S*, 5*R*)-disubstituted pyrrolidines. [A] First step, regio- and stereoselective amination of 1,4-diketones catalyzed by the (*S*)-selective ATA-113. [B] Second step, the MAO-N/NH_3·BH_3 system mediates the diastereoselective conversion of the (*S*)-pyrrolines into the corresponding (2*S*,5*R*)-pyrrolidines. *GDH* glucose dehydrogenase

has very recently been applied to a bacterial system with an expanded genetic code that can biosynthesize DOPA and employ it for protein synthesis [77]. An engineered variant of TPL from *Citrobacter freundii* (M379V) has been shown to accept a range of 2-substituted phenols as substrates, hence giving access to non-natural, monosubstituted L-tyrosine derivatives in moderate to excellent conversions (52–99%) and excellent optical purity (*ee* > 99%; Scheme 5). In all cases the C–C coupling occurred with excellent regioselectivity; therefore, only

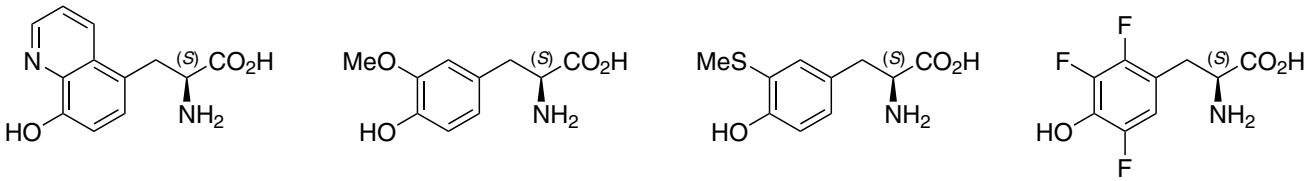


Scheme 5 Single-step biocatalytic synthesis of monosubstituted L-tyrosine derivatives catalyzed by the single mutant M379V of TPL from *Citrobacter freundii*

the product bearing the substituent in position 3′ of tyrosine was detected [78].

Moreover, different enzyme engineering approaches have taken advantage of the activity shown by TPLs to successfully incorporate unnatural amino acids (UAAs) into recombinant proteins. While traditional mutagenesis is limited to the 'chemical space' of the 20 proteinogenic amino acids, the introduction of non-natural residues gives access to novel side-chain functionalities that can lead to more robust enzymes with enhanced catalytic properties [79]. For instance, a double variant of the TPL from *Citrobacter freundii* (M288S/F448C) has been used to catalyze the formation of the metal-chelating UAA 2-amino-3-(8-hydroxyquinolin-5-yl)propanoic acid (HqAla, Scheme 6) from 8-hydroxyquinoline, ammonium chloride and pyruvate in high yield. After purification, HqAla was site-specifically incorporated into green fluorescent proteins, enabling them to sense Cu^{2+} ions, which opens the door for biosensing applications [80]. In addition, examples of improved enzymatic activity and modified selectivity resulting from the incorporation of UAAs were also reported by the same authors. In one study, a single variant of the *Symbiobacterium* sp. TPL (M379V) was used to access 3-methoxytyrosine (OMeY, Scheme 6) from 2-methoxyphenol. The tyrosine analog was selectively incorporated at a defined site in myoglobin, increasing the oxygen reduction activity of the protein and changing the predominant reaction product from H_2O_2 to water [81]. Likewise, the genetic incorporation of 3-methylthiotyrosine (SMeY, Scheme 6), also synthesized by a TPL-catalyzed coupling, into myoglobin provided a protein fourfold more active than the original enzyme towards the reduction of hydroxylamine to ammonia [82]. Both modifications mimic the active-site environment of other heme enzymes, namely cytochrome c oxidase (OMeY) and cyctochrome c nitrite reductase (SMeY). The preparation of various fluorotyrosines by TPL-catalysed C–C coupling as well as the incorporation of these UAAs into peptides and proteins has also been reported [83, 84].

The excellent performance shown by TPLs for the regio- and stereoselective preparation of L-tyrosine derivatives has enabled the coupling of this reaction to other biocatalytic processes, resulting in several elegant multienzymatic cascades. For instance, the combined use of a P450 monoxygenase with the TPL variant M379V from *Citrobacter freundii* gave access to tyrosine analogs from substituted benzenes, pyruvate and ammonia in a one-pot two-step cascade (Scheme 7a) [85]. In the first step, monosubstituted arenes were regioselectively hydroxylated in the *ortho*-position by the monooxygenase P450 BM3 at the expense of oxygen and NADPH, yielding the



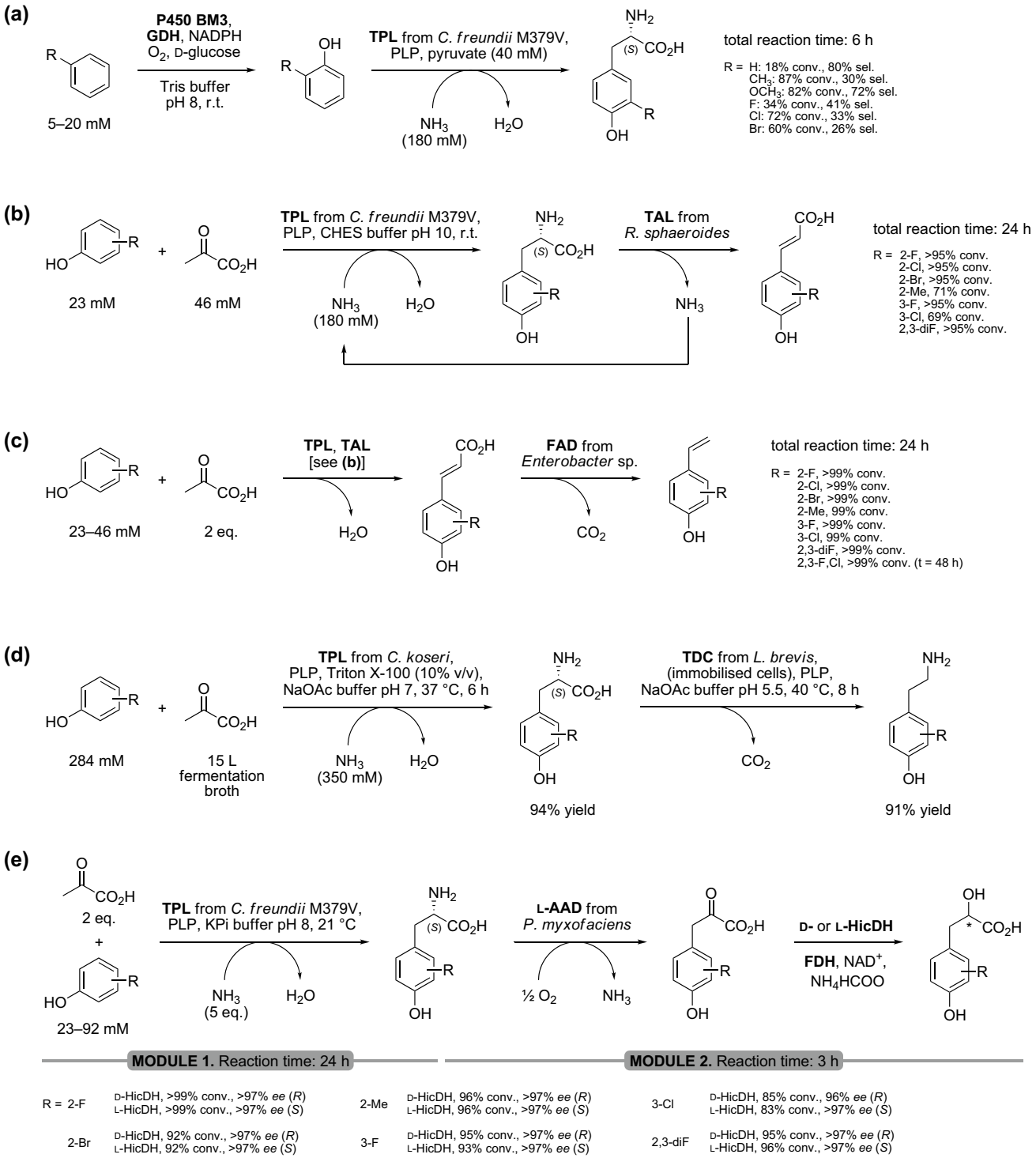
HqAla
C. freundii TPL
M288S/F448C

OMeY
Symbiobacterium sp. TPL
M379V

SMeY
C. freundii TPL
F36L

2,3,5-F_3Y
C. freundii TPL
wild type

Scheme 6 Examples of unnatural amino acids produced by TPL-catalyzed C–C coupling that have been incorporated into proteins. The source organism and any amino acid variations of the used TPL are specified below the structures and their abbreviations



Scheme 7 Multienzymatic syntheses involving the regio- and enantioselective TPL-catalyzed coupling of phenol derivatives with ammonia and pyruvate: **a** One-pot two-step P450 monooxygenase–TPL cascade for the synthesis of L-tyrosine analogs from benzene derivatives. **b** One-pot two-step TPL–TAL cascade for the *para*-selective alkenylation of unprotected phenols. **c** One-pot three-step TPL–TAL–FAD cascade for the *para*-selective vinylation of unprotected phenols. **d** Two-step enzymatic synthesis of tyramine combining the TPL-catalyzed synthesis of L-tyrosine with its TDC-catalyzed decarboxylation. **e** One-pot two-module three-step cascade for the preparation of (*R*)- and (*S*)-*p*-hydroxphenyl lactic acids from *p*-unsubstituted phenols

corresponding phenols. These compounds were excellent substrates for the subsequent TPL-catalyzed process, and the desired amino acids were obtained in moderate to good conversion (up to 72%) and chemoselectivity (up to 80%). In some cases, a lower selectivity was observed as a result of an undesired P450-mediated overoxidation of the monosubstituted phenol intermediates.

More recently, the regioselective transformation catalyzed by TPL was successfully combined with a tyrosine ammonia lyase (TAL) from *Rhodobacter sphaeroides*, which mediated the ammonia elimination that gave access to *p*-coumaric acid derivatives from phenols. This biocatalytic process constituted the first direct *para*-selective alkenylation of these derivatives without the presence of an auxiliary group in *para*-position. Only pyruvate was used as stoichiometric reagent, as the ammonia that is consumed in the TPL-catalyzed coupling was internally regenerated in the elimination step mediated by the TAL, thus making water the sole coproduct [86]. Seven phenols (including halogenated derivatives) were thus transformed into the α,β-unsaturated carboxylic acids with high to excellent conversions and perfect selectivity towards the *E*-isomer (Scheme 7b). The addition of a ferulic acid decarboxylase (FAD) to the bienzymatic process just described resulted in the formation of *para*-vinylphenols via decarboxylation of the corresponding *p*-coumaric acid derivatives (Scheme 7c). The FAD-catalyzed decarboxylation is an irreversible transformation that drives the equilibrium towards product formation, and consequently 2-, 3-, and 2,3-substituted phenols were transformed into the *para*-vinylated products in excellent conversion (> 99%) for all the cases studied [87]. To highlight the importance of this contribution, it must be mentioned that, while vinyl arenes are important building blocks in organic chemistry, their synthesis from unprotected phenols is not straightforward. The chemical reaction with $SnCl_4 \cdot Bu_3N$ leads to *ortho* functionalization [88], whereas the synthesis of *para*-vinylphenols involves transition-metal-catalyzed couplings in which the presence of auxiliary groups at the *para*-position is strictly necessary [89, 90].

In another bienzymatic approach, L-tyrosine formed by a TPL reaction was used as substrate for immobilized cells containing a heterologously expressed tyrosine decarboxylase (TDC). The latter mediated the decarboxylation of L-tyrosine, yielding tyramine [2-(*p*-hydroxyphenyl)ethylamine], a bioactive metabolite and valuable intermediate in the synthesis of pharmaceutical drugs [91]. The authors were able to scale up the two-step enzymatic process converting 15 L of pyruvate fermentation broth into the L-tyrosine intermediate in 94% isolated yield. The decarboxylation reaction provided the desired tyramine in 91% yield, thus reaching 86% overall yield after the two biocatalytic reactions (Scheme 7d).

Likewise, the TPL-catalyzed regio- and enantioselective tyrosine formation allowed the preparation of enantiopure (*R*)- and (*S*)-*p*-hydroxyphenyl lactic acids when it was combined with two additional biocatalytic reactions that employed an L-amino acid deaminase (L-ADD) and an enantioselective hydroxyacid dehydrogenase, respectively [92]. This elegant three-step cascade was performed in one pot and subdivided into two different modules that were run sequentially. The first module comprised the L-tyrosine formation catalyzed by the TPL from *Citrobacter freundii* M379V, whereas the second module consisted of two biocatalytic transformations: the oxidative deamination mediated by the L-ADD from *Proteus myxofaciens* and the reduction of the resulting 2-keto acid derivatives using as catalysts the two stereocomplementary 2-hydroxyisocaproate dehydrogenases from *Lactobacillus paracasei* (L-HicDH) and *Lactobacillus confusus* (D-HicDH) (Scheme 7e). The TPL–L-ADD–HicDH cascade led to the transformation of *p*-unsubstituted phenols to both enantiomers of the corresponding *p*-hydroxyphenyl lactic acids in excellent conversion (92% to > 99%), high isolated yield (58–85%) and excellent optical purity (96% to > 97%) for all the cases studied.

4 Conclusion and Outlook

Enzyme catalysis has become a well-established discipline that provides valuable and efficient tools for the synthesis of pharmaceuticals and other bioactive compounds with excellent chemo-, regio- and stereoselectivity. This contribution focuses on two regioselective processes that, by definition, allow the differentiation between two or more chemically identical functional groups at different positions of a substrate molecule. Thus, several examples of asymmetric monoamination of di- and triketones catalyzed by transaminases have been discussed in detail. Likewise, a compilation of strategies that have taken advantage of the ability presented by tyrosine phenol lyases to distinguish between different sites of phenols, leading to the synthesis of L-tyrosine analogues, have also been described in this review. Both these regioselective processes have attained well-deserved recognition in recent years as a consequence of having shortened sophisticated and time-consuming synthesis routes for the preparation of drugs and important building blocks, thus resulting in protecting-group-free strategies with considerably higher yield and overall efficiency than traditional approaches.

Overall, transaminases and tyrosine phenol lyases catalyze highly selective and versatile transformations with a large potential for synthetic application, especially when combined with other enzymatic or chemocatalytic reactions. They thus represent a valuable extension of the

organic chemist's toolbox for the preparation of chiral target molecules.

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