Biocatalysis for the synthesis of pharmaceuticals and pharmaceutical intermediates

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Abstract

Biocatalysis has been increasingly used for pharmaceutical synthesis in an effort to make manufacturing processes greener and more sustainable. Biocatalysts that possess excellent activity, specificity, thermostability and solvent-tolerance are highly sought after to meet the requirements of practical applications. Generating biocatalysts with these specific properties can be achieved by either discovery of novel biocatalysts or protein engineering. Meanwhile, chemoenzymatic routes have also been designed and developed for pharmaceutical synthesis on an industrial scale. This review discusses the recent discoveries, engineering, and applications of biocatalysts for the synthesis of pharmaceuticals and pharmaceutical intermediates. Key classes of biocatalysts include reductases, oxidases, hydrolases, lyases, isomerases, and transaminases.

1. Introduction

In the late 1980s, Roger Sheldon introduced the Environmental Impact Factor (E factor) (kg waste/kg product) to evaluate the environmental impact of manufacturing processes. In 1992, he initially estimated E factors for various chemical industries, which revealed that the pharmaceutical industry had the highest E factor among those chemical industries (Table 1). A higher E factor means greater waste burden and more negative environmental impact to the earth.

Anastas and Warner first developed the 12 principles of "Green Chemistry" in order to promote green and sustainable chemical manufacturing processes. Since then, "Green Chemistry" criteria have been highly recommended for the pharmaceutical industry to solve these severe environmental problems.

Biocatalysis has emerged as one of the best solutions to achieve "Green Chemistry" (Fig. 1), with many benefits over chemical...
synthesis to produce pharmaceuticals and pharmaceutical intermediates. Enzyme developers, such as Codexis and Novozymes, provide commercial biocatalysts and enzyme engineering services for pharmaceutical companies. Awards such as the Presidential Green Chemistry Challenge Awards (U.S. Environmental Protection Agency) have acknowledged and encouraged many efforts in novel processes using biocatalysts to synthesize pharmaceuticals. Bio-catalysis can shorten the synthetic route, be executed in mild conditions, avoid the use of toxic reagents, generate fewer by-products and wastes, and achieve high yields with excellent chemico-, regio-, and stereo-selectivities. New biocatalysts can be discovered by either screening novel microorganisms or identifying new genes via genome mining. Once discovered, these biocatalysts can be further optimized using robust enzyme engineering tools, such as rational design and directed evolution.

This review focuses on recent (mainly 2015 to date) discoveries, engineering, and applications of key classes of biocatalysts for the synthesis of pharmaceuticals and pharmaceutical intermediates. Biocatalysts such as reductases, oxidases, hydrolases, lyases, isomerases and transaminases will be discussed here.

2. Reductions

Regio- and stereo-selective reduction of the carbonyl functionality using biocatalysts is of great importance in the synthesis of chiral pharmaceutical intermediates. The biocatalytic toolbox has been expanded by discovery of new strains/enzymes and enzyme engineering. Novel microbial strains have been isolated from the environment with excellent carbonyl reduction activity and desired biochemical properties such as thermostability and tolerance to organic solvents. Wei and coworkers reported reduction of 4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4] triazolo[4,3-a]pyrazin-7(8H)-y]-yl-1-(2,4,5-trifluorophenyl)butan-2-one (OTPP) (Scheme 1a) by a novel isolate of an aerobic, Gram-negative lipolytica ACA-DC 50109 known, Xu and coworkers analysed and identified an NADPH-dependent carbonyl reductase (YlCR2) for the reduction of ethyl 4-chloro-3-oxobutanoate (COBE) to ethyl (S)-4-chloro-3-hydroxybutanoate (S-CHBE), a crucial intermediate for the synthesis of blockbuster drugs, statins (Scheme 1b). Impressively, the single enzyme YlCR2 can be used for both COBE reduction and NADPH self-generation using co-substrate mannitol or sorbitol. This substrate-coupled co-factor regeneration system with only a single enzyme is much simpler than conventional enzyme-coupled systems. Under optimized conditions, Escherichia coli cells overexpressing YlCR2 generated (S)-CHBE at 90% yield and 99% ee in 10 h. Another NADPH-dependent carbonyl reductase (RpCR) from Rhodococcus pyridinivorans was identified after genome mining and screening of a series of heterologously expressed potential COBE reductases. The purified RpCR exhibited high substrate affinity (Km 0.39 mM) and catalytic efficiency (kcat/Km 1747 s⁻¹ M⁻¹). Employing E. coli cells co-expressing RpCR and glucose dehydrogenase (GDH), (S)-CHBE could be produced at 91% yield and >99% ee. Meanwhile, carbonyl reductases have been engineered for improved catalytic activity and/or enantioselectivity. Chiral γ-amino alcohols such as 3-(dimethylamino)-1-phenylpropan-1-ol (2a) and 3-(dimethylamino)-1-(2-thienyl)-1-ol (2b) are important intermediates for the synthesis of some antidepressant drugs. Zhang and coworkers engineered a carbonyl reductase via a combinatorial active-site saturation test to increase the enantioselectivity of the enzyme for the reduction of 3-(dimethylamino)-1-phenylpropan-1-one (1a). The two mutants P170R/L174Y and P170H/L174Y reduced 1a and 3-(dimethylamino)-1-(2-thienyl)-1-ol (2b) with high ee, respectively. Remarkably, one single-point mutation L174W resulted in inverted enantioselectivity (Scheme 1c). Enantiopure t-butyl 6-cyano-(3R,5R)-dihydrohexanoate (4) is the key chiral precursor for Lipitor® (atorvastatin calcium). Luo and coworkers discovered a new carbonyl reductase KIAKR from Kluyveromyces lactis, which is capable of asymmetrically reducing t-butyl 6-cyano-(5R)-hydroxy-3-oxohexanoate (3) to 4 (Scheme 1d). A semi-rational design strategy was used to improve the enzyme activity. Briefly, two rounds of site-saturation mutagenesis based on homology modelling and molecular docking led to the isolation of a mutant Y295W/ W296L, which exhibited 11.25-fold higher catalytic efficiency than that of wild-type KIAKR.

3. Oxidations

Similar to reductions, bio-oxidation reactions have also been used in the pharmaceutical industry. For example, oxidases have been increasingly explored for biocatalysis due to their use of oxygen in air as the electron and hydrogen acceptor, leading to the generation of H2O2 that can be easily decomposed to H2O by catalase. Notably, the hepatitis C virus protease inhibitor telaprevir and boceprevir and the proton-pump inhibitor esomeprazole are manufactured industrially using oxidases.
Phytoestrogen pinoresinol is of interest in the pharmaceutical industry as it has a protective effect against multiple health disorders. Urlacher and coworkers reported an in vitro two-step one-pot synthesis of pinoresinol from the cheap starting material eugenol by employing the vanillyl alcohol oxidase from *Penicillium simplicissimum* and bacterial laccases.\(^{24}\) Under optimized conditions, pinoresinol was produced on a semipreparative scale up to a titer of 4.4 mM (1.6 g/L) (Scheme 2a). Later, the same group further developed their system to synthesize enantiopure pinoresinol by recruiting one more in vivo kinetic resolution reaction.\(^{25}\) This one-pot “two-cell” system could produce 876 mM (+)-pinoresinol with 98% ee when employing pinoresinol reductase from *Arabidopsis thaliana* and 610 mM (−)-pinoresinol with 97% ee when including pinoresinol lariciresinol reductase from *Forsythia intermedia*.\(^{26}\) Galactose oxidase mutants were used to catalyze the regioselective oxidation of *N*-carbobenzyloxy(Cbz)-protected aliphatic and aromatic amino alcohols to their corresponding α-hydroxyaldehydes under mild conditions.\(^{26}\) These aldehyde products enabled the synthesis of lactams such as 3,4-dihydronaphthalen-1(2H)-one, 2-pyrrrolidone, and valerolactam followed by reactions catalyzed by either xanthine dehydrogenase (XDH) or aldehyde oxidase (PaoABC) with up to 86% conversion (Scheme 2b).

In addition to alcohol oxidases, another class of oxidative enzymes that has attracted particular interest in the pharmaceutical industry are amine oxidases, especially monoamine oxidases. The monoamine oxidase from *Aspergillus niger* was engineered by a combination of directed evolution, rational design, and high throughput screening to exhibit broad substrate scope and tolerate bulky motifs in the synthesis of pharmaceutical building blocks.\(^{27}\) The mutant D11 found its application in deracemization reactions of pharmaceutical intermediates for the synthesis of levocitirizine and solifenacin with ≥97% ee (Scheme 2c). In another study, monoamine oxidase mutant D5 was applied in chemoenzymatic cascade reactions to selectively generate tetracyclic pyrroloindolines or tricyclic tryptamine derivatives, which could lead to the production of compounds such as serotonin receptor inhibitor and TRPV1 inhibitor with 99% ee.\(^{28}\) Recently, a patent application was filed for the synthesis of armodafinil, which is an FDA-approved stimulant-like drug to treat narcolepsy, shift work disorder, obstructive sleep apnea, and other sleep disorders.\(^{29}\) The synthetic route involves an enzymatic sulfoxidation reaction conducted by cyclohexanone monooxygenase to convert 2-benzhydrylthioacetic acid to 2-(benzhydrylsulfinyl)acetic acid.

### 4. Hydrolytic reactions

Hydrolases are useful biocatalysts for the resolution of racemates, leading to the synthesis of enantio-pure chiral drug intermediates. Lipases\(^{30}\) are the most frequently employed hydrolases.
in industrial applications due to their high activity and stability in organic solvents. To expand their practical applications, more novel lipases with increased thermostability and high activity in various types of solvents are needed. Qin and coworkers purified an organic solvent-tolerant lipase from a bacterial strain *Pseudomonas stutzeri* ZS04, which was isolated and screened from oil-contaminated soil samples. The thermostability of the lipase was significantly improved when stabilized by calcium ions. Impressively, the lipase exhibited excellent enantioselectivity toward the R-isomers of 1-(4-methoxyphenyl)-ethanol and its analogs, which are valuable chiral intermediates for pharmaceuticals. The bacterial strain *Burkholderia cepacia* RQ3 was identified from the screening using both polar and low polar organic solvents as stressors. With tolerance to a broad range of organic solvents, the lipase from this organism was successfully applied for chiral resolution of 1-phenylethanol, an important chiral building block in the pharmaceutical industry.

Recently, novel (+)-γ-lactamases have been discovered and applied to produce optically pure (−)-γ-lactam, a key chiral intermediate for the antiviral carbocyclic nucleoside drugs carbovir and abacavir used for the treatment of HIV infection and the "swine flu", respectively. The hydrolysed amino acid product can be used in the synthesis of drug candidates such as melogliptin (Scheme 3a). The (+)-γ-lactamase from *Bradyrhizobium japonicum* USDA 6 was the first (+)-γ-lactamase discovered by genome-mining. This (+)-γ-lactamase was overexpressed in *E. coli* and the purified enzyme is able to generate (S)-indanol (Scheme 3b) at >99% ee and full conversion in as short as 15 minutes under mild conditions. Metzner and coworkers reported the chemoenzymatic preparation of an alkene key intermediate of the "blockbuster drug" rosuvastatin via a seven-step synthesis without the isolation of intermediates. They integrated two recyclable hydrolases into the synthetic route, the first a dissolved α-chymotrypsin for desymmetrization and the second an immobilized cephalosporin C acetyl esterase for the catalysis of deacetylation (Scheme 3c). The chemical acetylation followed by two consecutive

Scheme 2. Representative biocatalysis using oxidases. a. Production of (+/-) pinoresinol in the cascade reaction with vanillyl alcohol oxidase from *Penicillium simplicissimum* (PsVAO) and a bacterial laccase. b. Lactams synthesis via galactose oxidase-PaoABC cascade reactions. c. Monoamine oxidase D11 involved in deracemization of intermediates for levocitirizine and solifenacin.
biocatalytic steps led to the synthesis of the chiral monoester intermediate \((R)\)-8 with overall yield of 95% from 5 and high enantioslectivity (>97% ee) using high substrate concentrations. Ghosh and coworkers designed and developed a new chemoenzymatic route for the S-isomer of moprofol, which is more potent than \((R,S)\)-moprofol, a \(\beta\)-blocker used to treat hypertension and certain arrhythmias. Under optimized conditions, the enzymatic kinetic resolution of \((R,S)\)-3-(2-methoxy-phenoxy)propane-1,2-diol \((\{R,S\}-9\) (Scheme 3d) by the lipase from *Aspergillus niger* reached ~50% conversion and 90% ee. The chiral diol intermediate was further converted to \((S)\)-moprofol by only two steps of chemical synthesis, which makes the chemoenzymatic route a cost-effective process.41

5. Lyase-catalyzed reactions

Lyases are enzymes that catalyze the removal of groups from their substrates by means other than hydrolysis and oxidation and generate new double bonds. The most prominent application of lyases is for the hyper-production of \(L\)-3,4-dihydroxyphenylalanine (\(L\)-DOPA), a drug predominantly used for treatment of Parkinson’s disease, which used whole *Erwinia herbicola* cells expressing a tyrosine phenol lyase.42 Lyases also find other applications in the pharmaceutical and pharmaceutical intermediate synthesis besides \(L\)-DOPA.

\(L\)-Tyrosine derivatives are key precursors for the synthesis of anticancer drugs, such as saframycin A and biomarkers. For instance, 3-methoxy-\(L\)-tyrosine shows positive effects in the treatment of Parkinson’s disease and is more stable than \(L\)-DOPA.43 Faber and coworkers developed an one-pot two-step cascade scheme combining a monooxygenase P450 BM3 and a tyrosine phenol lyase to produce 3-methoxy-\(L\)-tyrosine in a yield of 2 g/L and >97% ee from crude aromatic gasoline blends containing toluene (Scheme 4a). \(\alpha\)-Phenylalanines and substituted \(\alpha\)-phenylalanines are valuable building blocks for many natural products and drugs, such as nateglinide and PPACK (\(\alpha\)-phenylalanyl-\(\alpha\)-prolyl-\(\alpha\)-arginine chloromethyl ketone).44 The phenylalanine ammonia lyase (PAL) from cyanobacteria *Anabaena variabilis* was engineered and used to produce a range of \(\alpha\)-substituted phenylalanines with ≥98% ee, starting from cinnamic acids (Scheme 4b). This production was achieved through the PAL catalyzed amination reaction coupled with a chemoenzymatic deracemization reaction. The application of PAL was extended to the synthesis of unnatural \(L\)-amino acids by Turner and coworkers.45 They evolved PAL from *Rhodotorula graminis* for increased activity towards a panel of unnatural substrates, and the resulting mutant was able to produce \(\alpha\)-Br-phenylalanine in a preparative scale with a yield of 94% and >99% ee. The ammonia lyase EnCP from *Streptomyces maritimus* belongs to the same lyase family as PAL. This enzyme and its rationally designed mutants were explored for their abilities to

Scheme 3. Representative biocatalysis using hydrolases. a. Production of optically pure (\(\rightarrow\))-\(\gamma\)-lactam by (+)-\(\gamma\)-lactamase. The hydrolysed amino acid product can be used in the synthesis of drug candidates such as melogliptin. b. Resolution of \((R)\)-indanol by lipase, a key step in the chemoenzymatic synthesis of rasagiline mesylate. c. Two biocatalytic steps using hydrolases integrated in the chemoenzymatic synthesis of rosuvastatin intermediate. d. Resolution of \((R)\)-9 for the chemoenzymatic synthesis of \((S)\)-moprofol.
convert a range of arylacrylates to either (S)-α- or (S)-β-arylalanines with 99:1 selectivity and high ee (Scheme 4c).46

6. Isomerase-catalyzed reactions

Isomerases are enzymes that catalyze the conversion of a molecule from one isomer to another. In isomerase-catalyzed reactions, the substrate undergoes either intramolecular structure rearrangement or changes of bond connectivity, leading to a product that has the same molecular formula as the substrate.47 Isomerases can transform abundant, cheap sugars into expensive, rare sugars that possess great potential in synthetic pharmaceuticals and medicinal chemistry.48 The two isomerase classes are racemases/epimerases and cis–trans isomerases, and their applications will be detailed below.

L-ribose is a precursor for the synthesis of pharmaceutically important 1-form sugar based antiviral drugs including those targeting HIV, hepatitis B/C virus, and human cytomegalovirus (HCMV).49 L-ribose can be biologically produced from L-arabinose via β-ribulose with the consecutive functionalization from L-arabinose isomerase and mannose-6-phosphate isomerase (Scheme 5a). Hu and coworkers immobilized a new copper ion tolerant L-arabinose isomerase from Paenibacillus polymyxa on nanomaterials and achieved a conversion of 61.8% from L-arabinose to β-ribulose.49 6-Deoxy sugars are structural motifs for a panel of natural products.6-Deoxy-L-psicose was produced from L-arabinose through an enzyme cascade reaction combining L-rhamnose isomerase from Pseudomonas stutzeri and D-tagatose 3-epimerase (Scheme 5b).50 D-Psicose is well known for its ability to improve insulin sensitivity and β-glucose tolerance in type 2 diabetes.51 Panke and coworkers reported an efficient three-step separation-integrated route, comprising of an invertase, a D-xylose isomerase, and a D-tagatose epimerase, to synthesize D-psicose.7 These cascade reactions achieved the production of D-psicose with 99.9% purity and 89% yield from sucrose and high enzyme efficiency (300 g of D-psicose/g of enzyme).52 The D-tagatose epimerase was further tailored for better performance in the production of d-psicose by directed evolution. Two resulting mutants, namely IDF10-3 and Var8, were isolated for improved production of D-psicose from d-fructose.53 The total turnover number of these mutants was up to 108, and as high as 10.6 kg/L/d D-psicose was produced in an enzyme membrane reactor under optimal conditions (Scheme 5c).

Lactulose is widely used in pharmaceuticals, nutraceuticals, and food industries, and has a large market size with an increased annual demand in recent years.54 Ethanol permeabilised E. coli cells harbouring cellobiose 2-epimerase from Caldicellulosiruptor saccharolyticus was used as a whole cell catalyst to produce lactulose from its cheap and abundant isomer lactose (Scheme 5d). Under optimal conditions, 390.59 g/L lactulose was obtained from 600 g/L lactose, resulting in a conversion yield of 65.1%.54 Later, the performance of the particular cellobiose 2-epimerase used in the above study was enhanced by four rounds of random mutagenesis and high throughput screening.55 The best mutant G4–C5 with five point mutations (R5M/I52V/A12S/K328I/F231L) showed 2.8- and 3.0-fold increases in specific activity and kcat/Km values, respectively, and increased the conversion yield of lactulose to 76%.

Optically pure amino acids have long been attractive as building blocks for the synthesis of pharmaceuticals and agrochemicals. β-Phenylalanine was produced through dynamic kinetic resolution of N-succinyl-ω-phenylalanine using β-succinylase and N-succinylamino acid racemase, with a conversion yield of 91.1% and 86.7% ee (Scheme 5e).56 In another study, a panel of natural and unnatural amino acids were produced with high enantioselectivity (>99.5% ee) from racemic N-formyl- and N-carbamoyl-amino acids also through dynamic kinetic resolution with immobilized L-carnamoylase from Geobacillus stearothermophilus CECT43 and N-succinyl-amino acid racemase from Geobacillus kaustophilus CECT4264.57

7. Transaminations

Transaminases catalyze the exchange of an amine (NH2) group from an amino donor and a keto (C=O) group from an acceptor,
leading to a chiral amino acid or amine synthesis. Transaminases have been extensively studied for the synthesis of chiral amino compounds for their excellent stereoselectivities and concise reaction steps under mild conditions,\textsuperscript{58,59} offering an attractive alternative to transition metal catalyzed chemical synthesis. Chiral amines are important building blocks for many bioactive natural products and pharmaceuticals,\textsuperscript{60} such as Sitagliptin developed by Codexis\textsuperscript{61} and spiroindolone compounds for malaria treatment.\textsuperscript{62}

Vernakalant is an antiarrhythmic agent for the treatment of the most common cardiac arrhythmia, atrial fibrillation. Researchers from Merck & Co, USA evolved a transaminase mutant ATA-303 based on ATA-013 transaminase from Codexis to generate the chiral amine intermediate for the synthesis of Vernakalant via an enzyme catalyzed dynamic asymmetric-transamination reaction together with an esterification reaction and a pyrrolidine ring formation reaction.\textsuperscript{63} Under optimal conditions, the desired chiral

amine was obtained in 85% assay yield and >99.5% ee. Researchers at Pfizer recently reported a smoothened receptor (SMO) inhibitor 1-((2R,4R)-2-(1H-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea (PF-04449913) that has potential effects at Pfizer recently reported a smoothened receptor (SMO) inhibitor 1-((2R,4R)-2-(1H-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl)urea (PF-04449913) that has potential effects

Following this discovery, they developed a concise, asymmetric synthetic route through enzymatic transamination with the commercially available transaminase ATA-036 and concurrent dynamic kinetic resolution of a 4-piperidine (Scheme 6a). The transamination reaction produced the target chiral amine with 85% yield and 99% ee.45 Steroids and their derivatives have huge potential as pharmaceuticals. 17α-amino steroids are particularly interesting non-natural steroids that have been used as intermediates to synthesize bioactive steroidal derivatives, such as 17β-aryl sulfonamides, which are used in the treatment of breast cancer and 17β-aminoalkenones with anticoagulant effects in rodents. In spite of the wide accessibility of the β-epimer, the α-epimer is far less studied and their further derivatives are even less well characterized. Hailes and coworkers developed a novel route to synthesize 17α-amino steroids from Arthrobacter sp. on a preparative scale (Scheme 6b),46 resulting in >83% yield and 99% ee. Turner and coworkers reported a novel one-pot cascade reaction to synthesize 2,5-disubstituted pyrrolidines, which are key scaffolds for a variety of pharmaceutical compounds and natural products, using different combinations of α-transaminases and monoamine oxidases from their corresponding 1,4-diketones.67 Excellent enantioselectivity (>94% ee) and diastereoselectivity (>98% diastereomeric excess) were observed and these reactions can be carried out on a preparative scale. Another example of transaminase application is the production of (S)-phenylethanolamine and its derivatives, which are chiral precursors to many bioactive compounds such as antidepressant potential drugs BMS-53692468 and BMS-577098.69 Wu and coworkers developed modular cascade biocatalysis for novel type of asymmetric alkene functionalizations to produce (S)-phenylethanolamine and its derivatives in high ee and high yields. Two enzyme modules with five enzymes including α-transaminase were overexpressed in E. coli cells for one-pot conversion of styrenes to the corresponding (S)-aminoalcohols.70

In view of the broad applications of transaminases in the pharmaceutical industry, efforts have been devoted to make transamination reactions more efficient and sustainable. For example, diaminodonor, ortho-xylylendiamine, was newly reported to be compatible with most of the widely used (R)- and (S)-selective transaminases,71 and shifts the reaction equilibrium towards product formation through polymerizing by-product isoindole. The polymerization reaction generated colored derivatives, and this property was harnessed in a colorimetric high throughput screening method to isolate transaminase mutants. The substrate specificity of amine transaminase from Vibrio fluvialis was expanded towards bulky aromatic ketone 2-acetylbenzophenone for asymmetric synthesis of (1S)-1-(1,1'-biphenyl-2-yl)ethanamine by rational design. The mutant with seven point mutations (W57F/R88H/V153S/K163F/I259M/R415A/V422A) was generated with >1716 folds reaction rate improvement and produced pure (S)-amine (>99% ee).72 Recently, the transaminase from Ruegeria sp. TM1040 was engineered for the synthesis of bulky chiral amines, and the enzyme mutants exhibited up to 8900-fold higher activity improvement and high stereoselectivity (>99.9% ee) in the asymmetric synthesis of chiral amines bearing bulky substituents.73

8. Conclusions and future perspectives

Biocatalysis has been successfully applied in almost all types of biotransformation reactions in the last few decades, and it has benefitted the fine chemical and pharmaceutical research industries greatly. Many biological synthetic processes have been successfully established, which are environmentally friendly and more sustainable compared to routine chemical synthetic routes. The successful development of economically biocatalytic processes highly relies on the broader availability of biocatalysts with robust performance, high selectivity, increased stability, and increased activity. Advances in the areas of bioinformatics, recombinant DNA technologies, protein and strain engineering will continue to contribute to the discovery and design of new promising enzymes with practical applications, as well as the soluble expression of interesting enzymes. Biological cascade reactions and chemoenzymatic cascade reactions also make significant progress and continue to attract increasing attention.74,75 Another increasingly important challenge associated with pharmaceutical synthesis is the smartly designed and safety based process development to ensure the quality and productivity of the drugs manufactured.76 Taken together, we envision biocatalysis will become more widely used in the manufacture of pharmaceuticals and pharmaceutical intermediates in the future.
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