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Communication

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Chemoenzymatic synthesis of substituted azepanes by sequential biocatalytic reduction and organolithium-mediated rearrangement

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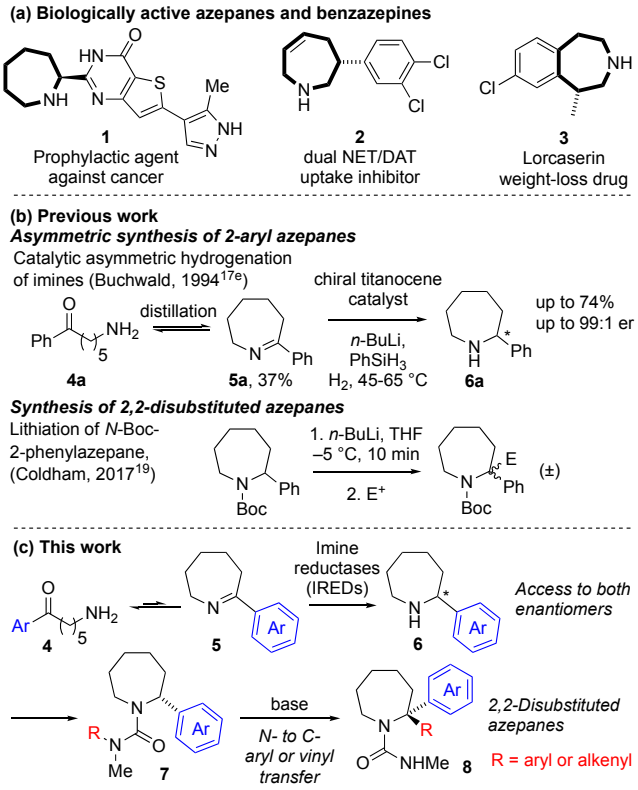
Supporting Information Placeholder

ABSTRACT: Enantioenriched 2-aryl azepanes and 2-arylbenzazepines were generated biocatalytically by asymmetric reductive amination using imine reductases or by deracemisation using monoamine oxidases. The amines were converted to the corresponding *N'*-aryl ureas, which rearranged on treatment with base with stereospecific transfer of the aryl substituent to the 2-position of the heterocycle via a configurationally stable benzyllithium intermediate. The products are previously inaccessible enantioenriched 2,2-disubstituted azepanes and benzazepines.

Biocatalysis provides a valuable enantioselective route to chiral amines. The discovery of enantiocomplementary imine reductases (IREDs) by Mitsukura *et al.*[1a,b] enabled direct stereoselective reduction of imines,[2a,b] and this approach has since been extended to intermolecular reductive amination.[3a,b] However, these reductive methods are applicable only to amines in which the stereogenic center α to nitrogen carries a hydrogen atom. In this paper we report a way to overcome this limitation, by coupling a biocatalytic reduction with the stereospecific intramolecular arylation[4a-e] of the resulting chiral amine.

The biocatalytic synthesis of seven-membered rings remains less explored[2a,5a,b] than smaller ring sizes, and we chose to apply our strategy to the synthesis of 7-membered heterocyclic α-tertiary amine derivatives of potential utility in medicinal chemistry. Molecules incorporating 7-membered heterocyclic rings, particularly azepanes and benzazepines, find many applications in medicinal and pesticidal chemistry.[6] Azepanes display activity as glycosidase inhibitors,[7a-e] norepinephrine and dopamine transporters[8] or protein kinase C inhibitors,[9] and are promising candidates for the treatment of viral infections,[7b] diabetes[10] or cancer.[7a,11a,b] Natural products and medicinal agents incorporating the azepane ring (Scheme 1a) include balanol,[9] zilpaterol,[9] azelastine,[12] capuramycin[6,13] and *Stemona* alkaloids.[14] Azepane **1** is a potential therapeutic agent against cancer,[15] and **2** is an inhibitor of NET/DAT.[8] The benzazepine core is also present in fenoldopam[16a] and lorcaserin **3**.[16b]

Strategies for the asymmetric synthesis of 2-aryl azepanes include C-H arylation of *N*-thioamide azepanes,[17a] cyclisation of entities containing pre-formed stereogenic centres,[17b-d] and enantioselective hydrogenation of the corresponding imines (Scheme 1b).[17e,f] However, formation of seven-membered heterocyclic rings is generally not straightforward.[18a-d] There are even fewer methods for the preparation of 2,2-disubstituted azepanes. Coldham *et al.* developed the lithiation-substitution of *N*-Boc-2-phenylazepane to yield racemic 2,2-disubstituted azepanes,[19] and the synthesis of enantioenriched compounds with this core is limited to quaternary α-amino acid derivatives prepared by ring-closing methathesis[20a] or structures obtained by the Schmidt rearrangement of enantioenriched α,α-disubstituted ketones.[20b,c]



Scheme 1. Substituted azepanes: biological activity and synthesis.

The 7-membered imine **5a** is a useful starting point for the asymmetric synthesis of 2-substituted azepanes, but its use is complicated by its equilibration to the corresponding aminoketone **4a**, even in organic solvents, and it must be purified by distillation.[17e] A biocatalytic approach to the synthesis of 2-substituted azepanes **6** (Scheme 1c) could overcome this problem, allowing reductive amination to take place directly from the equilibrating mixture. As a preliminary to an exploration of biocatalytic reduction, equilibrium between **4a** and **5a** was

quantified by acquiring ^{1}H NMR spectra of **5a** in aqueous 1 M phosphate solutions at pH values ranging from 1 to 8 (see SI for details). Across this whole pH range, the amount of 7-membered imine **5a** formed from aminoketone **4a** was undetectable by NMR. By comparison, the homologous 5-aminoketone **9** formed 80-90% of 6-membered cyclic imine **10** under the same conditions (Scheme 2).

This instability of the 7-membered imine in the aqueous medium makes the biotransformation much more challenging than for the 6-membered ring equivalent. Indeed, neither *R*-IRED[1a] nor *S*-IRED[1b] (both of which displayed activity towards **10**) reduced imine **5a** to 2-phenyl azepane **6a**. We therefore tested two other enzymes, both of which catalyse intermolecular reductive amination: the reductive aminase AspRedAm from *Aspergillus oryzae*[3a] and imine reductase IR-22 reported by Roiban *et al*. (Scheme 2 and Table 1).[3b] Remarkably, IR-22 gave the *R* enantiomer of **6a** from **5a** in good conversion and excellent e.r.

In order to find an enantiocomplementary IRED, we screened a small panel of novel IREDs, both genomic and metagenomic, against the 6-membered ring imine **10** (Table 1; see SI for full screening data). Those displaying good conversions with **10** were also screened against the 7-membered ring imine **5a**. Three of the novel IREDs gave excellent enantioselectivities, forming the *S* enantiomer of **6a** with conversions exceeding 60%. CfIRED from *Cystobacter ferrugineus* gave the best conversion (92%). Metagenomic mIRED 10 was *R* selective, giving 64% conversion and 94:6 e.r. The reduction of **5a** with CfIRED was repeated preparatively on a 50 mg scale and gave **6a** in 85% yield.

Scheme 2. Biocatalytic routes to enantioenriched 2-phenyl azepane **6a.**

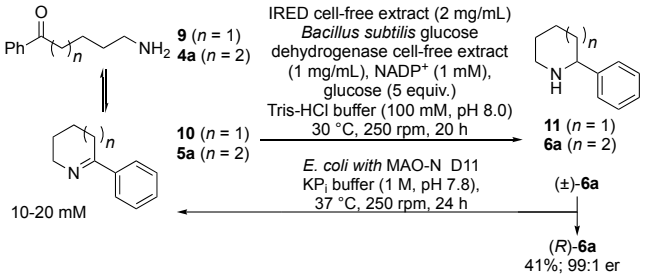


Table 1. Enantioselective reduction of cyclic imines **10** and **5a** by imine reductases.[a]

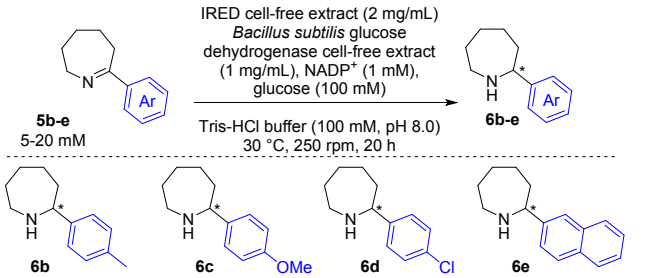
IRED	conversion to **11** /%; (*R*:*S*)[b]	conversion to **6a** /%;[c] (*R*:*S*)[d]
R-IRED[1a]	>99 (23:77)	0
S-IRED[1b]	>99 (96:4)	0
AspRedAm[3a]	0	0
IR-22[3b]	86 (93:7)	70[e] (98:2)
CfIRED	>99 (1:99)	92 (<1:99); 85[f] (<1:99)
PcIRED	>99 (<1:99)	62 (<1:99)
mIRED 02	>99 (<1:99)	81 (<1:99)
mIRED 10	>99 (>99:1)	64 (94:6)

[a]Experiments with **5a** performed with 2 mg/mL IRED cell-free extract, 20 mM substrate and 3 mL total reaction volume, while for **10** substrate concentration was 10 mM; [b]determined by GC; [c]determined by ^{1}H NMR; [d]determined by HPLC on chiral stationary phase; [e]5 mg/mL IRED cell-free extract concentration. [f]Isolated yield of preparative scale reaction per 50 mg batch.

As an alternative to the asymmetric reduction of **5**, racemic **6** was kinetically resolved with enantioselective amine oxidases (MAO-N) (see SI for full scope).[21a,b] On a 50 mg scale, *S*-selective oxidation of (±)-**6a** with MAO-N D11 gave (*R*)-**6a** in 41% yield and >99:1 er (Scheme 2). Attempts to incorporate this kinetic resultion into a deracemisation cycle by using ammonia-borane as a non-stereoselective reducing agent[21a] failed as a result of the ring opening of **5a** to **4a**, which was reduced to the corresponding alcohol.

Differently substituted 7-membered cyclic imines **5b-e** were reduced using the *R*- and *S*-selective IREDs that gave best conversions with **5a** (CfIRED, IR-22, mIRED 02 and mIRED 10, Table 2). With the *p*-tolyl-substituted substrate **5b**, all of the enzymes gave good conversions to **6b**, and most also gave excellent enantiomeric ratios. Both enantiomers of **6c** were obtained in >99:1 er and at least 60% conversion for the less electrophilic *p*-methoxyphenyl-substituted imine **5c**. The most electrophilic of the substrates tested, *p*-chlorophenyl-substituted **5d**, also gave excellent conversions and ers. Despite the insolubility of 2-naphthyl-substituted **5e** in the aqueous buffer, **6e** was formed from two of the enzymes. In all of the enantioselective reductions, CfIRED and mIRED 02 consistently gave (*S*)-**6**, while IR-22 and mIRED 10 gave (*R*)-**6**.

Table 2. Enantioselective reduction of differently substituted seven-membered ring imines **5b-e** by imine reductases.



substrate	conversion /%,[c] er (*R*:*S*)[d]			
	CfIRED	IR-22[3b]	mIRED 02	mIRED 10
5b[a]	75, 1:99	67, 99:1	72, 1:99	67, 62:38
5c[b]	69, 1:99	60, >99:1	65, <1:99	53, 50:50
5d[a]	92, <1:99	81, 96:4	84, <1:99	63, 70:30
5e	90, <1:99	0, -	64, <1:99	0, -

[a]5 mg/mL IRED cell-free extract concentration; [b]5 mM substrate and 25 mM glucose concentration; [c]determined by ^{1}H NMR spectroscopy; [d]determined by HPLC on chiral stationary phase.

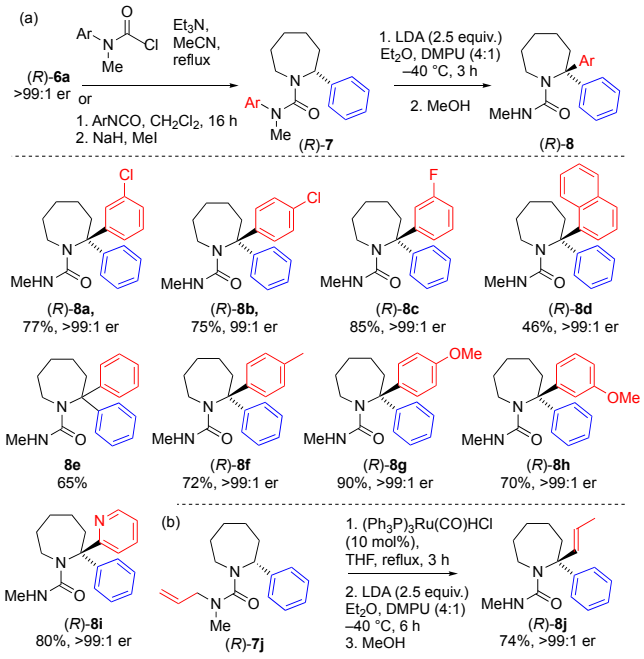
Although these 2-aryl azepanes are valuable scaffolds in their own right, they also offer a biocatalytic approach to the synthesis of synthetically challenging heterocyclic α-tertiary amines through stereospecific replacement of the α-CH bond by a carbon substituent. (Scheme 3). Such substitutions may be achieved by way of configurationally stable organolithium intermediates, with aryl migrations within lithiated ureas providing a method for stereospecific arylation.[4a-e] An *N'*-substituted urea lithiated α to N undergoes a stereospecific intramolecular transfer of an aryl,[4a] heteroaryl[4b,22a] or vinyl[22b] group to the α-position, giving α-tertiary amine derivatives that may be deprotected by solvolysis.

Ureas **7** were made from **6a** using standard methods, and rearrangement to **8a** was attempted by treatment of **7a** with base (Scheme 3). After a series of unsuccessful rearrangements (see SI for full details) we found that treatment of (*R*)-**7a** with LDA in a

4:1 mixture of Et_2O and DMPU generated a benzylic organolithium that rearranged by *N*- to *C*- aryl migration, giving enantiopure **8a** (>99:1 er) in 77% yield. We assign the configuration of the product as *R* on the basis that related reactions[4a,22a,23] proceed with retention of configuration.

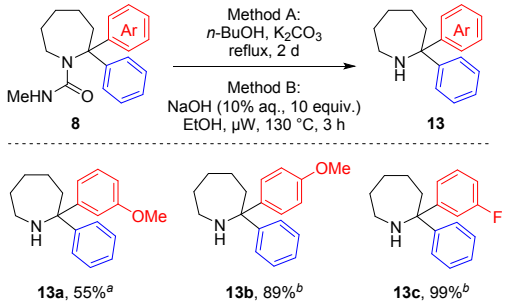
These optimised reaction conditions were applied to a range of 2-arylazepane-derived ureas **7** (Scheme 3a). These underwent organolithium-mediated arylation with a range of migrating groups to give products **8** with complete stereospecificity. Migrations of *meta*- (**7a** and **7c**) and *para*- (**7b**) halogenated aromatic rings gave excellent yields and enantiomeric ratios. Even transfer of a sterically demanding 1-naphthyl ring gave enantiomerically pure product **8d**, although in a lower yield. Despite the fact that this reaction is formally a nucleophilic aromatic substitution,[4a] yields and stereospecificity were maintained in the migration of electron rich tolyl (**8f**) and methoxyphenyl rings (**8g-h**). Migration of a 2-pyridyl ring gave enantiopure **8i** incorporating both an azepane and pyridyl ring in 80% yield. These results are particularly remarkable as cyclic benzyllithiums are generally characterized by poor configurational stability[24a-c] with racemization competing with rearrangement.[4e,25]

The method is not limited to aryl migrations.[22b] An *N*-(*E*)-propenylurea was made from the corresponding allyl urea **7j** (Scheme 3b; details of the synthesis in the SI) and treated under the same basic conditions. Stereospecific *N*- to *C*- alkenyl migration gave **8j** as a single geometrical isomer and in enantiomerically pure form, offering potential for further elaboration of the molecule at the double bond.



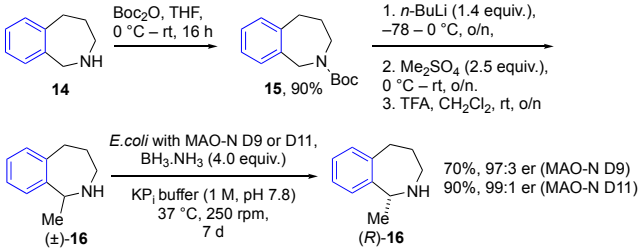
Scheme 3. Organolithium mediated α-functionalisation of azepine-derived ureas. (a) Arylation by *ipso* attack on an N-aryl group; (b) Alkenylation by stereo-retentive substitution.

The rearrangement products **8** were cleanly deprotected either by solvolysis in *n*-butanol or by alkaline hydrolysis using microwave irradiation (Scheme 4). The products are previously inaccessible α-tertiary amines with the azepane scaffold **13**.[26]



Scheme 4. Deprotection of ureas **8**. [a]Method A; [b]Method B

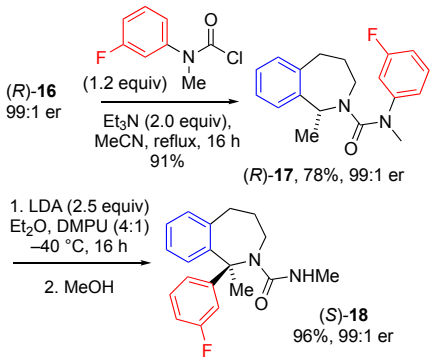
A similar chemo-enzymatic approach was applied to the biologically important 2-benzazepine scaffold, which is a component of a PNMT inhibitor.[27a,b] Boc-protected 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine **15** was methylated by way of its 2-lithio derivative[24a,28] and deprotected to give **16** (Scheme 5).



Scheme 5. Enantioselective synthesis of benzazepine **16** by alkylation and deracemisation.

Benzazepine **16** was deracemised by treatment with *S*-selective oxidants MAO-N D9 and D11, using the unselective reductant $BH_3.NH_3$ to recycle the imine product (Scheme 5). Excellent enantioselectivities were obtained. The stability of the imine oxidation product of **16** appears to prevent hydrolysis to the corresponding aminoketone, as was seen with **5a**: none of the corresponding aminoalcohol was evident in the crude ^1H NMR of the product. The methylation of **15** and deracemisation of **16** constitutes a novel approach to the asymmetric functionalisation of 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepines, which was previously achieved only with chiral auxiliaries.[30]

To demonstrate the potential for further functionalization at the 2-position, the enantioenriched 2-benzazepine (*R*)-**16** was converted into urea (*R*)-**17** and treated with LDA in Et_2O/DMPU (Scheme 6). The *meta*-fluorophenyl ring migrated successfully to the 2-position of the urea, giving the heterocyclic α-tertiary amine derivative (*S*)-**18** with a 2-benzazepine structure.



Scheme 6. Stereospecific arylation of a benzazepine-derived urea

In summary, we show that a chemo-enzymatic strategy for the preparation of heterocyclic α-tertiary amines with the azepane and

2-benzazepine scaffolds. The method makes use of enantioselective imine-reductase catalysed asymmetric imine reduction or deracemisation with amine oxidases, followed by stereospecific rearrangements of cyclic *N*-aryl benzyllithiums. Key aspects include the application of four novel imine reductases, and the stereospecific functionalisation of configurationally stable benzylic organolithium derivatives of nitrogen heterocycles. The products constitute a new class of functionalized azepanes and benzazepines of potential utility as drug molecules.

ASSOCIATED CONTENT

Supporting Information

Experimental desriptions for chemistry and biocatalysis; spectroscopic data for all new compounds.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interests.

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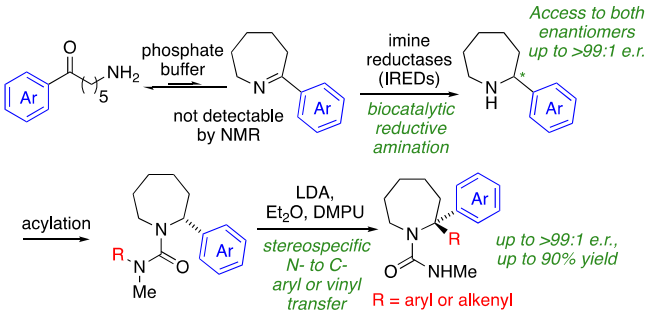
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Access to both
enantiomers
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acylation
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N
Ar
LDA,
Et2O, DMPU
stereospecific
N- to C-
aryl or vinyl
transfer
N
R
O
NHMe
Ar
up to >99:1 e.r.,
up to 90% yield
R = aryl or alkenyl