Flow Synthesis of L-Pipecolic Acid using a Lysine Cyclodeaminase

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L-Pipecolic acid (L-PA) is a non-proteinogenic amino acid widely used as a building block for the synthesis of various bioactive molecules such as anesthetics, immunosuppressants and antibiotics. Typically, L-PA synthesis has been performed using chemical methods that involve harsh conditions and hazardous reagents, mainly due to the difficulty to obtain optically pure L-PA[1]. Alternatively, biocatalytic approaches have been employed to synthesize L-PA in a more sustainable manner. Several examples showed the selective deamination and reduction of L-lysine to obtain L-PA by using whole cells[2,3] or by a bi-enzymatic cascade in the purified form[4]. Herein, we present the application of a purified lysine cyclodeaminase (LCD) for the synthesis of L-PA in only one step and with catalytic amounts of cofactor. Biotransformations in batch reached full conversion at 50 mM L-lysine in 24 hours using 0.5% w/v LCD. To enable the biocatalyst reusability, LCD was immobilized on microbeads with a retained activity of about 25%. To further intensify the synthetic process, the immobilized biocatalyst was integrated into a packed-flow reactor achieving full conversion at 10 mM scale with 90 min of residence time.

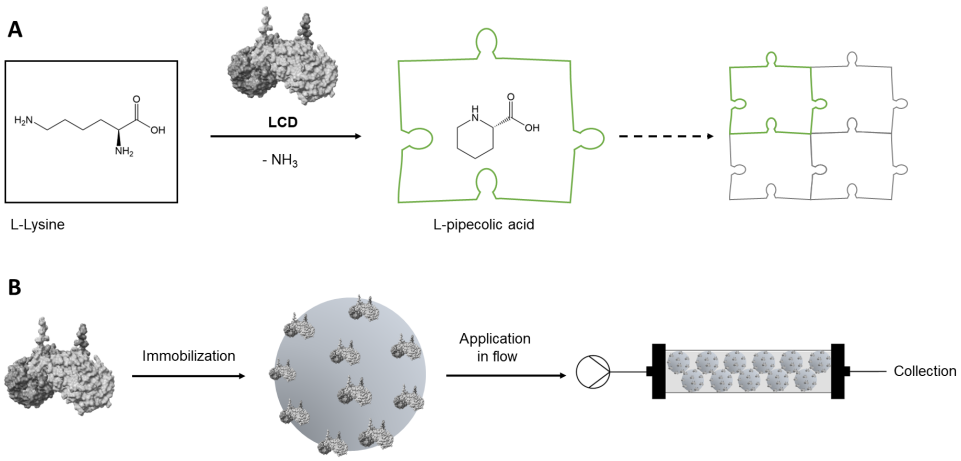


Figure 1. Synthesis of L-pipecolic acid (L-PA) from L-lysine using a Lysine Cyclodeaminase (LCD) (A). The enzyme was immobilized on microbeads for the application in continuous flow to optimize the reusability of the biocatalyst and the obtained yield (B).

[1] Cant, A. A., & Sutherland, A. *Synthesis*, **2012**, 44(13), 1935–1950
[2] Ying, H., Wang, J., Shi, T., Zhao, Y., Ouyang, P., & Chen, K., *Catal. Sci. Technol*, **2019**, 9, 398 -405
[3] Yang, Y.-H. et al. *Enzyme and Microbial Technology*, **2020**, 140, 109643
[4] Roura Padrosa, D., Benítez-Mateos, A. I., Calvey, L., & Paradisi, F. ***Green Chem.***, **2020**, **22**, 5310-5316