

Young Career Focus: Dr. Alberto Martinez-Cuezva (Universidad de Murcia, Spain)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Alberto Martinez-Cuezva (Universidad de Murcia, Spain).

Biographical Sketch



Dr. A. Martinez-Cuezva

Alberto Martinez-Cuezva received his B.Sc. (2004) at the Universidad de Burgos (Spain), where he also completed his Ph.D. under the supervision of Prof. R. Sanz (2010), developing novel catalytic systems. Upon graduation, he carried out a postdoctoral stage with Prof. B. List at the Max-Planck Institut für Kohlenforschung (Mülheim an der Ruhr, Germany). During this time (2010–2013), his research focused on the synthesis of new chiral organocatalysts and their applications in asymmetric transformations. In 2013, he joined the SOC-UMU research group at Universidad de Murcia as a Marie Curie researcher and, later, as a Juan de la Cierva fellow. In 2019, he was awarded a Ramón y Cajal contract, and in 2021 was promoted to assistant professor. His research interests are mainly focused on the synthesis of novel mechanically interlocked compounds oriented towards the development of advanced organocatalysts. He has been the recipient of the Lilly Award for Ph.D. students (2009) and the Thieme Chemistry Journals Award (2021).

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Dr. A. Martinez-Cuezva The SOC-UMU lab is a multidisciplinary group interested in diverse topics such as the design and applications of mechanically interlocked molecules, the discovery of new reactions of ketenimines, and the study of these and other transformations through computational calculations. I am mainly involved in the study of the reactivity of mechanized systems, including their use in organocatalysis. The mechanical bond present in such structures plays an interesting role in the activity and selectivity of these species when employed as catalysts or as starting materials for preparing value-added materials. Organic synthesis is fundamental in our research, which we combine with supramolecular and host-guest chemistry or with materials science for the design, for instance, of novel framework materials [metal-organic frameworks (MOFs), covalent organic frameworks (COFs)] by using rotaxane-based building ligands.

SYNFORM *When did you get interested in synthesis?*

Dr. A. Martinez-Cuezva My interest in organic synthesis started during the fourth year of my chemistry degree at the University of Burgos (Spain) – I was fascinated by the passion of one of my professors, who was eventually my Ph.D. supervisor. My early steps in the laboratory involved the use of organolithium compounds as starting materials for obtaining complex molecules and heterocycles, but I turned rapidly into the field of organo- and metal-catalyzed transformations. Importantly, during my Ph.D. studies, I also had the opportunity to spend three months in the laboratory of Professor Paul Wentworth Jr. at the Scripps Research Institute (USA) and, a year after, another period in the group of Professor Stephen L. Buchwald at the Massachusetts Institute of Technology

(USA) as a visiting student. These two external stages contributed to fix my scientific vocation firmly and paved my way to a research career in organic synthesis. During my postdoctoral stay with Professor Benjamin List, I started in the field of asymmetric organocatalysis, a very challenging, but at the same time, extremely pleasant area. Nowadays, I am merging all my previous knowledge in catalysis with the building of mechanically interlocked systems. The use of mechanized systems in catalysis is under-explored and thus, it is an interesting arena of research at the interface between both fields.

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Dr. A. Martinez-Cuezva Although organic synthesis is one of the most explored fields of research, the discovery of new transformations or activation modes is still an extremely challenging task. The synergy of organic synthesis with other disciplines is essential in order to attain key milestones. Thus, the combination of supramolecular chemistry with classical organic synthesis opens the door to the assembly of highly complex structures with novel reactivities and properties, as for example, the building of artificial molecular machinery inspired by Nature.¹ I find it fascinating how tiny molecules can be fueled (by light, chemically, etc.) and, as a response, a determined task is accomplished. The assembly and fine adjustment of the different components of the molecular machines, allowing programmed internal dynamics, remains highly challenging. This field is still in its infancy and demands extensive research.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Dr. A. Martinez-Cuezva As I commented above, our laboratory works in different research fields. I am mainly involved

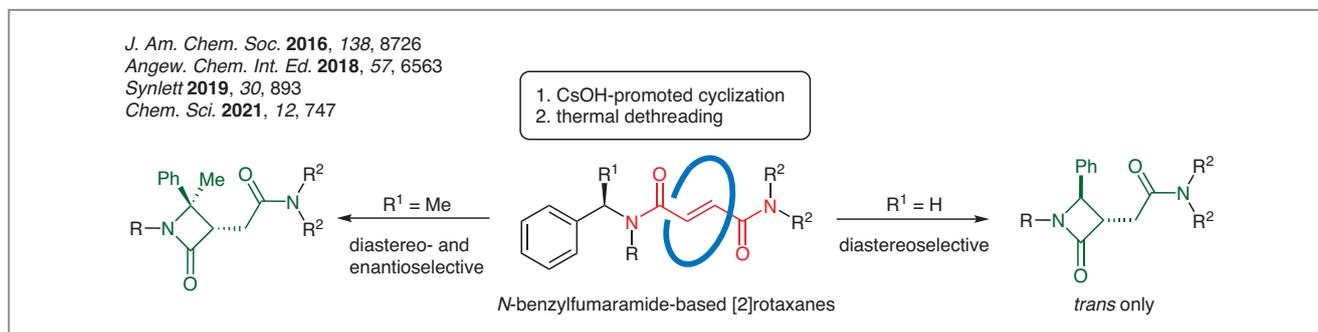
in the synthesis and applications of mechanically interlocked molecules, perhaps the most relevant and influential line. The key purpose of this research is the assembly of novel mechanized systems with interesting properties resulting from the presence of the mechanical bond. For this purpose, we use mainly hydrogen-bonded rotaxanes (Leigh's type rotaxanes), the preparation of which is at the interface of organic and supramolecular chemistry. We are also incorporating these systems as ligands for the assembly of stimuli-responsive materials, like MOFs.² I would like to highlight two recent projects that are currently under development in our labs, in which the mechanical bond makes the difference:

Synthesis of β -lactams from interlocked fumaramides (Scheme 1):

In 2016, we found that polyamide-based interlocked *N*-benzylfumaramides can be easily converted into β -lactams upon cyclization triggered by an inorganic base.³⁻⁵ The mechanical bond activates the cyclization inside the macrocycle void, simultaneously avoiding the formation of byproducts and fully controlling the diastereoselective course of these processes. In stark contrast, the cyclization of the free thread affords low yields of the expected products but as a mixture of isomers, along with huge amounts of undefined byproducts. By following this methodology, we were able to access a set of stereochemically well-defined lactams after removal of the macrocycle by a further dethreading reaction. We have also expanded this protocol for accessing enantioenriched systems.⁶ Nowadays, we are still focused on expanding this procedure to the use of other starting materials having different functionalities inside the macrocyclic void, with the aim of obtaining other classes of valuable compounds, including asymmetric versions of these processes.

Design of mechanically interlocked organocatalysts (Scheme 2):

The combination of my expertise in organocatalysis, acquired during my Ph.D. and postdoctoral stages, along with my



Scheme 1 Cyclization of interlocked *N*-benzylfumaramides mediated by CsOH

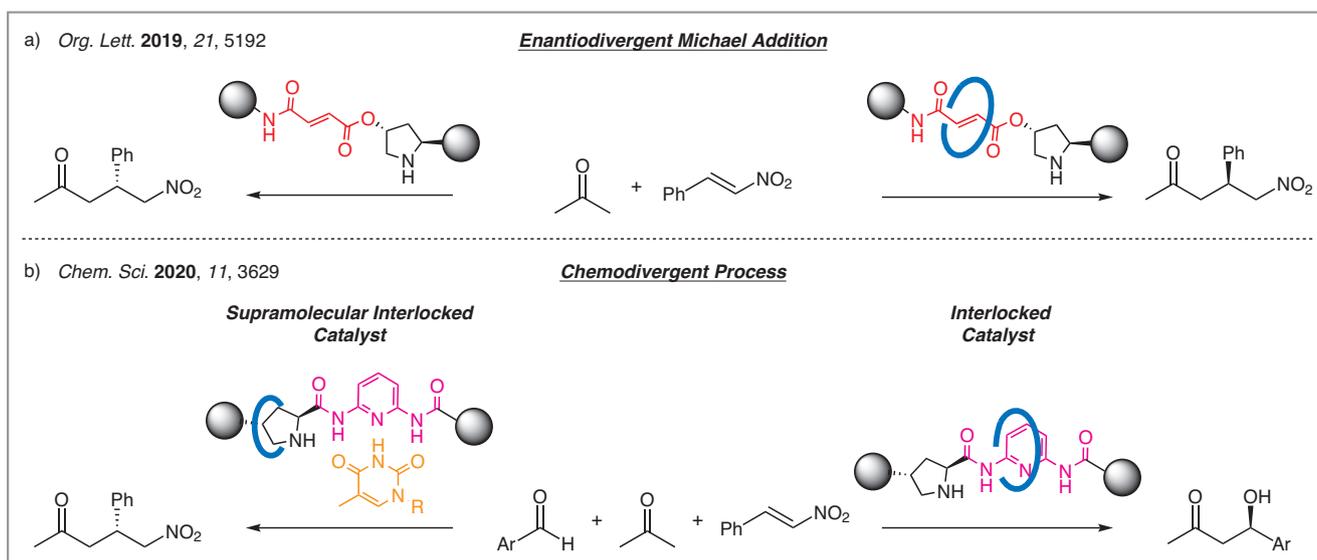
experience with mechanically interlocked molecules earned at the SOC-UMU lab of the University of Murcia, both allowed me to start this new research line. There is a common belief that the design and synthesis of novel catalysts able to overcome the actual limitations for accessing complex molecules, highlighting their asymmetric synthesis, is still an important task. Thus, the discovery of innovative catalyst motifs with unreported structural backbones or activation modes is highly desirable. The incorporation of the mechanical bond to a catalyst skeleton is an interesting strategy to modulate the reactivity and selectivity.⁷ Note that the control of the internal dynamics of these systems by the application of external stimuli could be a great advantage over the conventional catalysts, as it allows the building of switchable catalysts. Until now we have explored the behavior of mechanized organocatalysts in enamine and iminium-type transformations,⁸ by using threads bearing secondary amino groups as active sites. We found that the Michael addition of ketones to *trans*- β -nitrostyrene, catalyzed by either a prolinamide-containing thread or its rotaxane, yielded both possible enantiomers of the adducts in an enantiodivergent fashion (Scheme 2a).⁹ Later on, by using a template described by us for the assembly of hydrogen-bonded rotaxanes with diacylaminopyridine units, we accessed a set of prolinamide-based organocatalysts able to form supramolecular complexes with thymine derivatives (Scheme 2b).¹⁰ The use of these rotaxanes or their supramolecular complexes as catalysts allowed us to achieve a chemodivergent protocol in which three starting materials

react in an enantioselective manner for obtaining two alternative adducts. Currently, I am working on the incorporation of the mechanical bond into systems with other innovative activation modes.

SYNFORM What is your most important scientific achievement to date and why?

Dr. A. Martinez-Cuezva If I have to choose the most important scientific success to date and, at the same time, the most pleasant one, I would pick my contribution to mechanically interlocked organocatalysts. In the design, synthesis and application of these systems, an important part of the knowledge that I previously acquired along my scientific career comes into play. Thus, I would say this research is the icing on the cake. I believe that the incorporation of the mechanical bond into organocatalysts or ligands for metal-mediated processes can surpass in some aspects the standard catalytic ability of small organic molecules. Importantly, another strategy that we are currently exploring is the building of supramolecular mechanically interlocked catalysts, assembled by the establishment of host-guest interactions.

Martinez Cuezva



Scheme 2 Design of mechanized organocatalysts for enamine-type processes: a) Enantiodivergent Michael addition; b) Chemodivergent transformations mediated by interlocked organocatalysts or their supramolecular complex with a thymine derivative

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