MULTISTEP CONTINUOUS FLOW SYNTHESIS OF THE CHIRAL KEY INTERMEDIATE OF PAROXETINE

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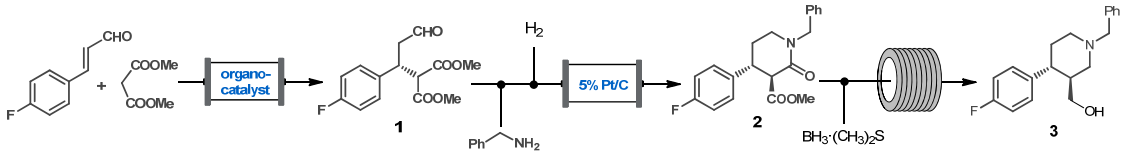
Enantiomerically pure drugs are crucially important in pharmaceutical research. However, single-enantiomer pharmaceuticals are challenging to synthesize, especially on a larger scale. Paroxetine is a selective serotonin reuptake inhibitor, which is widely used as antidepressant. Its industrial synthesis is typically focused on chiral auxiliary-assisted processes [1].



Our aim was to develop a highly productive telescoped continuous flow synthesis for the active pharmaceutical ingredient (API) of paroxetine without the need for chiral building blocks as costly starting materials. Instead, we relied on the polystyrene-supported *cis*-4-hydroxydiphenylprolinol-catalyzed asymmetric conjugate addition between 4-fluorocinnamaldehyde and dimethyl malonate to yield chiral key intermediate **1** with an excellent *ee* of 97%. The organocatalytic flow conjugate addition succeeded under neat conditions and offered an outstanding productivity of around 2.5 g pure product per hour. Adduct **1** was next combined with benzylamine to yield lactam **2** in a subsequent reductive-amination/cyclization step while passing through a Pt/C-loaded cartridge in the presence of H_2 gas. The last step of the process was an amide/ester reduction, using neat borane dimethyl sulfide complex as reducing agent in a heated coil. The neat borane reagent could safely be employed under flow conditions, and ensured excellent yields even with a substrate concentration of 1 M. After removal of excess hydrogen, the reductive-amination/lactamization step was successfully telescoped with the borane-mediated reduction, and the process offered API precursor **3** in multigram scales per hour.

[1] C. De Risi, G. Fanton, G. P. Pollini, C. Trapella, F. Valente and V. Zanirato, Tetrahedron: Asymmetry, 2008, 19, 131-155.