

Pericàs Research Group



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Abstract

Over the last years, the Pericàs laboratory at ICIQ has been engaged in a broad research program aimed at developing a complete toolkit of polymer-supported and magnetic nanoparticle-immobilized catalysts with optimized characteristics of catalytic activity,

high induced stereoselectivity and extended life cycle.

The ultimate goal of this research has been the development of single-pass, catalytic and enantioselective flow versions of the most relevant processes for organic synthesis, contributing in this manner to a more sustainable practice of chemical synthesis. Our laboratory at ICIQ has been pioneer in this effort, being recognized as one of the leaders in the field.



Supported organocatalysts and flow processes

Our main research line involves the preparation of solid-supported species for enantioselective catalysis. In previous years we had proven the robustness of Brønsted acids, which allowed for prolonged recycling. This prompted us to study the immobilization of the TRIP phosphoric acid catalyst, which was carried out through a copolymerization strategy. The resulting catalytic resin was extremely active in the asymmetric allylboration of aldehydes. Remarkably, the whole aldehyde scope was carried out reusing the same sample of PS-TRIP (18 examples, accumulated TON of 321 in batch), which could be reactivated by acidic washings in case of deactivation. This catalytic resin also allowed implementing a continuous flow experiment spanning 28 h, in which 4.60 g of highly enantioenriched allylboration were produced.



Fig. 1 – Polystyrene-Supported TRIP: A Highly Recyclable Catalyst for Batch and Flow Enantioselective Allylation of Aldehydes.

One of the main drawbacks of solid-supported catalysts is their increased cost when compared to their homogeneous counterparts. Consequently, we benchmarked a squaramide derivative previously prepared in our group to see how many of its components were actually indispensable. As a result, a streamlined, even more effective analog at a much lower price was prepared and tested in the asymmetric synthesis of pyranonaphthoquinones in flow. The set-up included an in-line work-up and phase separation, so only evaporation of the outstream and chromatography were necessary.



Fig. 2 – Removing the superfluous: a supported squaramide catalyst with a minimalistic linker applied to the enantioselective flow synthesis of pyranonaphthoquinones.

A polystyrene-based proline catalyst has been prepared by a polymerization strategy, which ensures complete control of all the parameters of the resulting material. The triazole linker allows swelling in water and the catalytic material can be reused with minimal loss of activity. It has been applied to the cross- and self-aldol reaction of aldehydes with excellent results. Remarkably, adding the wet resin to a flask with propanal (0.2 mol% catalyst loading) the desired self-aldol product was isolated in nearly 50% yield and 82% ee.



Fig. 3 – Asymmetric cross- and self-aldol reactions of aldehydes in water with a polystyrene-supported triazolylproline organo-catalyst.

Imidazolidinones are amongst the most successful types of organocatalysts. However, the so-called second generation MacMillan catalyst had never been supported onto a solid phase to fully ascertain their recyclability profile. Thus, we designed a versatile strategy that allowed grafting of these aminocatalysts onto both polystyrene and Fe₃O₄ magnetic nanoparticles (MNPs). After testing both catalytic materials in the enantioselective conjugate addition of indole derivatives to α , β -unsaturated aldehydes, the polystyrene-based species proved to be superior in terms of activity and stereoselectivity, probably due to some interaction deleterious of the reaction intermediates with the free OH groups on the surface of the MNPs.



Fig. 4 – Polystyrene or Magnetic Nanoparticles as Support in Enantioselective Organocatalysis? A Case Study in Friedel-Crafts Chemistry.



Chiral isothioureas have proven to be excellent Lewis base catalysts. After reaction with an activated carboxylic acid and formation of the corresponding acylammonium species they can be engaged in a variety of reactions. In this case, an immobilized analog of benzotetramisole was prepared and exploited in [4+2] cyclizations of arylacetic acids and α , β -unsaturated imines, giving rise to chiral lactams in good yields and enantioselectivities. Despite the fact that the acid has to be activated in situ, the system was shown to be recyclable in batch, as well as amenable for continuous flow operation.



Fig. 5 – A Recyclable, Immobilized Analogue of Benzotetramisole for Catalytic Enantioselective Domino Michael Addition/Cyclization Reactions in Batch and Flow.

The aminocatalytic enantioselective cyclopropanation that takes place between an α , β -unsaturated aldehyde and a bromomalonate in the presence of base was described by Wang and co-workers in 2007. However, sometimes the desired cyclopropane reacts with base to give a decomposition product. We reasoned that reducing the contact time between the final product and the base, the decomposition should be minimized. A possible strategy to this end was to carry out a flow process, as the products are then continuously removed from the catalyst and a work-up can be immediately carried out. Thus, we studied the immobilization of diarylprolinol derivatives with different strategies and supports (microporous resin vs monolith). The best candidate was selected and tested in the flow cyclopropanation of enals, showing that the decomposition could be minimized under these conditions. Up to 12 analogs were produced with the same sample of catalyst in a period of more than 12 months, which speaks of the great robustness of this catalytic material.



Fig. 6 – Organocatalytic Enantioselective Continuous-Flow Cyclopropanation. Metal-catalyzed transformations and flow processes

As part of an ongoing collaboration with the group of Prof. Montserrat Gómez in Toulouse, we have studied the use of glycerol as a sustainable reaction medium. In particular, we were intrigued by the copper-catalyzed azidealkyne cycloaddition in this solvent, which turned out to depend on the source of benzyl azide. We have identified long chain alkyl amine impurities to be responsible for this seemingly random behavior. These "key ingredient" plays a crucial role in the formation of small and well-dispersed Cu(I) nanoparticles, which are ultimately responsible for the catalytic process. Indeed, in the absence of these amines the process does not take place at all, but on the basis of our findings we have established a reproducible and sustainable reaction protocol.



Fig. 7 – Key Non-Metal Ingredients for Cucatalyzed "Click" Reactions in Glycerol: Nanoparticles as Efficient Forwarders.

This year we have also published a Feature Article in which we summarized the different methods for the synthesis of tris(triazolyl)methanol (TTM) ligands, first developed in our group, and their application in catalyisis. Special focus is put in the corresponding copper complexes as well as in the immobilization on solid supports and their application in flow processes.





Fig. 8 – Synthesis and catalytic applications of C_3 -symmetric tris(triazolyl)methanol ligands and derivatives.

Enantioselective homogeneous organocatalysis

In the homogeneous domain, we have also reported on the dienamine-mediated [4+2] cyclization of enals and alkylidenepyrazolones, a case of inverse electron demand Diels–Alder

Articles

"Organocatalytic Enantioselective Continuous-Flow Cyclopropanation"

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"Optical control of endogenous receptors and cellular excitability using targeted covalent photoswitches"

Nature Communications **2016**, *7*, 12221 M. Izquierdo-Serra, A. Bautista-Barrufet, A. Trapero, A. Garrido-Charles, A. Díaz-Tahoces, N. Camarero, S. Pittolo, S. Valbuena, A. Pérezreaction. The catalyst screening turned out to be challenging, but finally an unprotected dinaphthylprolinol derived from 4-hydroxyproline was identified, giving rise to 17 different tetrahydropyranopyrazoles in good yields and ee's.



Fig. 9 – H-Bond-Directing Organocatalyst for Enantioselective [4+2] Cycloadditions via Dienamine Catalysis.

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