

# **Accepted Article**

- Title: Biocatalytic Routes to Enantiomerically Enriched Dibenz[c,e]azepines
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# Biocatalytic Routes to Enantiomerically Enriched Dibenz[*c*,*e*]azepines

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**Abstract:** Biocatalytic retrosynthetic analysis of dibenz[c,e]azepines has highlighted the use of imine reductase (IRED) and  $\omega$ -transaminase ( $\omega$ -TA) biocatalysts to establish the key stereocentres of these molecules. Several enantiocomplementary IREDs were identified for the synthesis of (R)- and (S)-5-methyl-6,7dihydro-5H-dibenz[c,e]azepine with excellent enantioselectivity by reduction of the parent imines. Crystallographic evidence suggests that IREDs may be able to bind one conformer of the imine substrate such that, upon reduction, the major product conformer is generated directly.  $\omega$ -TA biocatalysts were also successfully employed for the production of enantiopure 1-(2-bromophenyl)ethan-1-amine enabling an orthogonal route for the installation of chirality into dibenz[c,e]azepine frameworks.

Dibenz[c,e]azepines belong to a class of privileged bridged biarvl frameworks that possess unique conformational features. These architectures feature in several bioactive compounds, such as anti-obesity drugs<sup>[1]</sup> and analogues of the alkaloid colchicine,<sup>[2]</sup> as well as providing key structural elements in chiral organocatalysts<sup>[3,4]</sup> and chiral bases<sup>[5]</sup> (Figure 1a). Dibenz[c.elazepines can also act as molecular switches, owing to the conformational influence of C-centred chirality on the azepine ring with the axial chirality of the system. In their lowest energy conformation, substituents at the C(5) or C(7) position of the azepine ring are found to occupy a pseudo-equatorial position, imposing a particular conformation on the biaryl axis. Therefore, setting the C-centred chirality during the synthesis of these compounds also establishes the preferred biaryl conformation. If the C(5) or C(7) substituent is perturbed from a pseudo-equatorial to a pseudo-axial position, for example after N-derivatisation, a resulting switch in axial conformation occurs via this centre-axis relay effect (Figure 1b).<sup>[6]</sup>

Enantiomerically pure dibenz[c,e]azepines have previously been synthesised by employing chiral pool starting materials,<sup>[5,7]</sup> chiral auxiliary methodology<sup>[6,8,9]</sup> or chiral transition metal catalysis<sup>[10]</sup>

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9PL, UK. Supporting information for this article is given via a link at the end of the document. employing synthetic routes identified by traditional disconnection strategies. In order to identify new and potentially more efficient routes to these compounds, we sought to apply the principles and continually expanding scope of biocatalytic retrosynthesis.<sup>[11-14]</sup>



**Figure 1.** Dibenz[c,e]azepine architectures. a) Dibenz[c,e]azepine frameworks found in active pharmaceutical ingredients, natural product analogues, organocatalysts and reagents in organic synthesis. b) Dibenz[c,e]azepine acting as a molecular switch with the axial conformation inverting upon *N*-Boc derivatisation.

The suite of biocatalysts available for the asymmetric synthesis of chiral amines currently includes  $\omega$ -transaminases ( $\omega$ -TAs),<sup>[15-18]</sup> imine reductases (IREDs),<sup>[19-22]</sup> reductive aminases (RedAms),<sup>[23]</sup> amine dehydrogenases (AmDHs)<sup>[24,25]</sup> and ammonia lyases<sup>[26]</sup> as well as hydrolases<sup>[27,28]</sup> and monoamine oxidases (MAOs)<sup>[29-31]</sup> for (dynamic) kinetic resolution or deracemisation procedures respectively.

With this toolbox of enzymes in mind, we initially envisaged setting the C(5) stereogenic centre of the dibenz[*c*,*e*]azepine framework by employing an IRED in the final step (Figure 2). IREDs catalyse the NADPH-dependent asymmetric reduction of prochiral imines to afford chiral amines and have been applied to the synthesis of a range of chiral pyrrolidines and piperidines.<sup>[32-</sup>

<sup>36]</sup> Recently, a sub-group of the IRED family, known as RedAms,<sup>[23]</sup> has been identified and shown to catalyse imine formation as well as imine reduction in reductive amination reactions of carbonyl compounds, although RedAms can also catalyse the reduction of preformed cyclic imines. The imine substrate **1** for the IRED mediated reduction could be derived from the corresponding Boc-protected amino ketone **3** which could itself be made *via* a Suzuki-Miyaura cross-coupling of aryl boronic acid **4** and aryl bromide **5**. Furthermore, we envisaged preparing the chiral amine **5** using an  $\omega$ -TA biocatalyst.  $\omega$ -TAs are pyridoxal-5'-phosphate (PLP)-dependent enzymes that

transfer an amino group from an amine donor, such as isopropylamine (IPA) or alanine, to a carbonyl compound.<sup>[15]</sup> This work



Figure 2. A biocatalytic retrosynthetic approach to the synthesis of 2 incorporating IRED and w-TA biocatalysts.

**D**4

The planned forward synthesis was carried out by preparing four model imine substrates **1a-d** that varied at R<sup>1</sup> and R<sup>2</sup> by H or Me. Suzuki-Miyaura coupling of boronic acids 4i-ii and N-Boc aryl bromides 5i-ii catalysed by Pd(amphos)Cl<sub>2</sub> successfully afforded biaryls 3a-d. Subsequent Boc deprotection by trifluoroacetic acid (TFA) and spontaneous intramolecular condensation furnished imines 1a-d which were isolated as their hydrochloride salts (Table 1). 1D selective EXSY experiments of 1a in D<sub>2</sub>O revealed a half-life to axis inversion of  $1.7 \pm 0.4$  seconds at 298 K with an energy barrier of 75.2 ± 0.5 kJ mol<sup>-1</sup> (see Supporting Information). Therefore, at room temperature there is fast interconversion between conformers.

#### Table 1. Synthesis of imines 1a-d



[a] Impure after several rounds of column chromatography therefore isolated yield given after the next step. [b] Yield over two steps from 5 as limiting reagent.

The panel of imine substrates 1a-d was then screened with a library of 49 IREDs<sup>[37,38]</sup> including three from the recently described fungal RedAm sub-group<sup>[23]</sup>; AspRedAm from Aspergillus oryzae, AdRedAm from Ajellomyces dermatitidis and AtRedAm from Aspergillus terreus. Biotransformation results showed that imine substrates 1a and 1b, when reduced by an IRED, typically gave high conversions (Table 2). Interestingly, in the reduction of 1a, the fungal RedAms and the IRED from Amycolatopsis orientalis (AoIRED)[38] gave the (R)-configured product while the other bacterial IREDs screened displayed opposite enantioselectivity with excellent ee. For substrate (±)-1c, the ability of the IREDs to perform a kinetic resolution by reducing a single enantiomer of this compound was assessed, however, this substrate proved to be generally more challenging with typically lower conversions, modest product ees and E values <5 observed in each case. Unfortunately, substrate (±)-1d showed little to no conversion across all the wild-type enzymes screened.

Table 2. Highlighted best performing enzymes from IRED screen with substrates 7a-d.



64. >99 (S) Reaction conditions: 5 mM 1, 20% v/v cell lysate (equivalent to 50 mg/mL wet cell weight final concentration), 0.3 mg/mL glucose dehydrogenase CDX-901 (GDH), 50 mM glucose, NADP<sup>+</sup> (0.4 mM), 100 mM NaP<sub>i</sub> buffer, pH 7.5, 25°C, 250 rpm, 24 h. Conversion and ee determined by HPLC or GC-FID analysis on a chiral phase.

>99

59

8

0

0

97, >99 (S)

IR92

IR93

Preparative-scale reactions with 1a were successfully performed with AspRedAm and IR91 to isolate opposite enantiomers of 2a in high conversion, yield and enantioselectivity, demonstrating the synthetic utility of this biocatalytic approach (Scheme 1). Product NMR spectra were identical to those previously reported,<sup>[6,7]</sup> confirming the predominant conformers as (R,aS)-2a and (S,aR)-2a respectively. The conformers obtained are the result of thermodynamic equilibration (86:14 major:minor at 298K).<sup>[6]</sup> As the conformers of imine **1a** can interconvert rapidly, it is possible the enzymes can carry out a dynamic process in which a single conformer of the imine is converted to the major product conformer (Scheme 1, Path A).<sup>[39]</sup> However, we cannot

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rule out whether the enzymes can reduce the imine conformer that would lead to the minor conformer (Scheme 1, Path B).



**Scheme 1.** Preparative-scale biotransformations to afford opposite enantiomers of **2a** employing *Asp*RedAm and IR91. A dynamic process could occur in which a single imine conformer is reduced to the major product conformer (A) although path B may also occur. The same process is envisaged to occur for the reaction with IR91 which is not shown in full for brevity.

A crystal structure of AtRedAm, which has a closely related active-site to AspRedAm, in complex with the imine substrate 1a was successfully obtained through co-crystallisation with the redox inactive cofactor analogue NADPH<sub>4</sub>. Interestingly, although the ligand is not bound in a mode that positions the electrophilic imine carbon atom close to the C4 atom of the cofactor analogue, the structure suggests that these enzymes may be able to selectively bind a single conformer of the biaryl imine 1a from a rapidly equilibrating mixture. Furthermore, this conformer, (aS)-1a, would lead directly to the lowest energy conformation of the product (R,aS)-2a upon reduction (Figure 3). Wild-type AspRedAm and AoIRED gave poor conversions of (±)-1c and (±)-1d, therefore mutagenesis was explored in attempts to improve activity towards these substrates. Analysis of the ligand binding site as revealed by the ternary structure of AtRedAm (Figure 3) and a sequence alignment with AspRedAm and AdRedAm highlighted the following conserved residues; (A)D175, (B)W215, (B)M219 and (B)Q245 [(A)D169, (B)W210, (B)M214 and (B)Q240 in AspRedAm respectively] that may play important roles in substrate binding and recognition. We therefore generated and screened AspRedAm site-directed mutants D169A, D169N, W210A, W210S, M214A and Q240A, in an attempt to open up the active site to allow these bulkier substrates to bind. Of these mutants, only the Q240A variant afforded significantly improved conversion of (±)-1c (67%), although with low enantioselectivity (7%, S). Furthermore, this variant was able to convert substrate (±)-1d in contrast to the wild-type (8% vs 0%).



**Figure 3**: Active site of *At*RedAm in complex with substrate **1a** and the inactive cofactor NADPH<sub>4</sub>. The active site is formed at the dimer interface between monomers A (light blue) and B (gold). Electron densities correspond to the  $F_{\sigma}$ - $F_{c}$  and  $2F_{\sigma}$ - $F_{c}$  maps at levels of 2.5  $\sigma$  and 1  $\sigma$  respectively. The structure suggests that the enzyme can selectively bind conformer (aS)-**1a** and subsequent hydride attack would lead directly to the lowest energy product conformer (*R*,aS)-**2a**.





		Conversion of substrate/%, ee/% (R or S)			
1	IRED	1a	1b	1c	1d
	AspRedAm WT	>99, >99 ( <i>R</i> )	98	5	0
	AspRedAm Q240A	>99, >99 ( <i>R</i> )	>99	67, 7 (S)	8
	AspRedAm M214A	92, >99 ( <i>R</i> )	>99	17, 30 ( <i>R</i> )	0
	AspRedAm W210A	95, >99 ( <i>R</i> )	>99	7, 9 ( <i>R</i> )	0
	AoIRED WT	51, >99 ( <i>R</i> )	5	<1	0
	AoIRED N241A	22, 92 ( <i>R</i> )	23	23, 40 ( <i>R</i> )	0
	AoIRED N241C	5	>99	16, 7 ( <i>R</i> )	0

Reaction conditions: 5 mM 7, 0.5 mg/mL purified IRED, 0.4 mg/mL glucose dehydrogenase CDX-901(GDH), 20 mM glucose, NADP<sup>+</sup> (0.3 mM), 100 mM NaP<sub>i</sub> buffer, pH 7.0, 30°C, 250 rpm, 24 h. WT = wild-type. † Conversion and ee determined by HPLC or GC-FID analysis on a chiral phase.

Mutagenesis of another enzyme, *Ao*IRED, was also investigated by performing alanine-scanning site-directed mutagenesis of amino acid residues within 8 Å of the ligand binding site. The single-point mutants generated (N171A, L175A, M178A, Y179A, N241A, T244A, Y282A and Y283A) were screened for activity towards (±)-**1c** in whole-cell biotransformations. The M178A and N241A variants displayed good activity towards (±)-**1c** with N241A showing higher conversion (23%). Attempts to further expand the binding pocket did not improve the efficiency of these variants as the double mutants M178A/N241A and Y179A/N241A afforded lower conversion when compared to N241A. Interestingly, residue Q240 in *Asp*RedAm and N241 in *Ao*IRED are in analogous positions within their respective active

sites and mutagenesis studies showed that alanine variants at these positions were the most successful for improving activity towards (±)-1c and (±)-1d. Therefore, this position is potentially an important target for expanding the substrate scope of IREDs/RedAms towards bulkier substrates.

The preparation of chiral imine (*S*)-1c in single enantiomer form was achieved with the aid of TA biocatalysts ATA-113 and Pc-SpuC from *P. chlororaphis* subsp. *aureofaciens*<sup>[40]</sup> for the synthesis of the intermediate (*S*)-7 from ketone **6** in high yield and enantioselectivity (Scheme 2). Imine (*S*)-1c is a versatile intermediate for the synthesis of various dibenz[*c*,*e*]azepine frameworks such as **8** *via* nucleophilic attack onto the imine.<sup>[41]</sup> This route could also provide access to compound 2d which was not possible in high conversion with IRED catalysis. (*S*)-1c was also reduced chemically with NaBH<sub>4</sub> to afford enantiopure (*S*,*aR*)-2a (major conformer), providing an alternative to the IRED biocatalytic route to this compound (Scheme 2).



Scheme 2. Synthesis of (S)-1c employing transaminase biocatalysts ATA-113 and Pc-SpuC.

In summary, we have demonstrated the synthetic utility of IRED and transaminase biocatalysts for the preparation of enantiomerically pure dibenz[c,e]azepine frameworks. By IRED screening range of biocatalysts, several а enantiocomplementary highlighted enzymes were with preparative-scale reactions successfully carried out in high yield and enantiomeric excess. For the first time, a dibenz[c,e]azepine imine has been crystallised in the active site of an IRED by employing the redox inactive cofactor  $\mathsf{NADPH}_4$  which informed mutagenesis studies by rational design. Furthermore transaminase biocatalysis has enabled the synthesis of enantiopure precursors of 5,7-disubstituted dibenz[c,e]azepine compounds.

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#### **Experimental Section**

See supporting information.

Keywords: dibenz[*c*,*e*]azepines • biocatalysis • biocatalytic retrosynthesis • imine reductase • transaminase

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