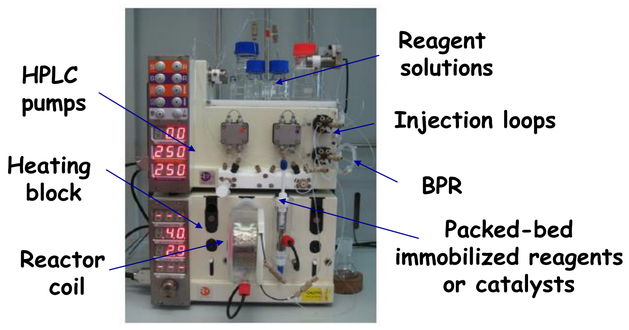
The chemoenzymatic continuous-flow synthesis of captopril

Federica Dall'Oglio,[a] Andrea Pinto, Valerio De Vitis,[b] Francesco Molinari,[b] Diego Romano,[b] Paola Conti [a] and Lucia Tamborini[a]

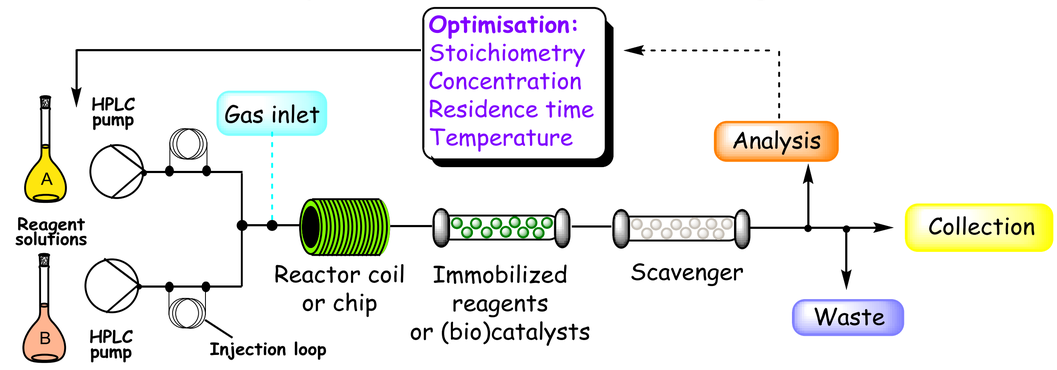
[a]Department of Pharmaceutical Sciences (DISFARM), University of Milan, via Mangiagalli 25, 20133, Milan, Italy
[b]Department of Food, Environmental and Nutritional Sciences (DeFENS), University of Milan, via Celoria 2, 20133 Milan, Italy
E-mail: federica.dalloglio@unimi.it

Flow reactor technology represents one of the new strategies introduced to advance the sustainability of organic synthesis and shows many advantages compared to the batch methods (*e.g.*, increased safety, high control of reaction parameters, reduced manual handling, in-line purifications, reaction telescoping). For these reasons, continuous-flow synthesis is receiving increasing attention also in the pharmaceutical industry and, as a result, in the last years many new flow-based routes have been designed towards commercially available APIs [1].

Equipment



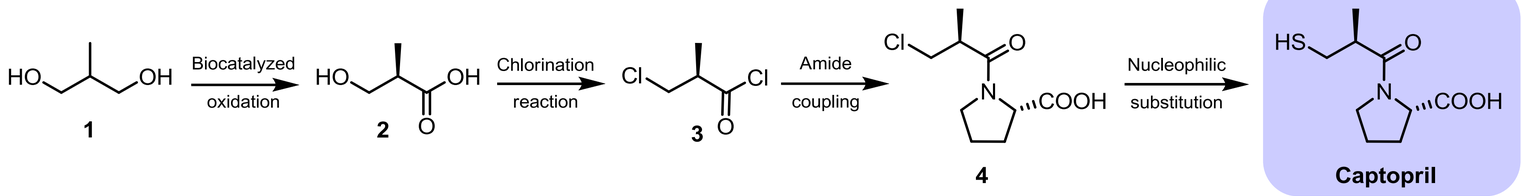
Schematic representation of a reactor configuration



Aim of the work

Exploiting the flow chemistry facilities, we developed an efficient chemoenzymatic synthetic route to obtain enantiomerically pure captopril, an ACE inhibitor widely used for the treatment of hypertension.

Synthetic strategy



1) Biocatalyzed regio- and stereo-selective oxidation

The oxidation of the cheap prochiral diol **1** was performed in flow using **dried alginate beads of *Acetobacter aceti* MIM 2000/28** packed in a reactor column. To provide the oxygen required, an **oxygen supply system** has been designed. The carboxylic acid **2** was isolated exploiting an **in-line catch and release strategy**.

Immobilised biocatalysts in flow reactors [2]

- ✓ high local concentration of biocatalyst
- ✓ limited product inhibition effect
- ✓ improved mass and heat transfer
- ✓ no mechanical stress

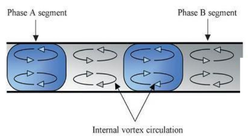
→

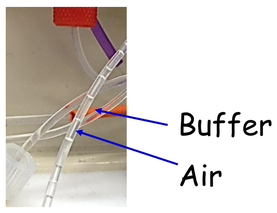
- ✓ faster kinetics
- ✓ easier scale-up
- ✓ improved productivity
- ✓ improved recyclability of the solid catalyst

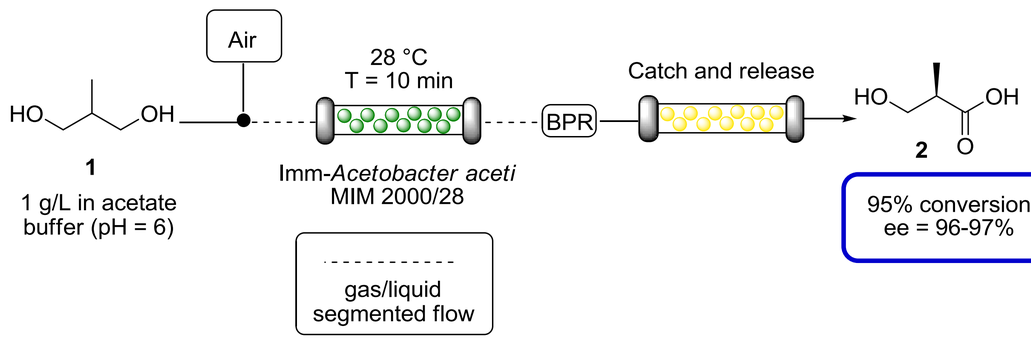
Whole cell dried alginate beads in a packed bed column [3]

Advantage: using whole cells for the oxidation, no additional cofactor regeneration system is required.

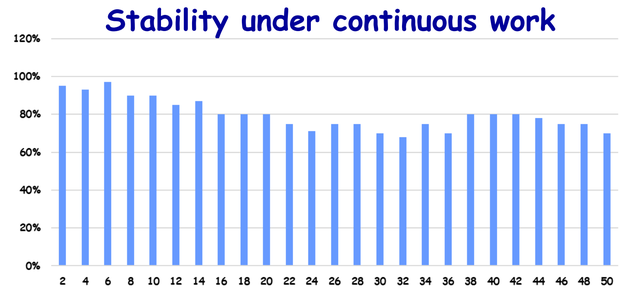
Gas/liquid segmented flow







Stability under continuous work



Batch

Conversion: 95%
Reaction time: 180 minutes
$r_{(batch)}$= **5.12** $\mu mol_p \cdot g^{-1}_{cell} \cdot min^{-1}$

Flow

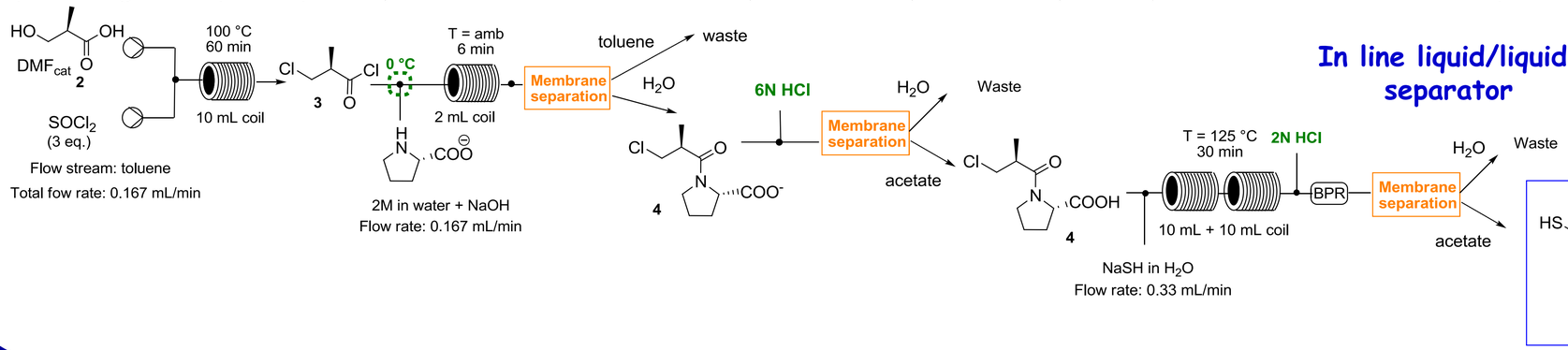
Conversion: 95%
Reaction time: 10 minutes
$r_{(flow)}$= **61.5** $\mu mol_p \cdot g^{-1}_{cell} \cdot min^{-1}$

Flow *vs* batch

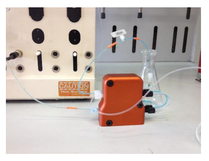
Time: 18 fold reduction
Productivity: 12 fold increase

2) Three sequential chemical steps

Starting from isolated compound **2**, three sequential chemical steps have been performed without any break and manipulation of intermediates thanks to in-line quenching and liquid/liquid separations. Each chemical step was first optimized separately and then connected in sequence.



In line liquid/liquid separator



Flow

Overall yield: 65%.
Overall time: 100 min.
1 column chromatography.

Batch

Overall yield: 45%
Overall time: 3 days
2 column chromatography
14 extractions

References

[1] a) Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329–332; b) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675 – 680; c) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2015**, *11*, 1194–1219; d) Ley, S. V. *Chem. Rec.* **2012**, *12*, 378–390. [2] S. G. Newman, K. F. Jensen *Green Chem.* **2013**, *15*, 1456–1472. [3] Zambelli P., Tamborini L., Cazzamalli S., Pinto A., Arioli S., Balzaretti S., Plou F. J., Fernandez-Arrojo L., Molinari F., Conti P., Romano D. *Food Chemistry* **2016**, *190*, 607-613.