

Pericàs Research Group



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Administrative Support: Núria Mas / Marta Moya (April-Nov) / Sara Garcia

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

In a recent review, we have covered the literature related to the use of solid-supported organocatalysts for the continuous flow production of enantiomerically enriched compounds in the last few years. The development of challenging flow chemistry applications with our toolkit of immobilized catalysts is an active topic of research in our group. Thus, remarkable examples have been reported recently and some new devices are being incorporated to the set-ups for continuous flow applications.

A novel polymer-supported fluorinated organocatalyst has been prepared and benchmarked in the enantioselective Michael addition of aldehydes to nitroalkenes. The system has proven to be highly efficient and displays excellent selectivities with a wide variety of substrates. Detailed deactivation studies have allowed the lifespan of this immobilized aminocatalyst to be significantly extended. These data have facilitated the implementation of enantioselective, continuous flow processes allowing either the multigram synthesis of a single Michael adduct over a 13 h period or the sequential generation of a library of enantiopure Michael adducts from different combinations of substrates (13 examples, 16 runs, 18.5 h total operation). A customized in-line aqueous workup, followed by liquid-liquid separation in flow, allows for product isolation without the need of chromatography.

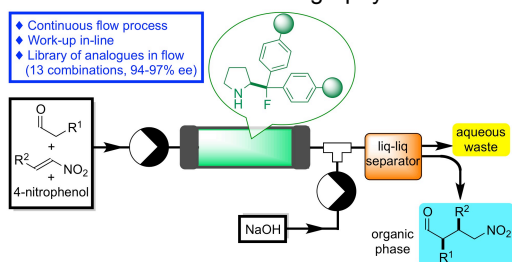


Fig. 1 – Translating the Enantioselective Michael Reaction to a Continuous Flow Paradigm with an Immobilized, Fluorinated Organocatalyst.

Also on the implementation of continuous flow asymmetric Michael processes, we have reported a polystyrene-supported 9-amino(9-deoxy)*epi* quinine derivative that catalyzes Michael reactions affording excellent levels of conversion and enantioselectivity using different nucleophiles and structurally diverse enones. The highly recyclable, immobilized catalyst has been used to implement a single-pass, continuous flow process (residence time: 40 min) that can be operated for 21 h without significant decrease in conversion and with

improved enantioselectivity with respect to batch operation. The flow process has also been used for the sequential preparation of a small library of enantioenriched Michael adducts.

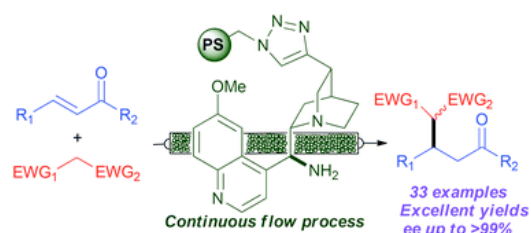


Fig. 2 – A polystyrene-supported 9-amino(9-deoxy)*epi* quinine derivative for continuous flow asymmetric Michael reactions.

A polymer-supported bifunctional thiourea organocatalyst (PS-TU) has been prepared and successfully used in the enantioselective α -amination of 1,3-dicarbonyl compounds with azodicarboxylates. In contrast to homogeneous thioureas, PS-TU is not irreversibly deactivated by the azodicarboxylate reagents, and simple washing with triethylamine between runs has allowed the reuse (9 cycles) of this catalyst. The α -amination mediated by PS-TU has also been adapted to perform the enantioselective amination (93% ee) of ethyl 2-oxocyclopentanecarboxylate in flow (7.5 h operation, 21 min residence time, TON = 37).

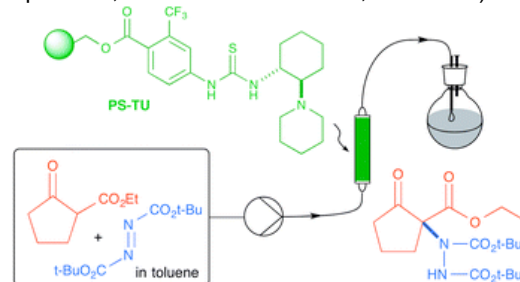


Fig. 3 – Enantioselective α -amination of 1,3-dicarbonyl compounds in batch and flow with immobilized thiourea organocatalysts.

In an effort to identify novel polymer architectures suitable for a covalent support for catalysts, L-proline derivatives have been immobilized onto rationally designed vinyl addition polynorbornene (VA-PNB) resins through copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions. These fully saturated resins have been found to be optimal catalyst supports and the resulting proline-functionalized resins behave as very active, easily recoverable and highly reusable organocatalysts for the asymmetric direct aldol reaction of benzaldehydes with ketones in aqueous media. This work has been developed in collaboration with the group of Prof. A. C. Albéniz at the Universidad de Valladolid.

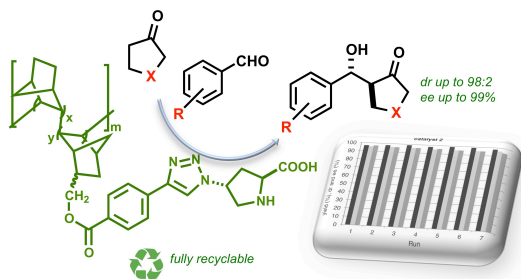


Fig. 4 – Asymmetric organocatalysts supported on vinyl addition polynorborenes for work in aqueous media.

Metal-catalyzed transformations and flow processes

As the result of a joint effort combining our experiences in the areas of metal-catalyzed transformations, catalyst immobilization and flow chemistry, we have developed several highly efficient heterogenized catalysts that can be repeatedly recycled and reused under batch conditions and used in continuous flow for prolonged periods of time.

We have developed a polystyrene-linked tris(triazolyl)methanecopper(I) cationic catalyst that operates under heterogeneous conditions for the general carbene transfer with high efficiency and recyclability. The use of this heterogenized cationic Cu catalyst in continuous flow has also been implemented. Key characteristics of the flow process are its high and constant turnover frequency (TOF) (residence times of 1 min still lead to full conversion in the reaction with ethanol after 48 h operation) and its suitability for the sequential performance of different types of carbene transfer reactions with a simple and affordable experimental setup. The work has been performed in collaboration with the group of Prof. P. J. Pérez at Universidad de Huelva.

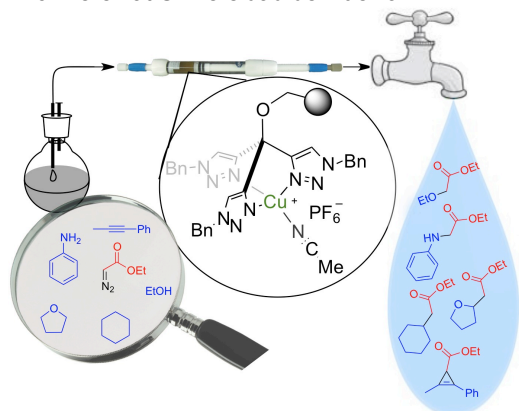


Fig. 5 – A fully recyclable heterogenized Cu catalyst for the general carbene transfer reaction in batch and flow.

Pd nanoparticles supported in a functionalized mesoporous MOF (8 wt % Pd@MIL-101-NH₂) developed by the group of Prof. B. Martín-Matute at Stockholm University were packed in a micro-flow reactor, which represents the first report of metallic nanoparticles supported on MOFs employed in flow chemistry for catalytic applications. A small library of *functionalized biaryls via Suzuki-Miyaura cross-coupling* was created in a continuous experiment without replacing the catalyst, showing the potential of the catalyst for large-scale applications.

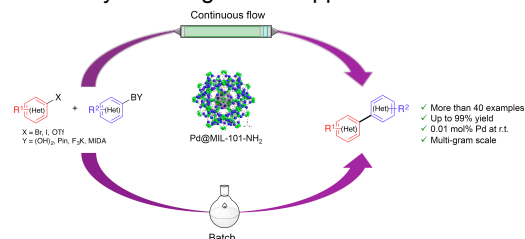


Fig. 6 – Highly Functionalized Biaryls via Suzuki-Miyaura Cross-Coupling Catalyzed by Pd@MOF under Batch and Continuous Flow Regimes.

Also in collaboration with the group of Prof. B. Martín-Matute we have reported a *double-supported silica-Metal-Organic Framework palladium nanocatalyst* (Pd@MIL-88B-NH₂@nano-SiO₂) for the aerobic oxidation of alcohols under batch and continuous flow regimes. This doubly supported catalyst displayed high activity and excellent performance in terms of endurance and leaching control. Under batch conditions, a very convenient and efficient recycling protocol is illustrated, using a “teabag” approach. Under continuous flow, the catalyst was capable of withstanding 7 days of continuous operation at 110 °C without deactivation. During this time, no leaching of metallic species was observed, and the material maintained its structural integrity.

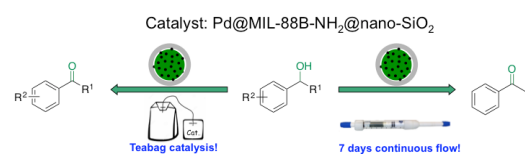


Fig. 7 – Double-Supported Silica-MOF Pd Nanocatalyst for the Aerobic Oxidation of Alcohols under Batch and Flow Regimes.

Bismuth oxide, an inexpensive and non-toxic semiconductor, has been successfully used as a visible light photocatalyst for the atom transfer radical addition (ATRA) reaction of organobromides to diversely functionalized terminal olefins. The reaction takes place under very mild conditions, in the absence of any additive, and with low catalyst loading (1 mol %). The corresponding ATRA products are obtained with moderate to excellent yields (up to 95 %).

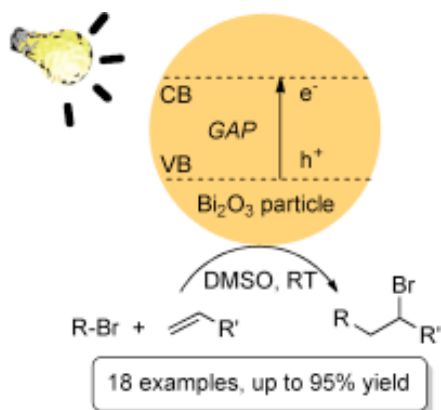


Fig. 8 – Visible Light-Driven Atom Transfer Radical Addition to Olefins using Bi_2O_3 as Photocatalyst.

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