Chemo-enzymatic flow synthesis of enantiopure piperidines

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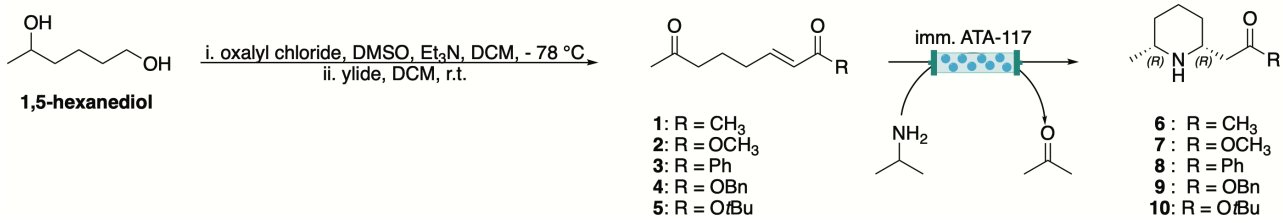
Chiral amines are important building blocks in 40–45 % of small molecule pharmaceuticals, as well as in numerous industrially important fine chemicals and agrochemicals[1]. Furthermore, environmental regulations and the increasing demand for enantiopure compounds as high-value products for different sectors necessitate the integration of traditional chemical synthetic methods with greener (bio)catalytic approaches[2]. Since nitrogen-containing heterocycles represent a privileged structure in many APIs[3], in this work we focused our attention on the asymmetric synthesis of enantiopure piperidines as high-value scaffolds for the synthesis of different alkaloids[4]. A pyridoxal 5'-phosphate (PLP)-dependent transaminase (ATA-117) was selected and immobilized to perform a stereoselective transamination, followed by a spontaneous intramolecular aza-Michael reaction (IMAMR, Scheme 1), to synthesize natural (-)-pinidinone (**6**)[5]. First, two chemical steps were performed in batch to prepare the desired substrate **1**, namely an oxidation reaction followed by a Wittig olefination using commercially available ylides. Then, after expressing and purifying the enzyme, various trials were conducted to immobilize the (*R*)-selective biocatalyst. Eupergit®C was chosen as the carrier for the covalent immobilization of ATA-117 to enhance its operational stability and reusability. The reaction was then optimized in a continuous flow system evaluating substrate concentration, isopropylamine equivalents, reaction temperature, residence time, type and amount of cosolvent. The protocol was extended to different substrates to isolate variuos 2,6-disubstituted chiral piperidines (compounds **7**-**10**).



Scheme 1: Chemo-enzymatic asymmetric flow synthesis of 2,6-disubstituted piperidines.

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