ABSTRACT: The development of efficient and sustainable methods for the synthesis of nitrogen heterocycles is an important goal for the chemical industry. In particular, substituted chiral piperidines are prominent targets due to their prevalence in medicinally relevant compounds and their precursors. A potential biocatalytic approach to the synthesis of this privileged scaffold would be the asymmetric dearomatization of readily assembled activated pyridines. However, nature is yet to yield a suitable biocatalyst specifically for this reaction. Here, by combining chemical synthesis and biocatalysis, we present a general chemo-enzymatic approach for the asymmetric dearomatization of activated pyridines for the preparation of substituted piperidines with precise stereochemistry. The key step involves a stereoselective one-pot amine oxidase/ene imine reductase cascade to convert N-substituted tetrahydropyridines to stereo-defined 3- and 3,4-substituted piperidines. This chemo-enzymatic approach has proved useful for key transformations in the syntheses of antipsychotic drugs Preclamol and OSU-6162, as well as for the preparation of two important intermediates in synthetic routes of the ovarian cancer monotherapeutic Niraparib.

INTRODUCTION

The ubiquity of saturated nitrogen heterocycles (N-heterocycles) in natural products and pharmaceuticals continues to drive the development of innovative strategies for their efficient synthesis. In particular, chiral piperidines are much sought after structures due to their prevalence as scaffolds in a range of bioactive molecules including market-approved active pharmaceutical ingredients (APIs). Nature provides highly efficient biocatalysts for the biosynthesis of N-heterocycles, offering high enantio- and regio-selectivity under benign conditions. These biocatalysts have previously enabled the development of one-pot cascade reactions to access stereo-enriched 2-, 2,6-, and 2,3-substituted piperidines. However, the translation of these methods to the corresponding stereo-enriched 3-substituted and 3,4-substituted scaffolds, the core of many important therapeutic compounds, remains challenging due to difficulties in stereoselectivity control combined with limited availability of suitable starting materials.

Asymmetric chemical synthetic approaches for the preparation of 3-substituted and 3,4-disubstituted piperidines include those based on metalation/cross-coupling, Grignard

Michael addition, ring closure, and transition-metal-catalyzed dearomatization of pyridines. However, limitations are associated with all of these approaches, including high reaction temperatures, sensitivity to moisture, lack of availability of starting materials, and the use of expensive noncommercial chiral ligands. Among reported methods, the catalytic asymmetric dearomatization of pyridines is achieved by quaternization-activation of the pyridine nitrogen, permitting access to mild reduction methods to chiral piperidines (Figure 1B, left). Whilst nature has yielded pyridine synthases to prepare pyridines, an effective biocatalyst for their dearomatization is yet to be discovered. With this in mind, we sought to combine mild chemical
reduction of pyridiniums to tetrahydropyridines (THPs) with the exquisite stereoselectivity of a biocatalytic cascade to reduce the final C=C bond as an efficient strategy for asymmetric dearomatization of activated 3- and 3,4-substituted pyridines (Figure 1C). Biocatalysts with broad substrate scope for the reduction of C=C bonds require the conjugation of the alkene to an electron-withdrawing group. Recently, C=C bonds conjugated to C=N bonds have been shown to undergo full reduction to amines through the combination of ene-reductases (EREDs) and imine reductases (IREDs), as well as the newly discovered ene imine reductase (EneIREDs). We reasoned that biocatalytic oxidation, using an amine oxidase (AmOx), of the THP in situ would generate the corresponding dihydropyridiniums (DHPs), generating an activated C=C bond conjugated to C=N bond, which could then be reduced with these biocatalysts to generate a cascade to the desired 3- and 3,4-substituted piperidines. This cascade complements a previous amine oxidase AmOx-IRED deracemization processes in which only amine oxidation and C=N bond reduction take place.

■ RESULTS AND DISCUSSION

A series of substituted N-alkyl THPs 1b-21b was prepared in good yields (50–90%) from activated pyridines (1a-21a) using NaBH₄ as previously reported. Initially, we explored the conversion of THPs to piperidines using AmOxs in combination with EREDs or EneIREDs (see Supporting Information 2.1.; Figures S1–S5 for the complete list of THPs screened). For the first step, we tested AmOx variants that have been shown to be effective biocatalysts for the oxidation of N-alkyl THPs. The 6-hydroxy-D-nicotine oxidase (6-HDNO) variant, E350L/E352D, was found to be effective, with a broad substrate scope, including oxidation of 1b, a precursor to Preclamol. We next screened for activity for the second step, namely, reduction of the C=C bond of the α,β-unsaturated iminium ion. Whereas the panel of EREDs displayed no activity, the EneIRED from an unidentified Pseudomonas sp. (EneIRED-01), in combination with 6-HDNO, was effective at reducing a number of THPs and could be used to prepare piperidine (R)-1c in good yield and with excellent enantioselectivity (see Supporting Information 2.1., Table S1; entry 1–3, ≥42% yield, 96% ee).

Next, we set out to identify further EneIREDs that could also generate enantiomERICALLY enantiomeric 3-substituted piperidines. By screening the recently reported metagenomic IRED collection, in combination with the 6-HDNO variant, we were able to quickly identify biocatalysts capable of generating either enantiomer of piperidine (R/S)-1c from THP 1b (see Supporting Information 2.2., Table S2). From this screen, we organized these EneIREDs into two groups: Series A (red: EneIREDs 01–04) that gave piperidine (R)-1c (Table S2, up to >99% ee) and Series B (blue: EneIREDs 05–09) that generated the enantiocomplementary piperidine (S)-1c (Table S2, up to 96% ee).

With effective EneIREDs for the preparation of both enantiomeric series, we probed the substrate scope of the 6-HDNO-EneIRED cascade (Table 1). Enzymes in Series A and B accepted a variety of aryl substituents at the C-3-position of the THP scaffold, affording products 1c-7c in high yields, conversion, and enantioselectivity. Five-membered heterocyclic 3-substituents such as furan 8c and thiophene 9c were also
Table 1. Scope of Chemo-Enzymatic Dearomatization of Activated Pyridines

**Series A and Series B provide enantiocomplementary stereopreference at C-3. All examples use EneIRED-01 except EneIRED-02, EneIRED-05, EneIRED-06, EneIRED-07, EneIRED-08, and EneIRED-09. **Switch in the Cahn-Ingold-Prelog (CIP) priority. Enantiomeric excess (ee) was determined by chiral high-performance liquid chromatography, supercritical fluid chromatography (SFC), and gas chromatography. See Supporting Information 4 for more details on the absolute configuration determination.

| **Series A** | **Series B** |
|--------------|--------------|
| ![Chemical Structures](image1) | ![Chemical Structures](image2) |

3- or 4-substituted

| R = -OMe | 79% yield 99% ee |
| R = -Br | 81% yield 99% ee |
| R = -SO₂Me | 89% yield >99% ee |
| R = -NH₂ | 83% yield >99% ee |
| R = -H | 86% yield 99% ee |
| R = -S | 85% yield 86% ee* |
| R = -Me | 64% yield |
| R = -PPG | 77% yield >99% ee |
| R = -Et | 42% yield |
| R = -Ph | 62% yield |

3,4-disubstituted

| ![Chemical Structures](image3) | ![Chemical Structures](image4) |
| ![Chemical Structures](image5) | ![Chemical Structures](image6) |
| ![Chemical Structures](image7) | ![Chemical Structures](image8) |

*Series A and Series B provide enantiocomplementary stereopreference at C-3. All examples use EneIRED-01 except EneIRED-02, EneIRED-05, EneIRED-06, EneIRED-07, EneIRED-08, and EneIRED-09. *Switch in the Cahn-Ingold-Prelog (CIP) priority. Enantiomeric excess (ee) was determined by chiral high-performance liquid chromatography, supercritical fluid chromatography (SFC), and gas chromatography. See Supporting Information 4 for more details on the absolute configuration determination.
well tolerated (≥62% yield, ≥86% ee). Sterically demanding substrates, for example, containing a 2-naphthyl substituent 10b, were also tolerated producing (R)- and (S)-10c in excellent yield and stereoselectivity (73% yield, >99% conv.,...
cascade, the conversion of THP-disubstituted piperidines provided an inverted diastereomeric configuration of the 3,4-
epimerization of the enantiomer in 3f via enamine 3e enables a dynamic kinetic resolution (DKR) to occur to generate piperidine (S)-3c mediated by the EneIRED.

Predominantly, EneIREDs in Series A yielded (R)-piperidines whilst enzymes in Series B such as EneIRED-07 yielded the (S)-product. In order to gain insight into the mode of substrate binding in the active site, we determined the structure of EneIRED-07 from Micromonaspora sp. Rc5 to a resolution of 2.55 Å in complex with NADP⁺ using X-ray crystallography. Crystals were obtained in the P2₁,2 space group and featured six molecules in the asymmetric unit, representing three dimers. EneIRED-07 displays the canonical fold observed for IREDs, with two monomers associating to form two active sites between the N-terminal Rossmann domain of one subunit and the C-terminal helical bundle of its neighbor (Figure 2D). Analysis using the DALI server suggested that the IRED with the most closely related structure was the IRED from Streptosporangium roseum (PDBe SCOM) with an rmsd of 1.0 Å over 288 Ca atoms. Following building and refinement of the protein atoms, clear omit density was observed in each active site corresponding to the cofactor NADP⁺. The iminium intermediate (S)-3f, the preferred enantiomer for EneIRED-07 imine reduction, was modeled into the active site using Autodock Vina (Figure 2E). The model suggests that the allyl group of (S)-3f is bound within a hydrophobic pocket formed by methionine residues M125, M183, and M214 at the rear of the active site as shown; the para-bromo-phenyl group projects toward the front of the active site bordered by L180, W184, and the NADP⁺ cofactor. This ligand conformation places the electrophilic carbon approximately 3.6 Å from the NADP⁺ pyridinium ring C4 atom, from which hydride is transferred. Modeling of the (R)-enantiomer of 3f places the allyl group at the base of the active site with less favorable interactions with hydrophilic residues Y225 and D238 (see Supporting Information 7.4, Figure S13).

The absolute configuration of 6c-10c was verified using VCD (Vibrational Circular Dichroism), a technique available for the determination of stereochemical configuration of chiral molecules in the solution phase. This was accomplished by the comparison of experimental infrared (IR) and VCD spectra to density functional theory (DFT)-calculated spectra of a specific configuration. Because this series of molecules was of low molecular weight with a limited number of low energy conformations (fewer than 10 in each case), four different DFT methods were employed for each compound. We tested two functionals (B3LYP and B3PW91) each with two basis sets (6-31G(d) and cc-pVTZ) to see which would have the best statistical results in each case. As expected, all five piperidine methods yielded consistent results for each enantiomer, with the best results coming from cc-pVTZ/B3PW91 for piperidines 6c and 9c, cc-pVTZ/B3LYP for piperidines 7c and 8c, and 6-31G(d)/B3PW91 for piperidine 10c. Neighborhood similarity values for IR and VCD, as well as confidence level (≥93%) were obtained using BioTools (Jupiter, FL) CompareVOA software (see Supporting Information 4.3, and 12.). Because of the similarity of the chiral core, the VCD experimental spectra were very similar for all tested compounds. Future work could therefore forego the calculations in order to streamline the process.
Finally, we sought to apply the chemo-enzymatic dearomatization of activated pyridines to several target bioactive molecules (Figure 3). First, we targeted the antipsychotic drug Preclamol. At preparative scale (1 mmol), THP-1b was converted to both \((\text{R})-\) and \((\text{S})-\) preclamol, using EneIRED-01 and EneIRED-05, respectively. Both enantiomers were prepared in four steps from 3-(3-methoxyphenyl)pyridine and were obtained in \(\geq 50\%\) overall yield and with 96\% ee (Figure 3A and see Supporting Information 5.1.). Next, we carried out the three-step syntheses of both enantiomers of OSU6162, using EneIRED-02 and EneIRED-06, and these were both accomplished in \(\geq 36\%\) overall yield and \(\geq 92\%\) ee (Figure 3B), respectively.

To further demonstrate the application of the cascade, we synthesized the two intermediates 23 and 24 en route to Niraparib (Figure 3C), the first poly ADP ribose polymerase (PARP) inhibitor to be approved as a first-line monotherapeutic for the maintenance treatment of patients with advanced ovarian cancer.\(^{49}\) For route I, we showed that commercially available 3-(4-bromophenyl)pyridine could be efficiently converted to piperidine \((\text{S})-3\text{c}\) in just three steps and 61\% overall yield (99\% ee). This was followed by deallylation and N-Boc-protection to yield \((\text{S})-23\) in 64\% yield, a key intermediate in Merck’s second-generation synthesis.\(^{50}\) Alternatively, in route II, by starting from commercially available 4-(pyridin-3-yl)aniline, we converted pyridinium salt 4a to \((\text{S})-24\) in 29\% overall yield and with 93\% ee, a key intermediate in Merck’s first-generation synthesis.\(^{51}\) The general applicability of the method was also showcased by the preparation of the corresponding \((\text{R})\)-enantiomers of both 23 and 24 in good yields and high enantioselectivity (see Supporting Information 5.1.).

In summary, we report the development of a versatile and highly efficient chemo-enzymatic dearomatization of activated pyridines for the preparation of stereo-enriched 3- and 3,4-disubstituted piperidines. The 6-HDNO-catalyzed oxidation of readily accessible THPs facilitates EneIRED-catalyzed conjugate reduction and iminium reduction to yield a broad range of chiral piperidines. The short syntheses of both enantiomers of Preclamol and OSU6162, as well as chiral precursors to Niraparib, highlight the flexibility and utility of the method presented, emphasizing the advantages of combining chemical synthesis with biocatalysis for developing new catalytic methods for the preparation of important chiral compounds. Furthermore, the increasing ability to systematically screen large panels of biocatalysts against new targets leads to the rapid identification of enzymes with applications in asymmetric synthesis.

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**Figure 3.** Application of the chemo-enzymatic dearomatization of pyridines for the preparation of APIs. (a) Synthesis of the antipsychotic drug \((-\)-preclamol. (b) Synthesis of \((-\)-OSU6162. (c) Two synthetic routes to Niraparib.

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**ASSOCIATED CONTENT**

**Supporting Information**
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c07143.

Experimental procedures including characterization of compounds, spectroscopic data of analytical biotransformations, and control experiments (PDF)

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