2017 Annual Scientific Report

Pericàs Research Group

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Laboratory Engineer: Patricia Llanes
Master Students: José Luis Capdevila (until Sept) / Stefan Simic
Visiting Students: Christian Nielsen (May-Jul) / Aleix Adell (May-Aug) / Rifahath Mon N. P. (Jul-Sept) / Iago Pozo (Sept-Oct)

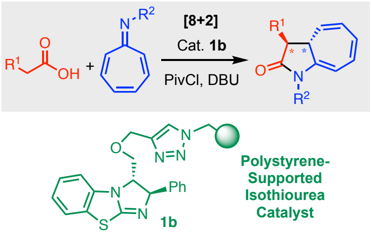
Abstract

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

Chiral isothioureas have also been successfully supported in our group. For instance, a peri- and enantioselective [8+2] cycloaddition between chiral ammonium enolates (generated in situ from carboxylic acids) and azaheptafulvenes has recently been reported. The resulting cycloadducts can be derivatized by means of a [4+2] cycloaddition to give bridged-polycyclic products in a regioselective manner. The resin has proven recyclable, allowing to re-use the catalyst for this higher-order cycloaddition.



- Periselective [8+2] Cycloaddition
- Regio- and Enantioselective
- 19 examples
- Up to 85% yield, 98% ee
- Derivatization of the Cycloadducts
- Recyclable Catalyst

Fig. 1. *Catalytic Asymmetric [8+2] Annulation Reactions Promoted by a Recyclable Immobilized Isothiourea.*

Supported isothioureas have also allowed to implement the catalytic enantioselective formal [4+2] cycloaddition of unsaturated heterocycles with *in situ* activated arylacetic acids. The annulation strategy described represents an efficient approach to access a series of pyranopyrazolone and pyranothiazolone derivatives, as well as spiropyranopyrazolones bearing a quaternary stereocenter, in excellent yields and stereoselectivities.

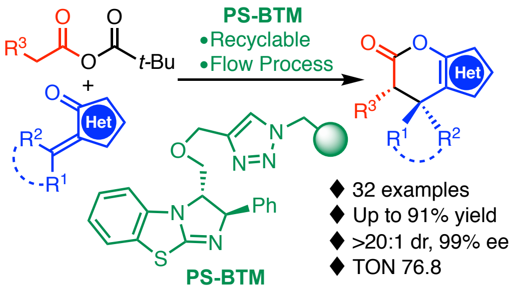


Fig. 2. *Asymmetric [4 + 2] Annulation Reactions Catalyzed by a Robust, Immobilized Isothiourea.*

A heterogenized organocatalyst based on Luo's diamine has been prepared and applied to the fast and asymmetric Robinson annulation reaction. This polystyrene-supported diamine enables the high-yield, highly enantioselective preparation of a wide scope of chiral bicyclic enones under mild conditions, with reaction times as short as 60 minutes (batch) or residence times of 10 minutes (flow).

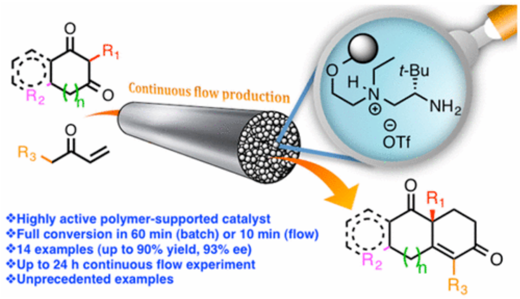


Fig. 3. *A Highly Active Polymer-Supported Catalyst for Asymmetric Robinson Annulations in Continuous Flow.*

Visible light-mediated catalytic processes

Following our pioneering work on the use of bismuth oxide as a photocatalyst, we have studied the application of this concept to the visible light-promoted arylation of heteroarenes with diazonium salts. The arylated products can be isolated in moderate to good yields using low catalysts loadings (1-5 mol%) and a 10-mmol scale-up experiment has been carried out. This protocol represents an attractive alternative ot the use of ruthenium or iridium-based photocatalysts or organic dyes.

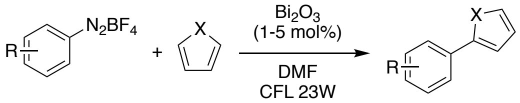


Fig. 4. *Visible-Light-Promoted Arylation Reactions Photocatalyzed by Bismuth(III) Oxide.*

A methodology for the catalytic asymmetric cross-coupling of two C(sp3)–H bonds employing visible light as an economical and environmentally benign source of energy has been reported. In this protocol, photoredox catalysis is used for the oxidation of a xanthene to the corresponding cation, which is then trapped by an enamine intermediate generated in situ from an aldehyde reactant and a secondary amine organocatalyst. This mild method does not require preinstallation of functional groups and allows the formation of a C–C bond with simultaneous installation of one or two new stereocenters in a highly enantio- and diastereoselective manner.

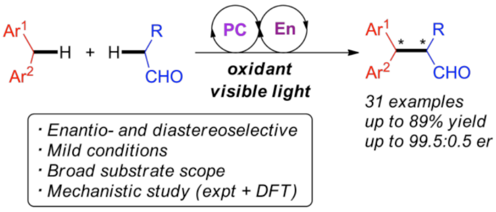


Fig. 5. *Asymmetric Visible-Light Photoredox Cross-Dehydrogenative Coupling of Aldehydes with Xanthenes.*

Enantioselective homogeneous organocatalysis

A diverse family (37 compounds) of *cis*-4-alkoxydiorganylprolinol derivatives has been prepared and evaluated in organocatalysis for the first time. The combined use of high throughput experimentation (HTE) techniques with efficient analytical methods has led to the identification of two superior catalysts for the enantioselective addition of succinimide to α,β-unsaturated aldehydes. Further optimization of the reaction conditions with design of experiments (DoE) techniques established the catalyst of choice for the considered *aza*-Michael reaction, the corresponding adducts (12 examples) being obtained in good yields and excellent enantioselectivities (succinimide and maleimide donors). The synthetic versatility of these Michael adducts is illustrated by a two-step sequence leading to enantiopure 1,3-amino alcohols.

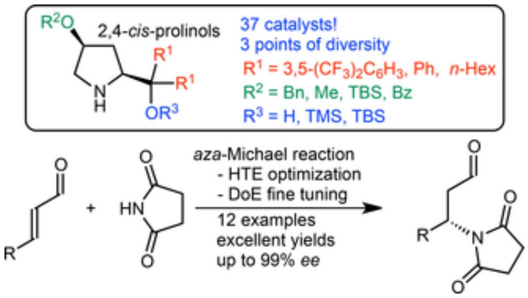


Fig. 6. *cis-4-Alkoxydialkyl- and cis-4-Alkoxydiarylprolinol Organocatalysts: High Throughput Experimentation (HTE)-Based and Design of Experiments (DoE)-Guided Development of a Highly Enantioselective aza-Michael Addition of Cyclic Imides to α,β-Unsaturated Aldehydes.*

Metal-mediated catalysis

The synthesis of axially chiral 5,5'-bistriazoles and their configurational stability has been studied. The products have been applied as ligands in the scandium-catalyzed addition of indoles to isatins.

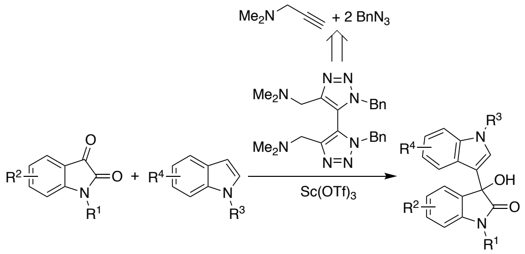


Fig. 7. *5,5'-Bistriazoles as Axially Chiral Multidentate Ligands.*

Articles

“Visible-Light-Promoted Arylation Reactions Photocatalyzed by Bismuth(III) Oxide”
L. Buglioni, P. Riente, E. Palomares, M.A. Pericàs
Eur. J. Org. Chem. **2017**, 6986-6990.

“Polystyrene-supported bifunctional resorcinarenes as cheap, metal-free and recyclable catalysts for epoxide/CO2 coupling reactions”
T. Jose, S. Cañellas, M.A. Pericàs, A.W. Kleij
Green Chem. **2017**,*19*, 5488-5493.

“5,5′-Bistriazoles as axially chiral, multidentate ligands: synthesis, configurational stability and catalytic application of their scandium(III) complexes”
P. Etayo, E.C. Escudero-Adán, M.A. Pericàs
Catal. Sci. Technol. **2017**, 4830-4841.

“Catalytic Asymmetric [8+2] Annulation Reactions Promoted by a Recyclable Immobilized Isothiourea”
S. Wang, C. Rodríguez-Escrich, M.A. Pericàs
Angew. Chem. Int. Ed. **2017**, 15068-15072.

“Asymmetric Visible-Light Photoredox Cross-Dehydrogenative Coupling of Aldehydes with Xanthenes”
E. Larionov, M.M. Mastandrea, M.A. Pericàs
ACS Catal. **2017**,7008-7013.

“Modular Synthesis of Triazole-based Chiral Iodoarenes for Enantioselective Spirocyclizations”
C. Hempel, C. Maichle-Moessmer, M.A. Pericàs, B.J. Nachtsheim
Adv. Synth. Catal. **2017**, 2931-2941.

“cis-4-Alkoxydialkyl- and cis-4-Alkoxydiarylprolinol Organocatalysts: High Throughput Experimentation (HTE)-Based and Design of Experiments (DoE)-Guided Development of a Highly Enantioselective aza-Michael Addition of Cyclic Imides to α,β-Unsaturated Aldehydes”
I. Arenas, A. Ferrali, C. Rodriguez-Escrich, F. Bravo, M.A. Pericàs
Adv. Synth. Catal. **2017**, 2414-2424.

“Asymmetric [4 + 2] Annulation Reactions Catalyzed by a Robust, Immobilized Isothiourea”
S. Wang, J. Izquierdo, C. Rodríguez-Escrich, M.A. Pericàs
ACS Catal. **2017**, *7*, 2780-2785.

“A Highly Active Polymer-Supported Catalyst for Asymmetric Robinson Annulations in Continuous Flow”
S. Cañellas, C. Ayats, A. H. Henseler, M. A. Pericàs.
ACS Catal. **2017**, *7* (2), 1383-1391.