THE USE OF ω-TRANSAMINASE FOR CHIRAL AMINE SYNTHESIS IN ORGANIC SYNTHESIS

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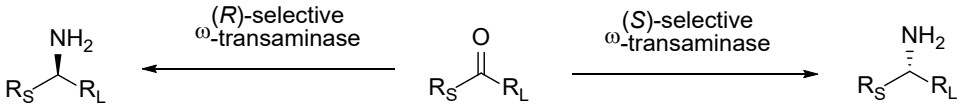
INTRODUCTION

In recent years, the importance and need for chiral amine synthesis has increased due to its uses in the pharmaceutical and agricultural industry.[1] Current chemical synthesis of these moieties is limited by several factors, including low enantioselectivity towards a preferred conformation, residue contaminants, and harsh synthetic conditions.[2] In recent years, biocatalysis has grown as a potential field for chemical synthesis which use mild conditions to catalyze reactions. An emerging system for chiral amine synthesis has been the development of highly stereospecific transaminase enzymatic reactions. Transaminases are pyridoxal 5'-phosphate (PLP)-dependent enzymes, these are known to stereo- and regioselectively aminate prochiral substrates. Transaminases, also known as amine transferases, transfer an amino group from an amine donor, typically amino acids, to a prochiral amine acceptor such as ketones or aldehydes. In comparison to α-transaminases, ω-transaminases are not confined to catalyzing amine transfers between an α-donor to an α-acceptor.[3] The development of (*S*)- and ®-selective ω-transaminases has grown exponentially in the last decade. This seminar serves as a guide to the current development of these enzymatic reactions and their uses in the pharmaceutical and agrochemical industries.

S-SELECTIVE VS *R*-SELECTIVE ω-TRANSAMINASES

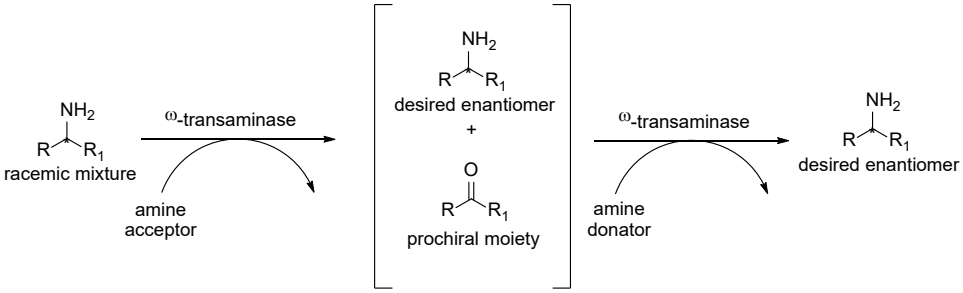
At the beginning of the last decade, most ω-transaminases used in biocatalysis for scalable synthetic reactions were designated as (*S*)-selective transaminases.[4] The lack of (*R*)-selective transaminases motivated researchers to search through known enzyme databases to identify, through homology and analogous active site, (*R*)-selective transaminases found in nature.[5,] This discovery opened up the field of transamination by allowing the formation of both (*R*)- and (*S*)-enantiomers of chiral amines with high optical purity (Scheme 1). Active site modeling on these enzymes has also allowed the expansion on the substrate scope that can be catalyzed by transaminases, demonstrated by Bornscheuer et al.[6] Another improvement these systems have seen in the last decade is the use of transaminases in organic solvent, which enhances the rate of the reaction and deters inhibition.[7]



Scheme 1: Stereoselectivity using ω-transaminases starting from a prochiral ketone.

DERACEMIZATION USING ω-TRANSAMINASE BIOCATALYSIS

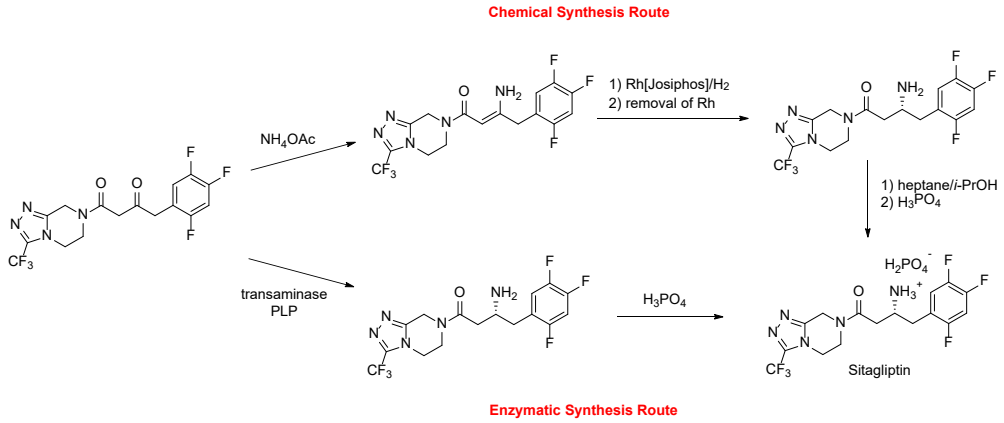
The availability of both (*S*)- and (*R*)-selective ω-transaminases has expanded the pool of aminated products obtained through biocatalysis. One of the fascinating aspects of these processes is the deracemizing potential they carry. The general mechanism of this resolution is the application of an ω-transaminase to deaminate the unwanted enantiomer, transforming it into a prochiral ketone, followed by biocatalysis using the opposing transaminase to convert the prochiral ketone into the desired enantiomer (Scheme 2).[8] This system has been implemented in various racemic mixtures including a therapeutically relevant drug called Mexiletine.[9]



Scheme 2: General mechanism for transaminase-catalyzed deracemizations.

CHIRAL AMINE SYNTHESIS IN INDUSTRY

In 2010, Savile and coworkers were able to biocatalytically synthesize sitagliptin, also known as Jenuvia® by its brand name which exceeds $4 billion in annual sales, using a commercially available (*R*)-selective ω-transaminase [ATA-117].[10] Sitagliptin synthesis, previous to this biocatalytic method, suffered from poor stereoselectivity and harsh conditions through asymmetric hydrogenation (i.e. high pressure). The reaction conditions and intermediates can be seen in Scheme 3. The enzymatic synthesis of sitagliptin had an overall increase of 10 to 13 % in yield when compared to the chemical synthesis. Its optical purity reached >99.95% *ee*. Other uses for ω-transaminases will be further discussed.



Scheme 3: Chemical vs enzymatic synthesis of sitagliptin.

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