

SYNTHESIS Best Paper Award 2021: An I(I)/I(III) Catalysis Route to the Heptafluoroisopropyl Group: A Privileged Module in Contemporary Agrochemistry

Synthesis **2021**, *53*, 4203–4212

Background. Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the ‘SYNTHESIS/SYNLETT Best Paper Awards’. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.

Professor Ryan Gilmour, together with Dr. Victor Martín and Dr. Constantin G. Daniliuc, from the Westfälische Wilhelms-Universität Münster, Germany, has received the SYNTHESIS Best Paper Award 2021. The authors are recognized for their strategy to generate the heptafluoroisopropyl group via I(I)/I(III) catalysis. Mark Lautens, Editor-in-Chief of SYNTHESIS, stated: “They describe a new way to access the heptafluoroisopropyl group, which is an emerging motif in drug discovery, agrochemistry and catalysis. Routes to fluorine-containing molecules continue to be of great interest in the design of functional small molecules. In this paper, the authors describe the use of a simple organocatalyst to promote the formal difluorination of α -trifluoromethyl- β -difluorostyrenes. A hypervalent iodine species, generated in situ, from Olah’s reagent and Selectfluor serves as the key catalytic species. An intriguing aspect of the work is the importance of A^{1,3} strain in determining the lowest-energy conformation of the product, which positions the benzylic C–F bond in alignment with the aryl *ortho* C–H group.”

SYNFORM spoke with Professor Ryan Gilmour, who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in his group.

Biographical Sketches



Dr. V. Martín-Heras

Victor Martín completed his undergraduate degree in chemistry at the *Universidad Complutense de Madrid* (Spain) before moving to the *Universidad Autónoma de Madrid* (Spain), where he completed a Masters degree under the supervision of Prof. Mariola Tortosa. He remained with Prof. Tortosa for his PhD studies where he worked on stereoselective borylation and C–N cross coupling technologies to facilitate drug discovery. During this time, he was also a visiting student in Prof. Matt Sigman’s group at the University of Utah (USA). Dr. Martín was an Alexander von Humboldt Foundation Research Fellow with Prof. Gilmour at the WWU Münster (Germany) where he worked on I(I)/I(III) catalysis for selective fluorination. He is currently a Research Chemist with Eurofins Villapharma in Murcia, Spain.



Dr. C. G. Daniliuc

Constantin G. Daniliuc was born in Romania and received his Diploma in 2002 at the ‘Alexandru Ioan Cuza’ University of Iași. He moved to the Technical University of Braunschweig/ Institute of Inorganic and Analytical Chemistry (Germany) for his Master’s studies as a beneficiary of an Erasmus/ Socrates Scholarship and received his Ph.D. from the same university in 2008 under the supervision of Professor W.-W. du Mont. Since 2012, he is Head of the Crystallographic Laboratory of Organic Chemistry Institute at WWU University of Münster (Germany), where he is associated with several projects in Prof. Gilmour’s research group.

>>



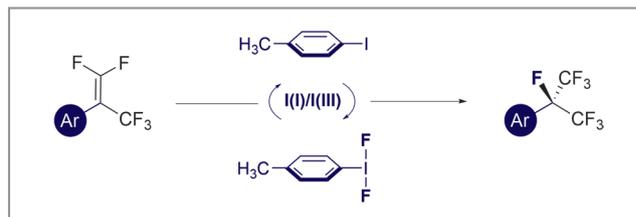
Prof. R. Gilmour

Ryan Gilmour was born in Ayrshire, Scotland (1980) and was educated at the universities of St Andrews and Cambridge. He held research fellowships at the Max-Planck-Institut für Kohlenforschung (A. Fürstner) in Germany and the ETH Zürich (P. H. Seeberger) in Switzerland before being appointed as the Alfred Werner Assistant Professor of synthetic organic chemistry at the ETH Zürich (2008–2012). In 2013 he moved to the WWU Münster (Germany) where he is Chair of Organic Chemistry and CiMIC Professor of Chemical Biology. He is the recipient of several awards including ERC Starter (2013) and Consolidator Grants (2019), and is a Corresponding Fellow of the Royal Society of Edinburgh (2021).

INTERVIEW

SYNFORM Could you highlight the value of your award-winning paper with respect to the state-of-the-art, as well as the potential or actual applications?

Prof. R. Gilmour The success of the heptafluoroisopropyl $[-CF(CF_3)_2]$ group, particularly in agrochemistry, is testimony to the success of $C(sp^2)-CF(CF_3)_2$ bond-forming processes. Many of these strategies are predicated on the generation of a pre-formed organometallic species, but metal-catalysed reactions have also been very impactful. Our complementary strategy expands the toolkit further to include an organocatalysis platform that allows the target $Ar-CF(CF_3)_2$ structure to be generated by a formal addition of F_2 to the alkene of α -trifluoromethyl- β -difluorostyrenes (Scheme 1). This alternative disconnection, involving the generation of two $C(sp^3)-F$ bonds, harnesses inexpensive aryl iodides as oxidative fluorination catalysts. The products that are generated are highly pre-organised and we have been able to analyse representative derivatives by single-crystal X-ray diffraction. It is interesting to note that the $C(sp^3)-F$ bond in the product is co-planar to the aryl ring, thereby minimising 1,3-allylic strain. Moreover, orthogonal multipolar $C-F\cdots C=O$ interactions were observed in a phthalimide derivative. We believe that this transformation will be highly enabling in exploring chemical space, and that the products themselves will be of value in the study of fluorine-based non-covalent interactions.



Scheme 1 I(I)/I(III) catalysis route to generate the heptafluoroisopropyl group

SYNFORM Can you explain the origin, motivations and strategy used for conducting the award-winning research?

Prof. R. Gilmour The heptafluoroisopropyl group has emerged as a privileged discovery module in the design and development of contemporary pharmaceuticals, organocatalysts and agrochemicals. This motif is particularly prominent in the current suite of leading insecticides, which provided the impetus for the study. Although heptafluoroisopropylation confers a range of desirable physicochemical properties, methods to install this ‘super CF_3 group’ remain limited. We have an interest in stereocontrolled fluorination and saw an opportunity to generate the target group by a formal 1,2-difluorination of simple α -trifluoromethyl- β -difluorostyrenes in a single operation. This disconnection was appealing due to our experience in developing catalysis-based processes to enable the *vicinal* difluorination of alkenes. Despite the highly deactivated nature of the fluorinated styrene substrates, we discovered that an I(I)/I(III) catalysis cycle enabled the transformation. The reaction proved to be operationally simple and uses inexpensive *p*-iodotoluene as an organocatalyst, Selectfluor[®] as the oxidant, and Olah’s reagent as the fluoride source. Key features of the process are (i) the *in situ* generation of *p*-TolIF₂, which eliminates the need to generate stoichiometric quantities of the I(III) species, and (ii) the dual role of the HF as both a fluoride source and a Brønsted acid to activate *p*-TolIF₂. The reaction enables diverse $Ar-CF(CF_3)_2$ products to be generated efficiently, thereby providing a new, catalysis-based strategy that will hopefully find application in functional small molecule discovery programmes.

SYNFORM What is the focus of your current research activity, both related to the award paper and in general?

Prof. R. Gilmour One of the greatest challenges facing organic chemistry is the synthesis of function, and so a central theme in the Gilmour Laboratory is molecular design and expanding the existing boundaries of chemical space. Fluorine

chemistry is a logical starting point on account of the rarity of organofluorines in nature, and the physicochemical impact that fluorine incorporation has. We are currently very interested in generating chiral, fluorinated groups due to the ubiquity of short alkyl groups in bioactive molecules and the biososteric nature of H-to-F substitution. Harnessing I(I)/I(III) catalysis has enabled us, and many others, to develop versatile platforms to access chiral, fluorinated building blocks that are finding application in medicinal chemistry. This interest in fluorination also manifests itself in our glycochemistry programme, where site-selective fluorination enables us to reconcile the ubiquity of sugars in human health with their conspicuous under-representation in pharmaceutical development. Fluorine can be leveraged for a multitude of purposes, which include to control glycosylation selectivity, to enhance hydrolytic stability, to function as an NMR active probe, and, finally (in the case of ^{18}F), to act as a positron emitter for PET. Although we start from a very physical organic approach, this research is translational and we work closely with microbiologists, virologists, neurologists and radiologists. Whilst these two research areas focus on 3D chemical space, part of the group is devoted to exploring 2D chemical space through photocatalysis-based alkene isomerisation strategies. $E \rightarrow Z$ alkene isomerisation underpins a range of functions in biology, but replicating this process in a laboratory setting is challenging due to thermodynamic constraints. Photochemical activation via triplet energy transfer is ideally suited to bypass these challenges and we have successfully leveraged this activation mode to generate a portfolio of methods to enable formally endergonic transformations using simple small-molecule catalysts. Overall, it is fair to say that physical organic and structural chemistry are at the core of our entire research programme and drive innovation.

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

Prof. R. Gilmour I think this is best answered with the following quote from my former office neighbour at ETH, Prof. Albert Eschenmoser:

"In my opinion, there is a problem that is central to organic chemistry alone and in which biologists cannot help us. We all agree...that the emphasis in synthetic research is the synthesis of properties, and not just compounds."

Albert Eschenmoser

SYNFORM *What does this award mean to you/your group?*

Prof. R. Gilmour We are honoured to receive the SYNTHESIS Best Paper Award 2021 and to join an impressive list of distinguished previous recipients. Knowing that it is the editorial board of the journal who make the decision makes this prize all the more special! We would like to express our sincere thanks to Editor-in-Chief Prof. Mark Lautens and his colleagues at SYNTHESIS!

