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With the emergence of tubular reactor devices for research, the field was opened to develop reactions that can rather easily be scaled up to higher volumes without the need of extensive engineering. Our aim was to combine two top-notch technologies into one simple process, featuring the excellent selectivity of enzymes and the high productivity of heterogeneous catalysts in continuous flow.

Our setup efficiently facilitates the stereocontrolled synthesis of Aerangis lactones and demonstrates the advantage of the chemo-enzymatic cascade concept: a 7-step synthesis [1] can be replaced with a single-operation process.

We chose a combination of heterogeneous metal-catalyzed hydrogenation and enzymatic Baeyer-Villiger oxidation (Scheme 1). In a continuous flow reactor cheap dihydrojasmone is reduced to the saturated ketone with excellent diastereoselectivity (>90 % cis). Operation at high product concentration allows for direct introduction of the efflux to an efficient batch biotransformation (>7 g/L, <25 min), yielding natural (S,S)-Aerangis lactone in perfect purity (>99 % ee, >99 % de) via kinetic resolution by cyclododecanone monoxygenase (CDMO). By re-direction of the first product stream through a second flow reactor diastereoselectivity is inverted in-line (90 % trans), giving access to epimeric (R,S)-Aerangis lactone with >99 % ee by employing cyclopentanone monoxygenase (CPMO) in the final biooxygenation.

Reference