

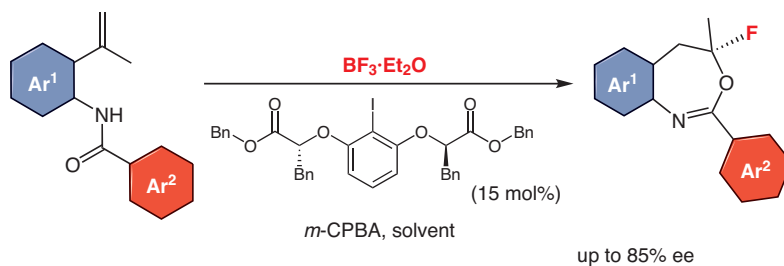
Synform

People, Trends and Views in Chemical Synthesis

2021/11

Catalytic Asymmetric Nucleophilic Fluorination Using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as Fluorine Source and Activating Reagent

Highlighted article by W. Zhu, X. Zhen, J. Wu, Y. Cheng, J. An, X. Ma, J. Liu, Y. Qin, H. Zhu, J. Xue, X. Jiang



Ar¹ = phenyl, 5-methylphenyl, benzo[d][1,3]dioxol

Ar² = 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 4-isopropylphenyl, 4-*tert*-butylphenyl, 3,5-di-*tert*-butylphenyl, 3,5-dinitrofluoromethylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 3,5-dimethoxyphenyl

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Dear Readers,

Early stage researchers (ESRs) represent a crucially important segment of readers and authors in scientific publishing. At Thieme Chemistry, we very much value ESRs, as demonstrated through a number of targeted editorial initiatives, including the Thieme Chemistry Journals Awards which are presented every year to up-and-coming researchers who are in the early stages of their independent career. In 2021, over 80 ESRs from all over the world were recognized with the award. A number of Thieme Chemistry Journals Awardees are then invited by SYNFORM for an interview – the Young Career Focus (YCF) – which covers several aspects of their professional and scientific activity and future perspectives. The YCFs are very popular articles and provide a unique opportunity for these brilliant ESRs to make themselves better known in the global research arena. Looking back at the archive of YCF articles, one can find interviews with Thieme Chemistry Journals Awardees who are now very well established and highly successful academics, and we are extremely proud that these colleagues were featured in SYNFORM back then, when they were highly promising ESRs. To continue this tradition, in this November issue we have not just one, but two YCF interviews: the first with Adelina Voutchkova-Kostal (USA), which opens the issue, and the second with Alberto Martinez-Cuezva (Spain), which is the closing article. Sandwiched between the two YCFs, there are two Literature Coverage *Nat. Commun.* articles: the first featuring a collaboration between the groups of M. Vendrell (UK) and L. Ackermann (Germany) and their highly innovative synthesis of novel fluorogenic probes, the second covering a novel nucleophilic fluorination method developed by X. Jiang (P. R. of China).

Enjoy your reading!



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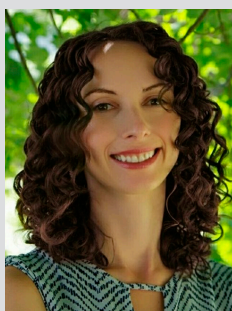
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Young Career Focus: Professor Adelina Voutchkova-Kostal (George Washington University, USA)

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 Professor Adelina Voutchkova-Kostal (George Washington University, USA).

Biographical Sketch



Prof. A. Voutchkova-Kostal

Adelina Voutchkova-Kostal received her B.A. in Chemistry and Biochemistry from Middlebury College, USA (2004), and her M.Sc. and Ph.D. (2009) from Yale University (USA) under the guidance of Bob Crabtree. She continued her post-graduate work at the Yale Center for Green Chemistry and Green Engineering (USA) with Paul Anastas and Julie Zimmerman, focused on the rational design of safer chemicals. She launched her independent career in the Chemistry Department at George Washington University (Washington, DC, USA) in 2012 and is currently an Associate Professor. Her research program is focused on the design of catalytic processes that can help facilitate circular economies. The catalytic systems being developed cross the boundaries of homogeneous and heterogeneous catalysis, and consider lifecycle and hazard factors. The group is also involved in development of tools for designing safer commercial chemicals in collaboration with computational chemistry and toxicology groups. She was a recipient of the Thieme Chemistry Journals Award in 2021.

INTERVIEW

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

Prof. A. Voutchkova-Kostal As a graduate student in the later 2000's, I remember noticing that research in catalysis almost exclusively focused on selective bond construction. It was clear why: making molecules creates value, unlike breaking them down. I wondered what the value proposition of bond cleavage might be, and indeed, within the next few years, that question was answered. Research in valorization of biomass through selective bond cleavage exploded. As numerous new catalytic routes for breaking bonds in lignocellulose were developed, chemists looked towards the next challenge in breaking bonds of synthetic polymers, like plastics. I have been interested in selective defunctionalization of chemicals for many years now, and especially in how it can be applied to creating circular economies and cleaner syntheses. Among the current research efforts in our group that exemplify these goals are the depolymerization of lignocellulose PET using ionic liquids designed to have low ecotoxicity, and the use of decarbonylation and dehydrogenation chemistry to defunctionalize and couple substrates. When designing new processes, we assess whether it can deliver a quantifiable decrease in environmental impact over alternatives, and minimize the hazard of chemicals we are using and making.

SYNFORM *When did you get interested in synthesis?*

Prof. A. Voutchkova-Kostal I got interested in synthesis through cooking. I loved cooking and baking when I was young, and later got interested in formulations for making cosmetics. In high school and college I enjoyed learning about the chemistry of cooking and baking. I really enjoyed organic labs in college, probably because we had a really engaging instructor who made them fun. I decided to try out synthesis

in industry, and got an internship in a pharma company one summer. In those few months I realized that while I did love synthetic chemistry, I did not want to just follow prescribed procedures. In fact, I kept modifying the protocols I was given and trying new reactions, which probably frustrated my poor mentor! He recommended that I pursue graduate school to see if I had what it takes to do research. At Yale I got to take organometallic chemistry with John Hartwig, who was an incredible instructor, and the course really opened my eyes to the potential creativity of catalysis in designing new and more efficient reactions. I do my best to pass on that spark to my students in organometallics now.

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

Prof. A. Voutchkova-Kostal Nature creates an impressive spectrum of biological structures and functions from a small handful of elements, efficiently cycling every nutrient in making and re-making living things. Traditionally, organic synthesis has been focused on bond construction to access some of nature's structural diversity (e.g. natural product synthesis), but not much emphasis has been placed on design for breakdown, either biological or synthetic, and on design for minimal hazard. I think we are at the brink of a revolutionary phase in organic synthesis: if we, as synthetic chemists, embrace the challenge of designing molecules and clean synthetic routes to allow for circularity and intentional minimization of hazard, we will play a critical role in the transition to circular economies. This is a very exciting time to be an organic chemist, and an opportunity to recruit a new generation of environmentally conscious chemists to help make this vision a reality!

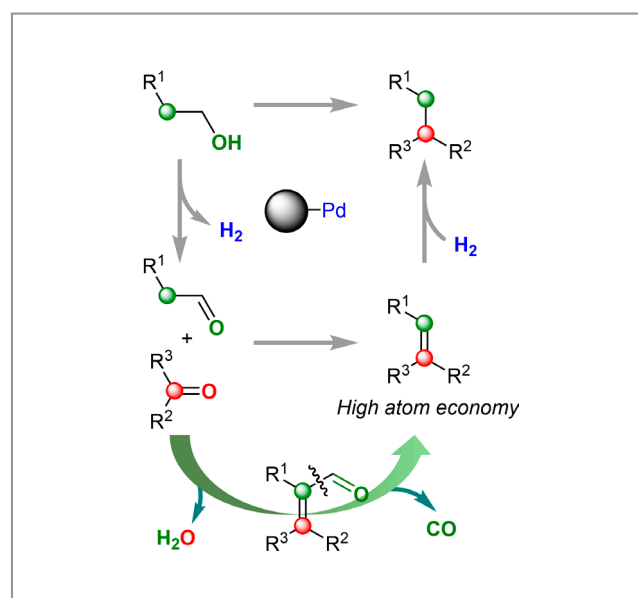
SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Prof. A. Voutchkova-Kostal Our group focuses on design of chemical processes that involve defunctionalization reactions, such as dehydrogenation, decarbonylation, decarboxylation, transfer hydrogenation and hydrolysis, among others. These kinetically challenging reactions have been traditionally catalyzed by organometallic catalysts consisting of precious metals, which are typically not feasible on a large scale. Our interest therefore lies in developing relatively cheap and robust heterogeneous catalysts for these transformations that can work under mild conditions. This requires understanding how to "tune" the reactivity of these materials, which has led us to explore the electronic effect of supports on immobilized nano

species. Our most successful and versatile catalyst system consists of group 10 metals immobilized on tunable layered double hydroxide clays (hydrotalcites). We have shown that these materials have a number of advantageous properties that we can exploit by incorporating a second transition metal with synergistic activity. For example, we find that Cu-doped hydrotalcite is an excellent support for iridium-based single-site catalysts for transfer hydrogenation from glycerol to CO₂, making two valuable products: lactic acid and formic acid (we thank the NSF CAREER program for supporting this work). We have also shown that these catalysts have multiple catalytic sites that we can exploit for tandem transformations: a feature we are now exploiting in the defunctionalization of lignocellulose.

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

Prof. A. Voutchkova-Kostal On the catalysis front, we are excited about expanding our work on multifunctional catalysts. For example, we designed a Pd-hydrotalcite catalyst that can facilitate decarbonylation, dehydrogenation and aldol condensation, which allows the conversion of alcohols into long-chain olefins (Scheme 1; *J. Am. Chem. Soc.* **2020**, *142*, 696–699; *ChemRxiv* **2021**, preprint, DOI: 10.26434/chemrxiv.14292311.v1). This chemistry can also be performed with



Scheme 1 Multicomponent catalytic system based on Pd-hydrotalcite heterogeneous catalyst, for the dehydrogenative and decarbonylative coupling of alcohols or aldehydes.

aldehydes, in which case it is an atom-economical analogue of a Wittig reaction. We have extended this chemistry recently to biomass-related substrates, such as lignin, allowing us to carry out multiple tandem reactions with just one catalyst. On the chemical design front, I am most proud of collaborative work on the development of in silico predictive tools for a number of toxicological endpoints, such as skin sensitization and aquatic toxicity. It has been extremely rewarding to see these tools used by industry to assess hazard of chemicals used in manufacturing. My colleagues and I hope this work helps protect human health, and hopefully also saves the lives of a few critters used in animal testing!

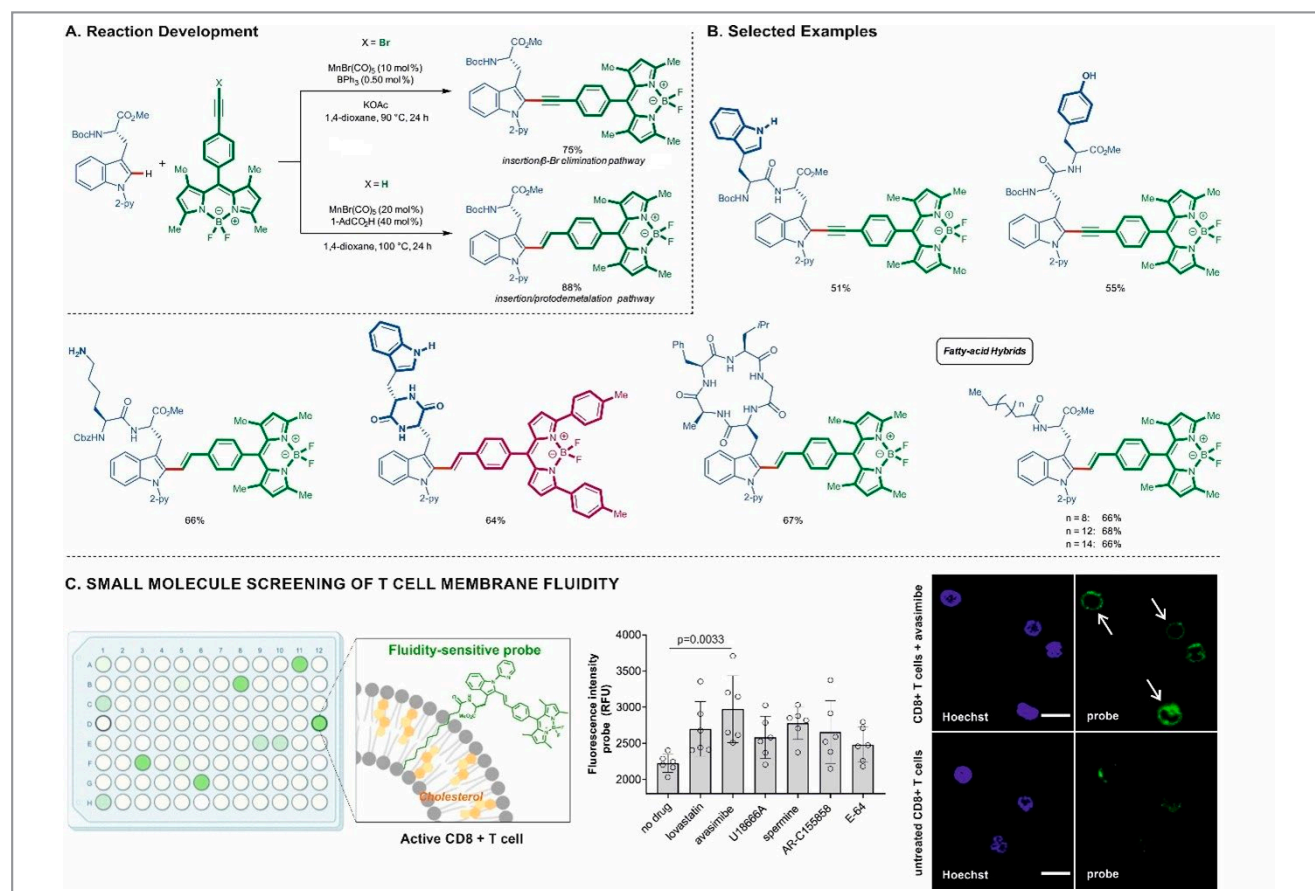
A handwritten signature in orange ink that reads "Matthew Farnok".

Chemodivergent Manganese-Catalyzed C–H Activation: Modular Synthesis of Fluorogenic Probes

Nat. Commun. **2021**, *12*, 3389; DOI: 10.1038/s41467-021-23462-9

In the past few years, environmentally sensitive fluorophores have been developed to image cell-specific events associated to – among others – infection, inflammation and cancer *in vivo*. However, the vast majority of these strategies rely on elements of substrate pre-functionalization. As a consequence, there is increasing interest in developing new approaches for late-stage fluorogenic labeling of biomolecules with the aim of assembling molecular probes enabling for real-time imaging. In this context, the chemo- and positional-selective modification of biologically relevant compounds is particularly important for the late-stage diversification of biomolecules endowed with new spectral and biological capabilities.

The groups of Professor Lutz Ackermann from the Georg-August-Universität Göttingen (Germany) and Professor Marc Vendrell from The University of Edinburgh (UK) engaged in a successful collaboration aimed at advancing the state-of-the-art in the area of fluorogenic probes suitable for real-time *in vivo* imaging, which resulted in the publication of the title paper in *Nature Communications*. Professor Ackermann said: “During the last decade, C–H activation has surfaced as an increasingly viable tool for molecular syntheses, with enabling applications to total syntheses, material sciences, medicinal chemistry, and – very recently – chemical biology. In this regard, major efforts have been devoted to establishing C–H



Scheme 1

functionalization of peptides with precious transition metals, such as palladium, while Earth-abundant 3d transition-metal catalysis continues to be scarce. Apart from being relatively inexpensive, 3d transition metals are generally less toxic and, more importantly, offer complementary reaction manifolds. Manganese complexes typically demonstrate low toxicity, thus their utilization in C–H functionalization of biomolecules is highly desirable. Moreover,” continued Professor Ackermann, “manganese(I)-catalyzed C–H activation represents a mild, robust platform for transformative C–H activation manifolds. Thus, our strategy for a divergent assembly point for the preparation of fluorescent peptides with tunable optical properties identified internal bromoalkynes and terminal alkynes as viable substrates (Scheme 1A). We envisioned that we thereby could gain access to fluorescent imaging probes, in which the phenyl-BODIPY fluorescent core would be stitched to the indole moiety of a tryptophan amino acid via a linear alkynyl or a bent alkenyl spacer, while at the same time extending the conjugate π -system to fine-tune the fluorogenic behavior.” The authors further wondered whether the nature of the linkage would not only alter the fluorescent properties of the peptide, but could also render fluorescent molecular rotors due to different rotation barriers. “Thus, within an insertion/ β -elimination sequence, the desired BODIPY-labeled amino acids with a linear linkage were obtained,” added Professor Ackermann. “In sharp contrast, 1-AdCO₂H as additive enabled a divergent pathway via an insertion/protodemetalation manifold when terminal BODIPY-alkynes were used, thus providing the bent spacer. The mildness of our approach was reflected by an outstanding functional group tolerance for the late-stage C–H labeling of complex peptides (Scheme 1B).”

Professor Vendrell explained that the fluidity of cell membranes is an essential microenvironmental parameter for the proper function of a plethora of biological processes. “Thus, the study of changes and dysregulations on the composition of the plasma membrane is key from a biomedical perspective, from the fundamental study of disease mechanisms, such as cancer or Alzheimer’s disease, to the translation of new therapeutics,” said Professor Vendrell, who added: “Recent studies have established a direct correlation between the composition of the plasma membrane of T cells, which are key mediators of the adaptative immune system against infections and cancer, and their cytotoxic activity. These discoveries immediately caught our attention due to their potential use for the development of new fluorogenic turn-on probes as reporters of CD8+ T cells. Here, we used a rational design of different BODIPY molecular rotors to discover highly sensitive fatty acid-conjugated viscosity probes, which emit bright fluores-

cence when in contact with the membranes of T cells. This smart probe allowed us to image, in real-time, changes in the activation state of live human CD8+ T cells under physiological conditions.”

The new fluidity-sensitive probe was used to establish a rapid fluorescence-based platform for the identification of small molecule modulators of CD8+ T cells (Scheme 1C). “Interestingly, among all drugs tested, cells treated with the Acyl-CoA:cholesterol acyltransferase inhibitor avasimibe exhibited the highest fluorescence emission,” explained Professor Vendrell, adding: “Confocal microscopy experiments showed bright staining of the membranes in avasimibe-treated cells when compared to untreated cells.” The team also confirmed the functional state of labeled CD8+ T cells by measuring the expression of receptor markers that are directly associated to immune activity. “This simple and cost-effective chemical platform to study immune responses could help in accelerating the design of more efficient immunotherapy treatments that invigorate the activity of CD8+ T cells in different diseases, including cancer,” said Professor Vendrell.

“This project clearly demonstrates the strength of the combination of chemical, biological and medical studies, which allow the direct observation of cell-specific events. Furthermore, the successful collaboration between groups from different disciplines ensures that our discoveries not only have an immediate impact in the field on synthetic chemistry, but also in the area of biomedical sciences to tackle real-life problems,” Professor Ackermann concluded.

Matthew Fenske

About the authors



N. Kaplaneris

Nikolaos Kaplaneris was born in 1992 in Athens, Greece. He received his bachelor's degree in chemistry from the National and Kapodistrian University of Athens (Greece) in 2014. He obtained his master's degree in organic chemistry from the same university in 2016 following studies in the area of organocatalysis and photochemistry under the supervision of Prof. Christoforos G. Kokotos. In the same year, he joined the group of Prof. Lutz Ackermann at the Georg-August-Universität Göttingen (Germany) as a PhD student, working on late-stage peptide diversification and remote functionalization.



Prof. J. Son

Jongwoo Son obtained his B.S. and M.S. degrees in chemistry at Chungnam National University (Daejeon, South Korea). He continued to study organic chemistry at the University of Illinois at Chicago (USA) and received his Ph.D. with Prof. Laura L. Anderson in 2018. He then joined the research group of Prof. Lutz Ackermann as a postdoctoral researcher at the Georg-August-Universität Göttingen (Germany). He spent another one-year postdoctoral stay in the research group of Prof. Jennifer E. Golden at the University of Wisconsin-Madison (USA). In 2020, he joined Dong-A University (Busan, South Korea) as an assistant professor of chemistry. His current research interest is aimed toward sustainable organic synthetic methodologies and functionalization studies to complex molecules.



Dr. L. M. Tapia

Lorena Mendive Tapia was born in Mexico City (Mexico). She studied chemistry (B.Sc. and M.Sc.) at the University of Barcelona (Spain), and received her Ph.D. from the same university in 2017 in the fields of organic and medicinal chemistry. She was awarded the Enrique Fuentes Quintana Award for her work on the post-synthetic modification of peptides using chemoselective C-arylation methodologies. In 2018, she joined the group of Prof. Marc Vendrell at the

University of Edinburgh (UK). Currently she is a postdoctoral research fellow and her research is focused on the development of new fluorescent probes for bioimaging in the areas of cancer and immunology.



A. Kopp

Adelina Kopp was born and raised in Hamburg (Germany). She obtained her B.Sc. in biochemistry in 2017 and M.Sc. in chemistry in 2020 at the Georg-August-Universität Göttingen (Germany). Currently, she is a doctoral student in the group of Prof. Lutz Ackermann at the same university.



Dr. N. Barth

Nicole Barth graduated in biochemistry from the University of Würzburg (Germany) in 2016. She started working and publishing in the field of immunology throughout her Master's studies. She finished her Ph.D. in winter 2020 in Optical Medical Imaging with Healthcare Innovation and Entrepreneurship, jointly awarded from the University of Edinburgh (UK) and the University of Strathclyde (UK). Her Ph.D. was highly interdisciplinary using chemistry, molecular biology and immunology to validate Apo-15/ ApotrackerTM Green as a novel probe for the detection of apoptosis. She was recently awarded a Sir Henry Wellcome Postdoctoral Fellowship for studying immune responses in the primary and metastatic tissue upon chemotherapy in vivo in real-time.



I. Maksso

Isaac Maksso was born in Frankfurt am Main (Germany). He received his B.Sc. (2019) and M.Sc. (2020) degrees from the Georg-August-Universität Göttingen (Germany), where he carried out undergraduate research under the direction of Prof. Selvan Demir and Prof. Lutz Ackermann. While completing his B.Sc., he took a DAAD RISE summer internship in the laboratory of Prof. Venkata Krishnan (2018; IIT Mandi, India). He is current-

ly a member of the Prof. Lutz Ackermann group at the Georg-August-Universität Göttingen (Germany) as a doctoral student.



Prof. M. Vendrell

Marc Vendrell graduated in chemistry at the University of Barcelona (Spain) in 2007. He then joined the Singapore Bioimaging Consortium to work in synthetic fluorophores for optical imaging. In 2012 he started his independent career as an academic fellow at the University of Edinburgh (UK) to develop and translate fluorescent peptide probes for imaging immune cells in humans. His research

has led to several license agreements with industry to commercialise fluorescent probes worldwide (Trp-BODIPY, ApoTracker™ Green, SCOTfluors) and has been recognised with international awards and distinctions: SEQT Young Investigator Award (2007), SBIC Chairman's Prize (2010), ERC Consolidator Grant (2017), Fellow of the Royal Society of Chemistry (2017), Marcial Moreno Lectureship (2018) and SRUK Emerging Talent Award (2019). Since 2020, he is appointed as Chair of Translational Chemistry and Biomedical Imaging at the College of Medicine in Edinburgh.



Prof. L. Ackermann

Lutz Ackermann studied chemistry at the Christian-Albrechts-Universität Kiel (Germany) and obtained his Ph.D. in 2001 working with Prof. Alois Fürstner at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr (Germany). He was a postdoctoral fellow with Prof. Robert G. Bergman (University of California, Berkeley, USA) before initiating his independent research in 2003 at the Ludwig-Maximilians-Universität München

(Germany), supported within the Emmy Noether Program of the Deutsche Forschungsgemeinschaft. In 2007, he became a full professor at the Georg-August-Universität Göttingen (Germany), where he served as the Dean of Research and Dean of Chemistry as well as the director of the Wöhler Research Institute for Sustainable Chemistry (WISCh). The development of novel concepts for homogeneous catalysis and their applications in sustainable organic synthesis, late-stage peptide diversification, and molecular imaging are among his main current research interests. His contributions have been recognized with awards such as the ERC Advanced Grant (2021), the Gottfried-Wilhelm-Leibniz-Prize (2017) and the ERC Consolidator Grant (2012). He has held various visiting and distinguished professorship positions in Huaqiao University (P. R. of China), Université de Strasbourg (France), École Polytechnique (France), IIT Bombay (India), Kyoto University (Japan), Università di Pavia (Italy) and Università degli Studi di Perugia (Italy).

Catalytic Asymmetric Nucleophilic Fluorination Using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as Fluorine Source and Activating Reagent

Nat. Commun. **2021**, *12*, 3957; DOI: 10.1038/s41467-021-24278-3

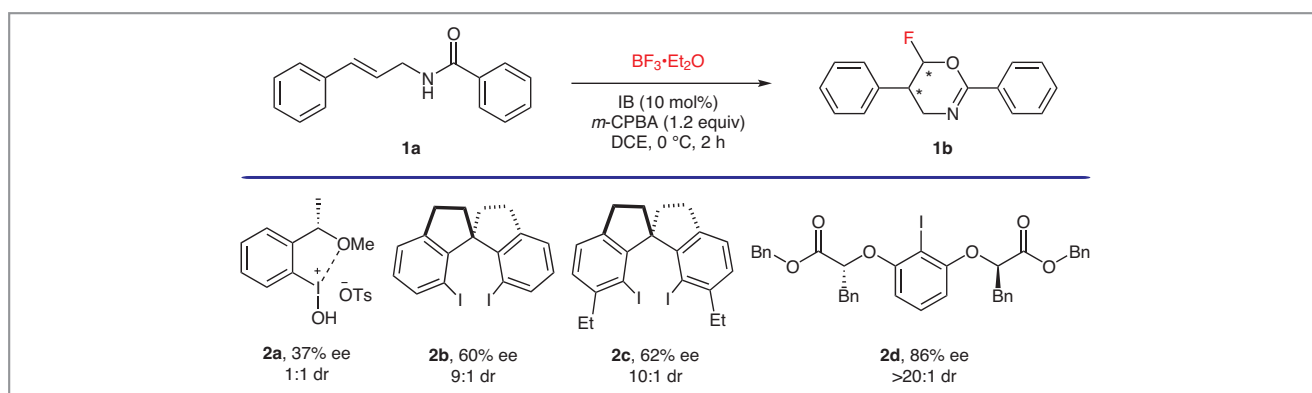
With the growing applications of fluorinated compounds in modern organic chemistry, pharmaceutical sciences, agrochemistry and materials chemistry, the development of innovative strategies for achieving the selective fluorination of organic molecules represents one of the most hectic areas in chemical research.^{1,2} In particular, the construction of stereogenic C–F bond-substituted centers is a critically important, albeit still challenging, task in fluorine chemistry.³ Professor Xianxing Jiang from Sun Yat-sen University (P. R. of China), who is strongly interested in organofluorine chemistry, reckons that asymmetric fluorinations using nucleophilic fluorine sources are much less developed as compared to electrophilic strategies, due to the unique features of fluorine atoms (such as high oxidation potential, high hydration energy).¹ “In current research, the main nucleophilic fluorine sources applied in asymmetric fluorinations are PhCOF , $\text{pyridine} \cdot \text{HF}$, $\text{Et}_3\text{N} \cdot \text{HF}$ and metal fluorides,” he noted, adding: “Despite elegant works reported in the literature, several practical disadvantages discouraged further large-scale utilization of these compounds for nucleophilic fluorinations: for example, the high toxicity and biohazardous nature of HF-bases, and the poor solubility of metal fluorides in organic solvents, coupled with limited strategies to control their reactivity, are among the main reasons.”⁴

According to Professor Jiang, compared to metal catalysts, chiral hypervalent iodine catalysts have recently attracted much attention in organic synthesis due to their excellent pro-

perties, such as mild reaction conditions, ease of preparation, the ability to dispense with complex ligands, and being metal-free.^{5,6} “Importantly, Jacobsen and co-workers reported the viability of catalytic asymmetric nucleophilic fluorinations using a chiral iodine catalyst and $\text{pyridine} \cdot \text{HF}$ in the presence of $m\text{-CPBA}$,” he noted.⁷

Professor Jiang and his research group have been interested in hypervalent iodine catalyzed/promoted reactions (such as asymmetric halogenations, oxidative cyclization and oxyaminations) and Lewis acid catalyzed/mediated chemical synthesis. Professor Jiang explained: “The initial phase of our research was focused on catalytic asymmetric nucleophilic fluorinations using the ‘chiral iodine catalyst + $\text{pyridine} \cdot \text{HF}$ ’ catalytic system, inspired by Jacobsen’s work. We found that $\text{BF}_3 \cdot \text{Et}_2\text{O}$, which is a versatile and cheap Lewis acid, could also be applied as fluorine source in some fluorinations. We thought that if we could combine the hypervalent chiral iodine catalyst and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ together, we could then apply the ‘combination’ to reactions with appropriate substrates to form chiral fluorinated products. If so, it would be a welcome and significant step in fluorine chemistry.”

Professor Jiang continued: “Firstly, we applied the combination of hypervalent iodine compound and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to reactions with the amide **1a** in DCM at 0 °C (Scheme 1). To our delight, the fluorinated products **1b** could be generated through the catalytic process. On the basis of this experimental result, we then used chiral iodine reagents instead of iodobenzene



Scheme 1 Catalyst screening

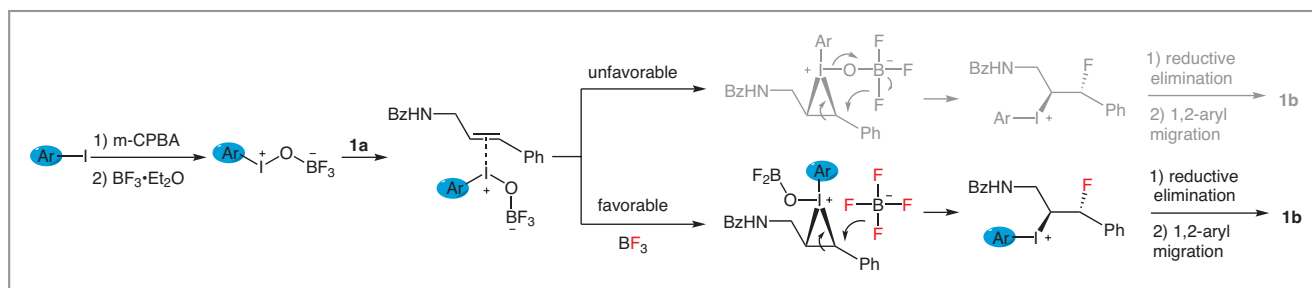
(IB) to carry out the reaction. At first, the chiral iodine(III) reagent **2a** was applied to catalyze the fluorinations, affording the desired product with 37% ee (major diastereomer). Next, we examined spirobiindane chiral iodine catalysts **2b** and **2c** which gave the desired products with higher ee and dr values. Axisymmetric chiral iodine catalysts were then examined to improve the stereoselectivity of the fluorinated product. Catalyst screening indicated that **2d** was the best choice (Scheme 1). After several initial trials aimed at studying the effect of different experimental factors such as solvents, reaction temperature, concentration, we set out to optimize the model catalytic asymmetric aminofluorination of **1a** in the presence of 15 mol% of ligand loading, using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as the fluorine reagent in DCE at -25°C . This part of the research project was carried out by Dr. Weiwei Zhu and Xiang Zhen.”

To gain a better understanding of this catalytic fluorination system, the authors conducted control experiments and DFT calculations. Professor Jiang said: “It is worth noting that when PhIF_2 , $\text{Py} \cdot \text{HF}$ or $\text{Et}_3\text{N} \cdot \text{HF}$ were used as fluorine source, **1b** could NOT be obtained. In the beginning we thought fluoride was produced from Ph-I-OBF_3 directly during the ca-

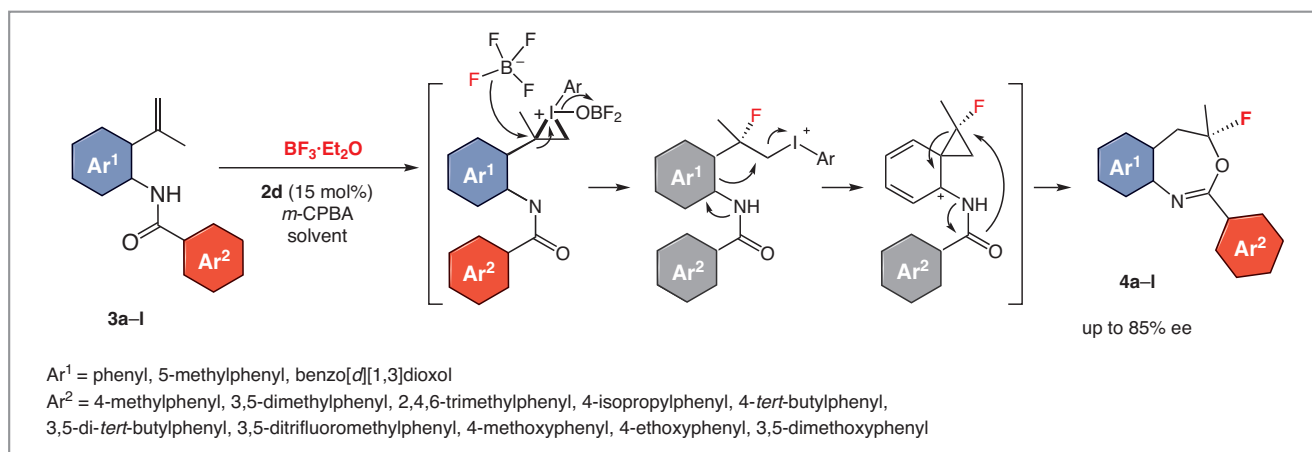
talytic cycle. However, DFT calculations didn't support this initial hypothesis, as it was found to be energetically disfavored. Then we modified the possible mechanism: the ‘fluorine source’ was hypothesized to be the BF_4^- anion (generated in situ) and this turned out to be energetically possible (Scheme 2). The process would thus follow a fluorination/1,2-aryl migration/cyclization cascade.⁸ In this scenario, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ plays the role of a fluorinating reagent, as well as the activating reagent for activation of iodosylbenzene.”

In order to expand the applications of this catalytic fluorination system, Professor Jiang and co-workers designed and synthesized substrates **3a–l** to undergo the fluorination reaction (Scheme 3). “As expected, the fluorinated products **4a–l** could be obtained as we hoped, based on the possible catalytic cycle. Screening of different reaction parameters gave the optimal reaction conditions for the formation of fluorinated products with good to excellent ee values,” remarked Professor Jiang.

Professor Jiang recalls at the onset of this novel research program, three main challenges were identified. “The first was the choice of the fluorinating reagent. As mentioned above,



Scheme 2 Mechanistic studies



Scheme 3 Substrate scope expansion

currently the most applied fluorine sources in nucleophilic fluorinations are $\text{Py}\cdot\text{HF}$, $\text{Et}_3\text{N}\cdot\text{HF}$ or metal fluorides, which have been used in elegant works, but the practical disadvantages described earlier are detrimental in terms of large-scale utilization. Considering that $\text{BF}_3\cdot\text{Et}_2\text{O}$ could be applied in achiral fluorinations as nucleophilic fluorine source and inspired by the asymmetric fluorinations achieved with chiral iodine catalysts, we came up with the idea that the combination of 'chiral iodine catalyst and $\text{BF}_3\cdot\text{Et}_2\text{O}$ ' may be an alternative for asymmetric fluorinations. The second was the design of the substrates. Based on the previous related work on fluorination reactions and the possible mechanism of hypervalent iodine catalyzed fluorination reactions, we designed and synthesized the original substrate **1a**. By the way, **1a** was tested for halogenations in previous work.^{9–11} What inspired us to study the catalytic system further for catalytic asymmetric fluorinations was that the substrate **1a** could react with the 'IB + $\text{BF}_3\cdot\text{Et}_2\text{O}$ ' system in the presence of *m*-CPBA to generate fluorinated products. The third challenge was the possible competition between Lewis acid promoted cyclization reaction and catalytic fluorinations. In our previous work, we reported a Lewis acid promoted cyclization of unsaturated alkenes."¹²

The current catalytic system had an important influence on the group's research. In view of the advantages of using $\text{BF}_3\cdot\text{Et}_2\text{O}$ as fluorine source in asymmetric nucleophilic fluorinations, Professor Jiang revealed that his group will continue to focus on catalytic, asymmetric nucleophilic fluorinations using $\text{BF}_3\cdot\text{Et}_2\text{O}$ as fluorine source and activating reagents in their future research. Professor Jiang explained: "We aim to expand the substrate scope and synthesize more chiral fluorinated molecules using our "chiral hypervalent iodine + $\text{BF}_3\cdot\text{Et}_2\text{O}$ " catalytic system. In addition, asymmetric fluorinations using other nucleophilic fluorine sources are still one of our main research topics."

Professor Jiang concluded: "Fluorinated oxazine derivatives could be obtained with high stereoselectivities (up to > 20% ee and > 20:1 dr), whereas benzocycloheptane derivatives could be synthesized with high enantioselectivities (up to 85% ee) and in one step, through this metal-free and complex-ligand-free catalytic system. Oxazine derivatives are widely present in bioactive and pharmaceutical molecules, and fluorinated 1,2-amino alcohols, which are important intermediates in organic synthesis and pharmaceutical chemistry, could be obtained through hydrolysis of the products. Besides, ring-opening polymerization of the N,O-heterocycles can be applied to prepare functional materials. We believe that this process provides not only a direct access to fluoro-oxazine/benzoxazepine skeletons, but also a foundation for further development of new types of asymmetric nucleophilic fluorinations in

future applications. Studies on the applicability of this asymmetric fluorination methodology using other substrates are presently ongoing in our group."

REFERENCES

- (1) P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin *Chem. Rev.* **2015**, *115*, 9073–9174.
- (2) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho, F. D. Toste *Chem. Rev.* **2018**, *118*, 3887–3964.
- (3) J. A. Ma, D. Cahard *Chem. Rev.* **2004**, *104*, 6119–6146.
- (4) W. Zhu, X. Zhen, J. Wu, Y. Cheng, J. An, X. Ma, J. Liu, Y. Qin, H. Zhu, J. Xue, X. Jiang *Nat. Commun.* **2021**, *12*, 3957.
- (5) A. Yoshimura, V. V. Zhdankin *Chem. Rev.* **2016**, *116*, 3328–3435.
- (6) T. Wirth *Angew. Chem. Int. Ed.* **2005**, *44*, 3656–3665.
- (7) S. M. Banik, J. W. Medley, E. N. Jacobsen *Science* **2016**, *353*, 51–54.
- (8) A. Ulmer, C. Brunner, A. M. Arnold, A. Pöthig, T. Gulder *Chem. Eur. J.* **2016**, *22*, 3660–3664.
- (9) Y. Kawato, A. Kubota, H. Ono, H. Egami, Y. Hamashima *Org. Lett.* **2015**, *17*, 1244–1247.
- (10) Y. Nagao, T. Hisanaga, H. Egami, Y. Kawato, Y. Hamashima *Chem. Eur. J.* **2017**, *23*, 16758–16762.
- (11) G.-Q. Liu, C.-H. Yang, Y.-M. Li *J. Org. Chem.* **2015**, *80*, 11339–11350.
- (12) J. An, J. Liu, Y. Shi, W. Zhu, G. Guo, X. Jiang, J. Xue, H. Zhang *Curr. Org. Chem.* **2020**, *24*, 1263–1273.

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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

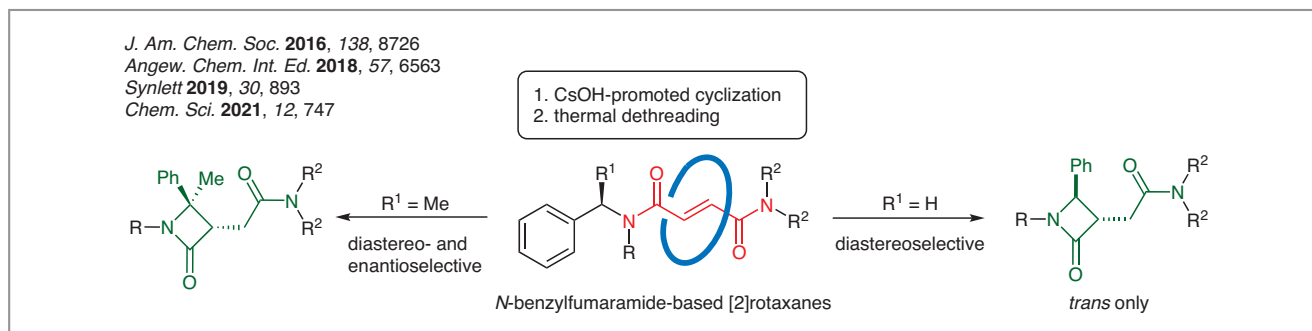
in the synthesis and applications of mechanically interlocked molecules, perhaps the most relevant and influential line. The key purpose of this research is the assembly of novel mechanized systems with interesting properties resulting from the presence of the mechanical bond. For this purpose, we use 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

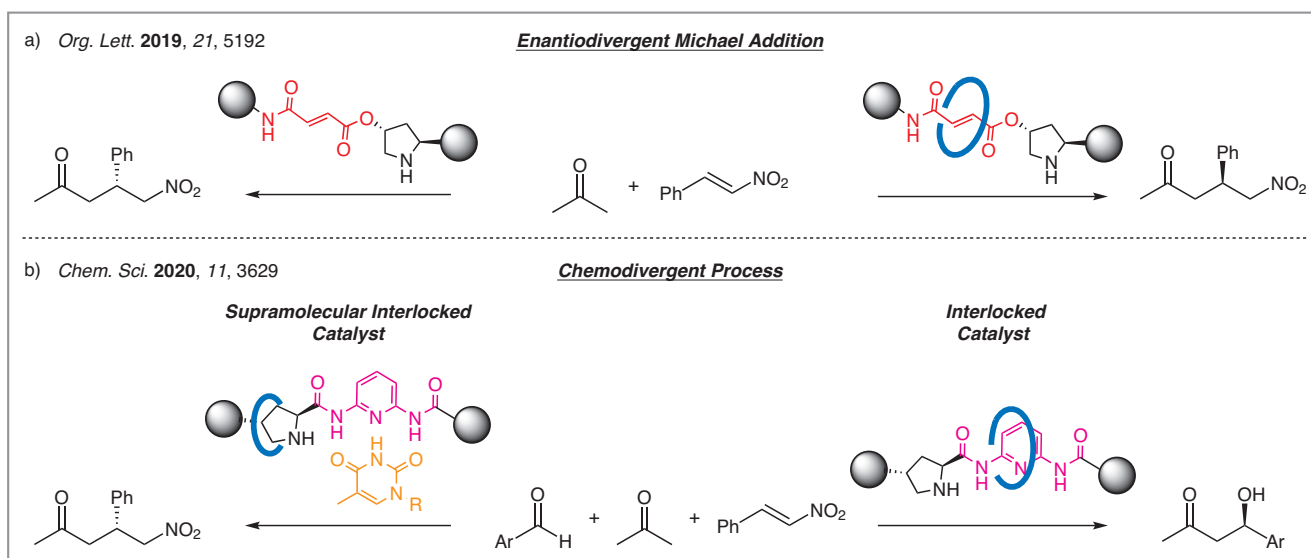
experience with mechanically interlocked molecules earned at the SOC-UMU lab of the University of Murcia, both allowed me to start this new research line. There is a common belief that the design and synthesis of novel catalysts able to overcome the actual limitations for accessing complex molecules, 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

REFERENCES

- (1) D. A. Leigh *Angew. Chem. Int. Ed.* **2016**, *55*, 14506–14508.
- (2) A. Saura-Sanmartin, A. Martinez-Cuezva, D. Bautista, M. R. B. Marzari, M. A. P. Martins, M. Alajarin, J. Berna *J. Am. Chem. Soc.* **2020**, *142*, 13442–13449.
- (3) A. Martinez-Cuezva, C. Lopez-Leonardo, D. Bautista, M. Alajarin, J. Berna *J. Am. Chem. Soc.* **2016**, *138*, 8726–8729.
- (4) A. Martinez-Cuezva, C. Lopez-Leonardo, M. Alajarin, J. Berna *Synlett* **2019**, *30*, 893–902.
- (5) A. Martinez-Cuezva, A. Pastor, M. Marin-Luna, C. Diaz-Marin, D. Bautista, M. Alajarin, J. Berna *Chem Sci.* **2021**, *12*, 747–756.
- (6) A. Martinez-Cuezva, D. Bautista, M. Alajarin, J. Berna *Angew. Chem. Int. Ed.* **2018**, *57*, 6563–6567.
- (7) A. Martinez-Cuezva, A. Saura-Sanmartin, M. Alajarin, J. Berna *ACS Catal.* **2020**, *10*, 7719–7733.
- (8) J. de Maria Perez, J. Puigcerver, T. Orlando, A. Pastor, M. A. P. Martins, M. Alajarin, A. Martinez-Cuezva, J. Berna *Org. Chem. Front.* **2021**, *8*, 4202–4210.
- (9) A. Martinez-Cuezva, M. Marin-Luna, D. A. Alonso, D. Ros-Níguez, M. Alajarin, J. Berna *Org. Lett.* **2019**, *21*, 5192–5196.
- (10) M. Calles, J. Puigcerver, D. A. Alonso, M. Alajarin, A. Martinez-Cuezva, J. Berna *Chem. Sci.* **2020**, *11*, 3629–3635.

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