A Chemo-Enzymatic Cascade Process for Single-Operation Synthesis of Chiral Aroma Lactones

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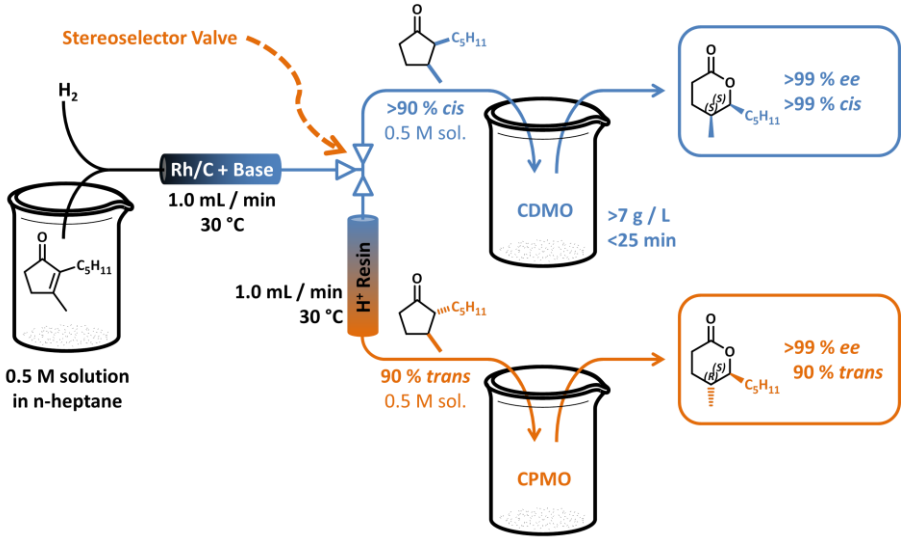
With the emergence of tubular reactor devices for research, the field was opened to develop reactions that can rather easily be scaled up to higher volumes without the need of extensive engineering. Our aim was to combine two top-notch technologies into one simple process, featuring the excellent selectivity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



Scheme 1 Flow scheme of the semi-continuous production of *cis* and *trans-Aerangis* lactone

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 monooxygenase (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 monooxygenase (CPMO) in the final biooxygenation.

Reference

[1] Y. Wu, X. Shen, C.-J. Tang, Z.-L. Chen, Q. Hu, W. Shi, *J. Org. Chem.* **2002**, *67*, 3802-3810.