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Chiral Amine Synthesis and Recovery by Using High Molecular Weight Amine Donors

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Abstract : Chiral amines integrate the backbone of several active pharmaceutical ingredients (APIs) used in modern medicine for the treatment of a vast range of diseases. Despite the demand, their synthesis remains challenging. Besides a range of chemicals and enzymatical methods, chiral amine synthesis using transaminases (EC 2.6.1.W) represents a useful alternative to access this important class of compounds. Even though transaminases exhibit excellent stereo and regioselectivity and the potential for high yield, the reaction suffers from a number of challenges, including the thermodynamic equilibrium, product inhibition, and low substrate solubility. In this work, we demonstrate a membrane assisted strategy for addressing these challenges. It involves the use of high molecular weight (HMW) amine donors for the transaminase-catalyzed synthesis of 4-phenyl-2-butylamine in both aqueous and organic solvent media. In contrast to common amine donors such as alanine or isopropylamine, these large molecules, provided in excess for thermodynamic equilibrium shifting, are easily retained by commercial nanofiltration membranes; thus a selective permeation of the desired smaller product amine is possible. The enzymatic transamination in aqueous media, combined with selective product removal shifted the equilibrium enhancing substrate conversion by an additional 25% compared to the control reaction. Along with very efficient amine product removal, there was undesirable loss of ketone substrate and low product concentration was achieved. The system was therefore further improved by performing the reaction in organic solvent (n-heptane). Coupling the reaction system with membrane-assisted product removal resulted in a highly concentrated and relatively pure (> 97%) product solution. Moreover, a product yield of 60% was reached, compared to 15% without product removal.

Keywords : amine donor, chiral amines, in situ product removal, transamination
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