A Transaminase Triggered Aza-Michael Approach for the Enantioselective Synthesis of Piperidine Scaffolds

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Supporting Information Placeholder

ABSTRACT: The expanding "toolbox" of biocatalysts opens new opportunities to redesign synthetic strategies to target molecules by incorporating a key enzymatic step into the synthesis. Herein, we describe a general biocatalytic approach for the enantioselective preparation of 2,6-disubstituted piperidines starting from easily accessible prochiral ketoenones. The strategy represents a new biocatalytic disconnection, which relies on an ω-TA-mediated aza-Michael reaction. Significantly, we show that the reversible enzymatic process can power the shuttling of amine functionality across a molecular framework, providing access to the desired aza-Michael products.

The intramolecular aza-Michael reaction (IMAMR) is a powerful method for the preparation of simple and architecturally complex nitrogen heterocycles and alkaloid skeleta.\(^1\)

An ideal strategy for the synthesis of such heterocycles and alkaloids is a tandem reductive amination/IMAMR sequence (Figure 1), allowing direct, one-pot conversion of readily available prochiral ketoenones 2 to stereodefined, highly functionalized cyclic products 1. However, the approach is dependent upon amination conditions where there is i) no reduction of the double bond, ii) no amination of the enone carbonyl, iii) stereoselective amination of the desired ketone and iv) no amination of the pendent piperidine ketone. Owing to these demands, the strategy outlined in Figure 1 is currently beyond traditional chemical synthesis and IMAM strategies are characterised by step-wise introduction of N/O-functionality with a consequent reliance on protecting group manipulations.\(^3\)

Biocatalysis allows us to reevaluate synthetic strategies and enables disconnections that are not possible using traditional chemical synthesis or catalysis.\(^3\) ω-Transaminase (ω-TA) enzymes are emerging as extremely important catalysts for the synthesis of optically pure chiral amines starting from readily available prochiral ketoenones.\(^4\) Despite the challenges associated with the use of ω-TAs, including the necessity for high equivalents of sacrificial amine donor, the application of an (R)-selective ω-TA variant for the industrial-scale synthesis of the anti-diabetic drug, Sitagliptin, highlights their enormous synthetic potential.\(^5\) These enzymes rely on the cofactor pyridoxyl-5'-phosphate (PLP) to mediate the amination of ketones,\(^5\) with no requirement for reducing agents, and therefore have the potential to be applied effectively for the synthesis of a broad range of piperidines following the strategy outlined in Figure 1. While previous studies have shown that excellent regioselectivity can be achieved in the conversion of sterically demanding 1,4- and 1,5-diketones bearing one bulky group,\(^6\) there is no literature precedence for such selectivity on substrates with two accessible ketones.

Here we describe a new biocatalytic disconnection for the regio- and stereoselective synthesis of a range of 2,6-disubstituted piperidines exploiting a key biocatalytic transamination followed by a spontaneous IMAMR. Furthermore, for substrates where high regioselectivity is not expected, we specifically exploit the reversible nature of the biocatalytic amination process to ensure that the amine functionality is ultimately installed at the desired position in a strategy that would not be possible using a classical reductive amination.

Two commercially available ω-TA biocatalysts from Codexis, which have complementary selectivity, were chosen to evaluate the methodology on a small panel of diketones 3a-e. These diketones are readily available via oxidative cleavage of 1-methylcyclopentene followed by reaction with a suitable
phosphorus ylid (see ESI). Complete regioselectivity in the amination step of ketones 3a-d was anticipated from previous literature. As expected, both the (S)- and (R)-selective ω-TA enzymes mediated the transamination reaction exclusively on the methyl ketone in >99% ee (Table 1). Following transamination, a spontaneous IMAMR occurs, providing the 2,6-disubstituted piperidines as a mixture of diastereoisomers. Conveniently, epimerization readily occurred upon standing in MeOH, presumably via a retro-aza-Michael reaction, providing products 4a-d in >99% de. A particularly important aspect of this transformation is the requirement for only 2 equivalents of the low-cost isopropylamine donor in the absence of in-situ by-product removal strategies, owing to the powerful driving force of the 1,4-addition reaction. Firstly, this gave us confidence that the reversible amination strategy could be successfully exploited for the conversion of substrates with two accessible ketones. Additionally, employing these conditions does lead to any undesired amination of the product pendant ketone.

Table 1. ω-TA-mediated transamination/IMAMR cascade of ketoenones 3a-d.

![Diagram](diagram.png)

Table 2. Results from biotransformations with 3e employing ATA113 and ATA117.

<table>
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<tr>
<th>Substrate</th>
<th>ω-TA</th>
<th>Conv (%)</th>
<th>ee (%)</th>
<th>de (%)</th>
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</tr>
</tbody>
</table>

Notes: *See Table 1 footnotes. 1 This transformation could also be carried out using 1 eq. of isopropylamine (55 mM) with identical conversion. 2 Absolute configuration determined by correlation with known compounds (see ESI).*

Scheme 1. Preparative scale conversion of 3e to 4e (-)-pinidinone using (R)-selective ATA117.

In light of this, it was envisaged that the same methodology could be employed to access the naturally occurring defense alkaloid (-)-pinidinone 4e from the corresponding dimethyl ketoene 3e (Scheme 1). An additional level of complexity is associated with this diketone as the ω-TA is not expected to show any regioselectivity in the amination step. We reasoned that while two amine products would initially be formed resulting from amination of the methyl ketone and enone, the reversible nature of the biocatalytic amination coupled with the spontaneous 1,4-addition would drive the shutting of the undesired amine to allow exclusive isolation of (-)-pinidinone 4e and trans-5e. As expected, incubation of 3e with ATA117 afforded a mixture of diastereoisomers 4e and 5e with >99% conversion and >99% ee, which was easily epimerized to (-)-pinidinone 4e with >99% de (Table 2). Comparable results were obtained with (S)-selective ATA113. We have also demonstrated that 1.1 equivalents of the amine donor were sufficient to achieve >99% conversion (Table 2, footnote f). The synthetic utility of our methodology is showcased by the ease of upscaling, allowing access to 0.48 g of (-)-pinidinone employing only 2 eq of isopropylamine (Scheme 1).
Scheme 2. Proposed mechanism for the formation of (−)-pinodinone 4e and trans-5e from the single amine equivalent 6e.

In conclusion, we have developed an extremely efficient biocatalytic aza-Michael strategy for the enantioselective conversion of pro-chiral ketoenones to 2,6-disubstituted piperidines, with excellent conversion and isolated yield. Our approach reveals that coupling a reversible ω-TA reaction with a strong thermodynamic driving force allows the amine functionality to be shuttled across a molecular framework to form the desired product. This work significantly expands the scope of ω-TA methodology in total synthesis and we are currently exploring the utility of this dynamic chemistry for the synthesis of more complex alkaloid scaffolds.

ASSOCIATED CONTENT

Supporting Information
The supporting information contains details of compound preparation, characterization and NMR/GC/HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES


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