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Synergistic chemo/biocatalytic synthesis of alkaloidal tetrahydroquinolines

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ABSTRACT: The power of complementary chemo- and biocatalytic transformations is demonstrated in the asymmetric synthesis of 2-substituted tetrahydroquinolines. A series of racemic tetrahydroquinolines were synthesized through a convergent one-pot Rh(I)-catalysed addition/condensation sequence of alkyl vinyl ketones and aminophenylboronic acids. The resulting tetrahydroquinolines were thereafter shown to be substrates for the flavin-dependent enzyme cyclohexylamine oxidase, and preparative-scale deracemizations have been demonstrated on these high-value targets.

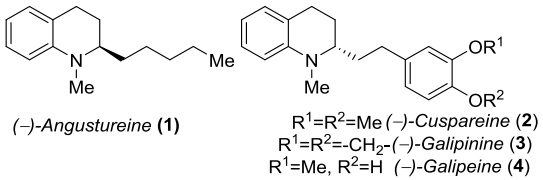
KEYWORDS: rhodium catalysis, biocatalysis, amine oxidase, alkaloidal tetrahydroquinoline, enzymatic deracemization

Introduction

Amines are an important class of molecule that are present in many biologically-relevant compounds. A recent analysis of FDA registered pharmaceuticals revealed that 84% contained an amine moiety, with 59% of these being cyclic.[1] Particularly relevant are chiral amines, which are subunits of *ca*. 40% of all pharmaceuticals.[2] A variety of strategies have been developed for the preparation of enantiopure amines, from classical resolution through to asymmetric chemocatalysis.[3,4]

Biocatalysis has found numerous applications in chiral amine synthesis[5] and the toolbox of enzymes that can be used to synthesise chiral amines includes transaminase,[6] amino acid dehydrogenase,[7–9] imine reductase,[10,11] reductive aminase[12] and phenylalanine ammonia-lyase.[13] In addition, amine oxidase (AOx) has been applied by many groups in biocatalytic deracemization reactions.[14,15] Several flavin-dependent AOx enzymes have been used in the deracemization of racemic amines including the *S*-selective monoamine oxidase from *Aspergillus niger* (MAO-N)[16,17] and cyclohexylamine oxidase (CHAO),[18] and 6-hydroxy-D-nicotine oxidase (6-HDNO)[19] which demonstrates complementary *R*-selectivity and has also been engineered to generate a more active mutant.[20–22]

Tetrahydroquinolines (THQs) are an important class of biologically-active amines, found in a range of synthetic pharmaceuticals and naturally-occurring alkaloids.[23] As typical examples, a family of 2-substituted THQs **1**-**4** isolated from *Galipea officinalis* are shown in Figure 1, several of which have biological activity against certain malarial strains (Figure 1).[24] Methods for the asymmetric synthesis of THQs are therefore of interest in medicinal chemistry.



(–)-Angustureine **(1)**

R^1=R^2=Me *(–)-Cuspareine* (**2**)
R^1=R^2=-CH_2-*(–)-Galipinine* (**3**)
R^1=Me, R^2=H *(–)-Galipeine* (**4**)

Figure 1. Alkaloids isolated from *Galipea officinalis*

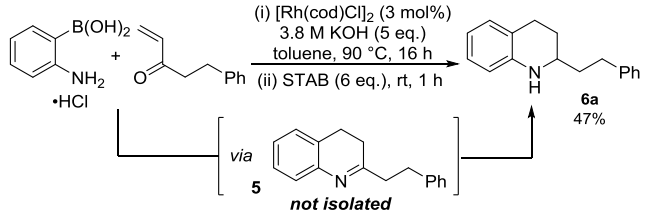
While many cyclic amines have been deracemised by AOx enzymes, studies on deracemization of THQs have been limited.[25–27] Lau engineered CHAO using iterative mutagenesis, producing a mutant which fully deracemized 2-methylTHQ on a preparative scale, but no activity was seen against other THQ substrates.[26] More recently this group demonstrated that the selectivity of CHAO could be reversed through a single point mutation of the wild-type, and showed an improved substrate scope of the enzyme.[28] Deng found that a novel AOx from *Pseudomonas monteilii* could catalyse selective oxidation of THQ derivatives to the respective quinolines, and demonstrated mutants that could be used for a traditional kinetic resolution of 2-methyl-THQs.[29]

For these deracemisation studies, the majority of the racemic THQs were prepared by reduction of the corresponding quinolines and they are therefore contingent upon the availability of these compounds. A more direct and modular approach would be attractive. A powerful emerging synthetic strategy is the union of chemo- and biocatalysis to achieve cascade or sequential transformations.[30] This approach is particularly powerful when harnessing metal-catalysed C-C bond forming processes for which there are no direct biocatalytic equivalents, hence greatly expanding the range of substrates for the biocatalytic transformation.[31–37] Herein we show that the synergistic application of a chemocatalytic one-pot, two-component condensation and biocatalytic deracemisation enables the efficient asymmetric synthesis of THQ natural products.

Results

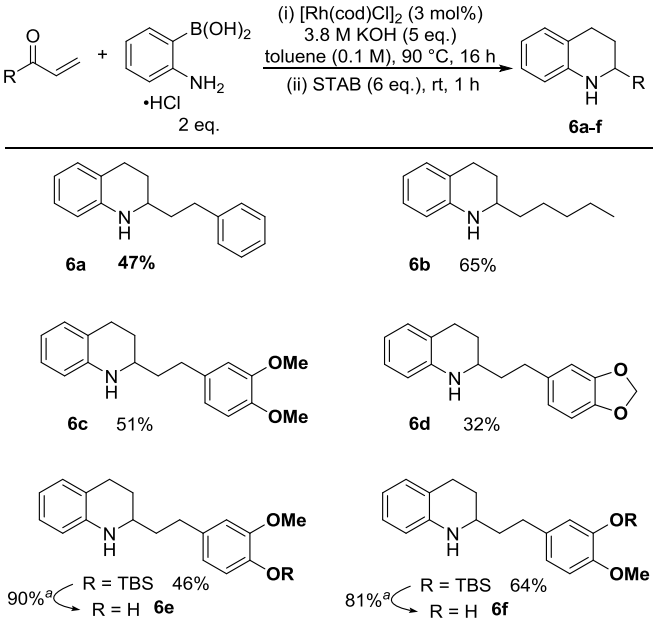
Previously, we have demonstrated a formal [4+2] approach to the assembly of nitrogen heterocycles through rhodium-catalysed conjugate addition/condensation of *ortho*-aminophenylboronic acids with Michael acceptors.[38–40] In the case of enone acceptors, the addition/condensation generates unstable dihydroquinoline intermediates which can be reduced in the same pot to give tetrahydroquinolines.[40] Chemocatalytic asymmetric addition to beta-substituted enones (using a chiral phosphine/rhodium complex) followed by a diastereoselective *syn*-reduction allowed access to highly enantioenriched 2,4-disubstituted THQ products.[40] However, many valuable products (including alkaloids **1**-**4**) feature stereocentres only at the 2-position, which cannot be accessed asymmetrically through this approach.

The approach to simple 2-substituted THQs requires the use of highly reactive unsubstituted vinyl ketones, and modification of the previously disclosed conjugate addition conditions was required for good conversion. Specifically, we found that introduction of the phenylboronic acid as its HCl salt rather than the free base and operating at elevated (90 °C) rather than room temperature gave the optimal results. Initially, we examined the use of imine reductases to reduce the prochiral dihydroquinoline intermediates **5**; however exposure of the crude reaction mixture following filtration to both (*R*) and (*S*)-IREDs failed to give any observable THQ product. The racemic 2-substituted THQ was therefore produced in a one-pot process by addition of sodium tri(acetoxy)borohydride to the reaction mixture on completion of the conjugate addition. Under these conditions, the model 2-(2-phenylethyl)THQ **6a** could be assembled efficiently (Scheme 1).



Scheme 1. Conditions for Rh(I)-catalysed 2-substituted-tetrahydroquinoline synthesis

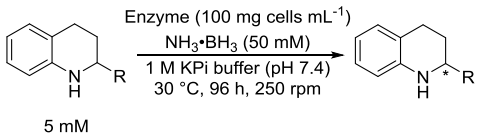
We next used these optimized conditions to extend the substrate scope to encompass the 2-substituents found in alkaloids **1**-**4** (Scheme 2). Pleasingly, incorporation of a simple pentyl substituent gave **6b** in good yield, while (3,4-dimethoxyphenyl)- and (3,4-methylenedioxyphenyl)ethyl substituents were also tolerated in **6c/d**. Galipeine **4** features both hydroxyl and methoxy substitutents on the phenyl ring; the natural product was originally assigned the 3-hydroxy-4-methoxy substitution but this has recently been revised.[41] We prepared both isomeric forms, with the phenolic function introduced as the TBS ether, which was readily deprotected to give **6e/f**. The *N*-methylations of compounds **6b**-**e** are known in the literature[41,42] and were repeated here (Supporting Information), thus completing racemic total syntheses of all four alkaloids **1**-**4** along with the regioisomeric analogue derived from **6f**.



Scheme 2. Synthesis of 2-substituted tetrahydroquinolines [a]TBAF, THF, rt., 16h

We then turned to the AOx-mediated deracemisation of the THQs **6a-f** in order to complete formal asymmetric syntheses of the alkaloids. The analytical scale biotransformations were run using whole *E. coli* cells expressing three AOx enzymes described previously: MAO-N D9,[15] the CHAO variant described by Lau *et al*.,[26] and 6-HDNO[20] which was engineered previously in the Turner group. On an analytical scale almost full deracemization of **6a** was observed with the CHAO variant, with an *ee* of 94% after 96 h. With MAO-N D9 only trace activity was observed, and 6-HDNO gave no activity towards this substrate. Pleasingly, CHAO also displayed good activity towards the natural product substrates **6b-f**, with cuspareine precursor **6c** giving 90% *ee*, galipinine precursor **6c** being converted to a lower *ee* of 70%, galipeine substrate **6e** also giving an *ee* of 70% and the isomeric substrate **6f** was fully deracemized in only 48h. Interestingly, when the angustureine precursor **6b** was subjected to deracemization by CHAO, an *ee* of only 47% was observed, but inspection of the HPLC trace showed a new peak not corresponding to either enantiomer which was subsequently shown to be the fully oxidised 2-pentylquinoline (see below). The THQ **6b** was however a suitable substrate for the MAO-N D9 enzyme, giving an *ee* of 85% after 96 h. Interestingly, it also showed limited activity towards 6-HDNO, with selectivity shown for the opposite enantiomer (Table 1).

Table 1. Analytical scale MAO deracemizations of THQ substrates

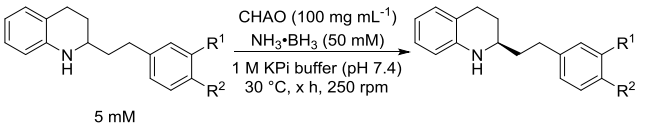


Substrate	CHAO *ee*[a]	MAO-N D9 *ee*	6-HDNO *ee*
6a	94%[b]	trace	0%
6b	47%[c]	85%	13%
6c	90%	0%	0%
6d	70%	0%	0%
6e	70%	0%	0%
6f	>99%[d]	0%	0%

Standard Conditions: THQ (5 mM), $NH_3{\cdot}BH_3$ (50 mM), *E. coli* cells (100 mg mL^{-1}), 1 M phosphate buffer (pH 7.4), 500 µL total vol. [a] Enantiomeric excess determined by chiral phase HPLC [b] 72 h instead of 96 h [c] Contained additional peak in HPLC trace when compared with racemic standard [d] 48 h instead of 96 h

We then examined the preparative scale deracemisation of several substrates (Table 2). The model substrate **6a** delivered the *R*-enantiomer (determined by comparison of the optical rotation with the literature value) with an *ee* of 94% and an isolated yield of 84% on a 50 mg scale. Deracemisation of the alkaloidal precursors **6c** and **6e** stalled at around 50% *ee*, however. Interestingly, the isomeric 3-hydroxy-4-methoxyphenyl variant **6f** gave complete deracemisation, delivering a single enantiomer in 65% yield, so it is possible the 3-methoxy substituent in **6c** and **6e** is responsible for the limited activity. The configuration of deracemized **6f** was based on the assignement of **6a** and that of literature precedents for the genuine natural product.[43] This limitation could potentially be addressed through protein engineering of CHAO to create more tolerant mutants.

Table 2. Preparative-scale deracemization reactions using CHAO



Substrate	R^1	R^2	Time	Yield[a]	ee[b]
6a	H	H	96h	84%	94%
6c	OMe	OMe	96h	64%	52%
6e	OMe	OH	96h	80%	50%
6f	OH	OMe	48h	65%	>99%

Standard conditions: THQ (5 mM), $NH_3{\cdot}BH_3$ (50 mM), *E. coli* cells (100 mg mL^{-1}), 1 M phosphate buffer (pH 7.4) [a] Isolated yield [b] Enantiomeric excess determined by chiral HPLC

Attempted preparative-scale deracemisation of the angustureine precursor **6b** with CHAO showed almost full conversion to the fully oxidized 2-pentylquinoline, allowing confirmation that this was the additional peak observed on the analytical scale HPLC trace (See SI). At this stage it is unclear whether the second oxidation is a result of non-catalysed aerobic oxidation, dihydroquinoline disproportionation, or an enzymatically-mediated oxidation step.[29] Work is currently underway to establish the mechanism of this aromatization.

Conclusions

In conclusion, Rh(I)-catalysed conjugate addition/condensation sequence allows for the one-pot synthesis of 2-substituted THQs, including des-methyl variants of a range of *Galipea* alkaloids. We have also demonstrated application of AOx enzymes in the deracemization of these high-value products on preparative scale. The synergies between C-C bond forming chemocatalysis and biocatalysis for the rapid assembly of enantioenriched products are thus further demonstrated and provide inspiration for future studies.

ASSOCIATED CONTENT

Supporting Information available: experimental procedures, spectroscopic data for all new compounds, including ^1H and ^{13}C NMR spectra, HPLC conditions and traces for all chiral compounds, and procedures for bacterial culture growth. This material is available free of charge via the Internet at http://pubs.acs.org.

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All authors have given approval to the final version of the manuscript.

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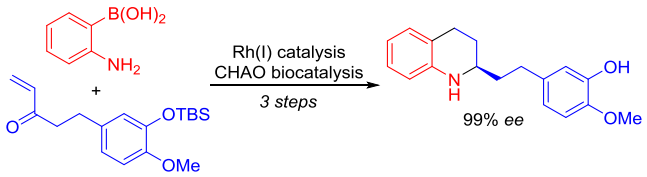
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+
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OTBS
OMe
Rh(I) catalysis
CHAO biocatalysis
3 steps
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H
OH
OMe
99% ee