Continuous Flow Multi-step Catalytic Organic Synthesis: Multireactor Networks.

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Many research efforts need to be driven to the development of practical processes for the preparation of Fine Chemicals and Pharmaceutical products. In this context, a large number of catalytic transformations have been described. One straightforward approach to implement the potential for practical use and their "Green character" is the catalyst immobilization on a solid support. This facilitates the work-up, particularly recycling and reuse, decreases the toxicity of catalytic materials and can significantly reduce the final amount of waste. In recent years, we have been exploring the use of continuous flow systems based on functionalised polymers as heterogeneous reagents and catalysts.

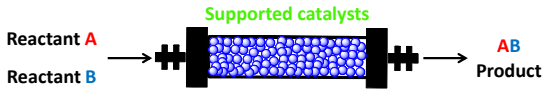

Fig.1 Sustainable Chemical transformations under continuous flow.

Functionalized resins of different nature (gel or macroporous type) and shapes (beads or monolithic polymer) are suitable to prepared fixed-bed catalytic microreactors that can be used efficiently even under flow conditions.

In Continuous Flow Chemistry, two or more reagents are continuously pumped into a flow-reactor, where they mix and subsequently react under thermal control. Continuous Flow Chemistry has some major advantages. Mixing can be achieved within seconds and reaction temperature can raised above the solvent's boiling point, resulting in faster reactions. Flow Chemistry enables excellent reaction selectivity. The rapid diffusion mixing avoids the issues found in batch reactors. The high surface area to volume ratio (1000x greater than a batch reactor) enables almost instantaneous heating or cooling and therefore ultimate temperature control, resulting in cleaner products.

It allows only a small amount of hazardous intermediate to be formed at any instant. The high surface area also allows excellent control of exothermic reactions using Flow Chemistry, resulting in safer reactions. Flow Chemistry with automation enables the quick variation of reaction conditions on a µl-scale. Parameters such as reaction time, temperature, flow, pumped volumes and pressure can all be rapidly varied. One reaction can follow another, separated by solvent, each cleaning out the previous reaction enabling quick reaction optimization. Scale-up issues are minimized due to maintaining excellent mixing and heat transfer. Higher flow rates and correspondingly larger reactors can be used to easily produce kilogram or tonne-scale quantities using Flow Chemistry.

The minireactors are based on functional polymers with different catalytic sites. Such minireactors were assayed for different chemical transformations under continuous flow conditions. Interesting results were obtained in some cases including long-term stability or improvement of the activity and selectivity over the homogeneous analogues. Furthermore, the use of continuous flow techniques for multi-step synthesis enables multiple reaction steps to be combined into a single continuous operation allowing the sequential multicatalytic reaction in a multireactor network (see Fig 2).

Here, we report the use of our last results in the development of such multicatalytic networks for the synthesis of some chiral key intermediates of the synthesis of different APIs.

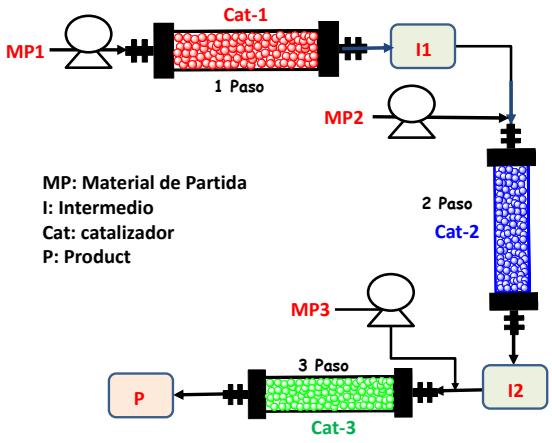

Fig.2 Multireactor network for the synthesis of a product through the integration of three catalytic steps.

We have developed and optimized different biocatalytic process and supported-catalysts in continuous obtaining good results.

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References

1 R. Porcar, V. Sans, N. Ríos-Lombardía, V. Gotor-Fernández, V. Gotor, M. I. Burguete, E. García-Verdugo, S. V. Luis, *ACS Catal.*, 2012, **2**, 1976-1983.
2 S. V. Luis, E. García-Verdugo, Chemical Reactions and Processes under Flow Conditions, RSC Green Chemistry Series; The Royal Society of Chemistry: Cambridge, U.K., 2010.
3 P. Lozano, E. García-Verdugo, J. M. Bernal, D. F. Izquierdo, M. I. Burguete, G. Sánchez-Gómez and S. V. Luis, *ChemSusChem*, 2012, **5**, 790-798.