

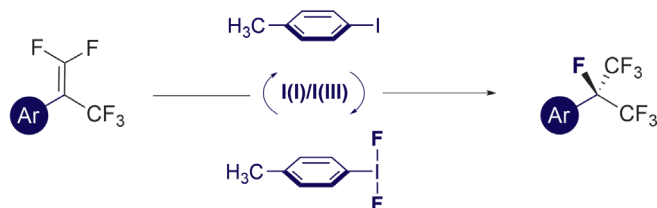
Synform

People, Trends and Views in Chemical Synthesis

2022/06

An I(I)/I(III) Catalysis Route to the Heptafluoroisopropyl Group: A Privileged Module in Contemporary Agrochemistry

Highlighted article by V. Martín-Heras, C. G. Daniliuc, R. Gilmour



Contact

Your opinion about Synform is welcome,
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Dear Readers,

In this June issue of SYNFORM we honour the second – although there is no particular order here – 2021 Best Paper Award winners. Last month we interviewed Professor Elizabeth Jarvo and co-authors from the University of California-Irvine (USA), who were the recipients of the SYNLETT Best Paper Award 2021. In this issue we have the great pleasure to host the interview with Professor Ryan Gilmour and co-authors Dr. Victor Martín and Dr. Constantin G. Daniliuc, from the Westfälische Wilhelms-Universität Münster (Germany), who are the recipients of the SYNTHESIS Best Paper Award 2021 for their article “An I(I)/I(III) Catalysis Route to the Heptafluoroisopropyl Group: A Privileged Module in Contemporary Agrochemistry” (*Synthesis* **2021**, *53*, 4203–4212). The interview – in classical SYNFORM style – provides background information on their prize-winning research, as well as about current research activities ongoing in the group. The second article of the issue covers the photoredox-catalyzed approach designed by P. Musacchio (USA), which results in a formal hydride abstraction from benzylic positions and their consequent C(sp³)-H functionalization with a range of nucleophilic and heteronucleophilic partners. Next is a Literature Coverage article on a very exciting C-H activation of arenes, which can be performed with excellent remote control for the *meta*-position according to the study – published in *Science* – by S. Asako and L. Ilies (Japan). Finally, the issue-closing article covers the enantioselective borylative cyclization of enone-tethered cyclohexadienones to give fused heterobicyclic compounds under Cu(I) catalysis, as reported in *Nat. Commun.* by R. Chegondi (India).

Enjoy your reading!



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If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

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.

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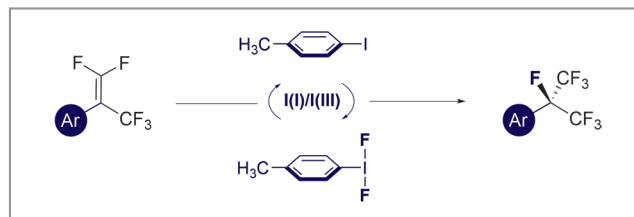
Prof. R. Gilmour

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(CF₃)₂] group, particularly in agrochemistry, is testimony to the success of C(sp²)–CF(CF₃)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(CF₃)₂ structure to be generated by a formal addition of F₂ to the alkene of α-trifluoromethyl-β-difluorostyrenes (Scheme 1). This alternative disconnection, involving the generation of two C(sp³)–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(sp³)–F bond in the product is co-planar to the aryl ring, thereby minimising 1,3-allylic strain. Moreover, orthogonal multipolar C–F...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 CF₃ 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(CF₃)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!

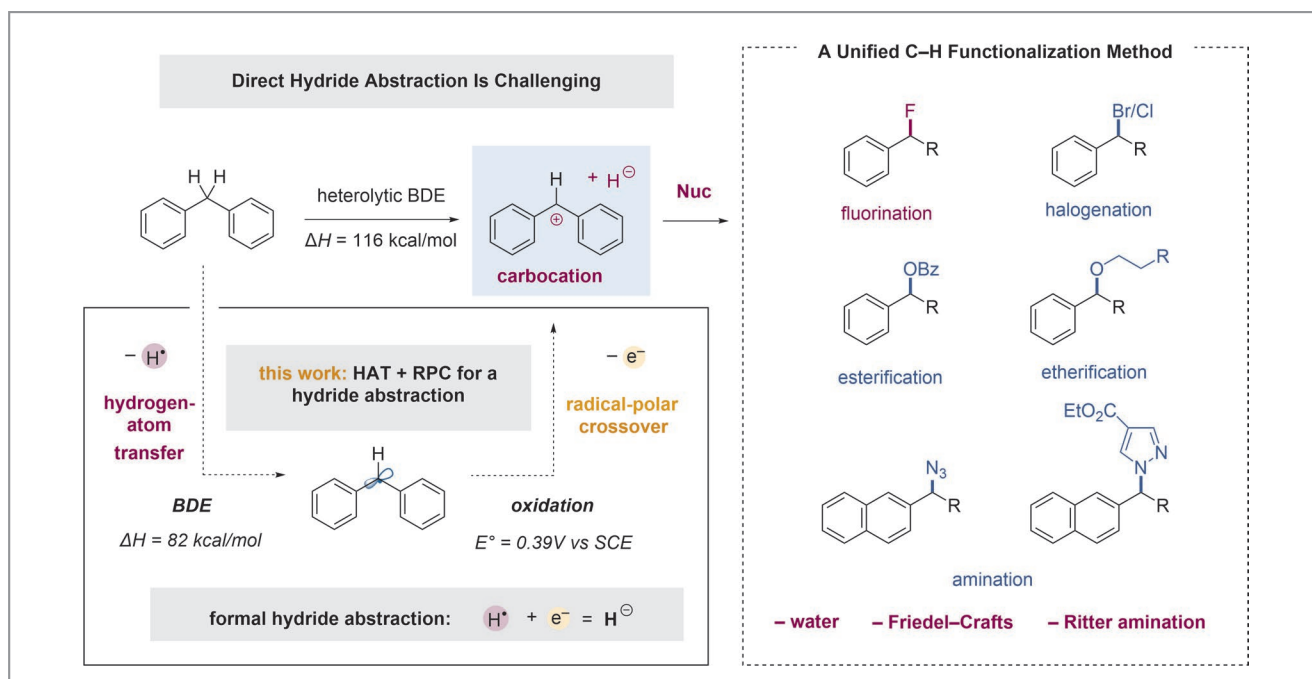


A Photoredox-Catalyzed Approach for Formal Hydride Abstraction To Enable C(sp³)-H Functionalization with Nucleophilic Partners (F, C, O, N, and Br/Cl)

Chem Catal. **2022**, *2*, 292–308

Carbocations are very reactive intermediates but are rarely present in C–H functionalization mechanisms, which are dominated by carbon radical and metal alkyl intermediates. It has been a goal for the lab of Professor Patricia Musacchio at the Worcester Polytechnic Institute (USA), ever since its inception as a new lab, to develop mild strategies that can ‘dismantle’ a C(sp³)-H bond all the way down to a carbocation. “Formally, this means we were tasking ourselves with removing a hydride from a C(sp³)-H bond,” explained Professor Musacchio. She continued: “In looking at heterolytic bond dissociation energies needed to do this, we immediately recognized this was only feasible for a few types of activated molecules and it could not be a reliable general strategy across all C(sp³)-H bonds.¹ Thus, we focused in on the hydride entity and played around with the idea of breaking up the hydride into constituents that could be more easily removed from a

C–H bond.” The group began questioning whether they could sequentially remove a hydrogen atom (H•) and an electron (e⁻) from a desired C–H bond, the sum of which would give a hydride, H⁻ = H• + e⁻ (Scheme 1). The group thought this could be a simple alternative to a direct hydride abstraction as both hydrogen-atom transfer (HAT) and oxidation of radicals, otherwise known as radical-polar crossover (RPC), have both been demonstrated as reliable reaction processes in recent enabling methods.^{2,3} Moreover, they wondered whether they could accomplish both steps, [HAT + RPC], in one catalytic cycle and do it in a mild fashion. Professor Musacchio remarked: “We saw an opportunity in the redox neutral nature of visible-light photoredox catalysis and its reported efficiencies at facilitating both HAT and RPC processes, thus we started our efforts there.”



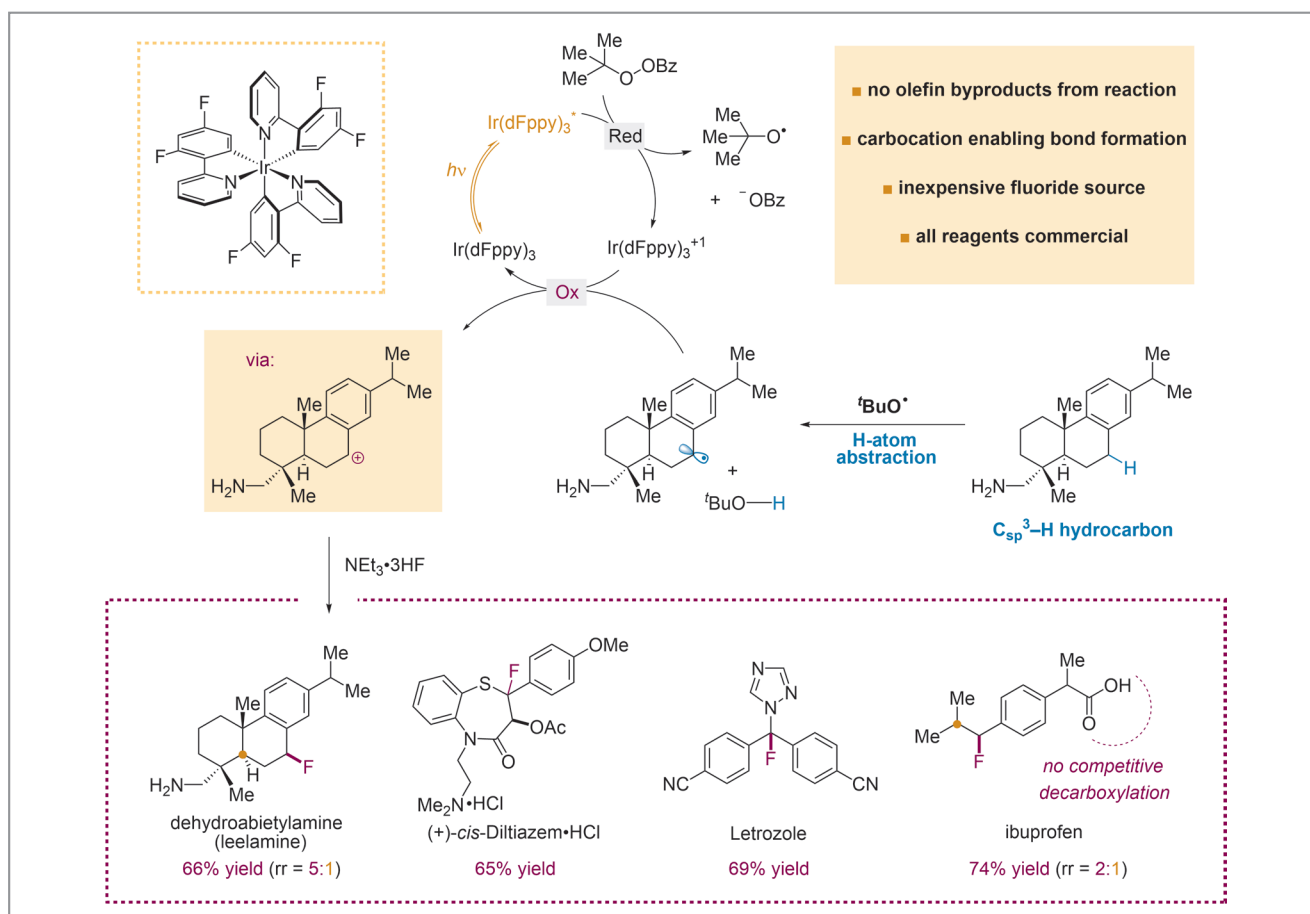
Scheme 1 Finding a way around a direct hydride abstraction

She continued: “As a bonus, this same [HAT + RPC] mechanistic design is hypothesized to be the mechanism ethylbenzene dehydrogenase (EBDH) operates by to enantioselectively hydroxylate ethylbenzene with water as the oxygen atom source.⁴ So we knew nature would be on our side.”

Early on in the process, the group was in discussion with medicinal chemists Dr. Hatice Yayla and Dr. Manj Lall at Pfizer in Groton, CT (USA). “It became clear we were all interested in exploring the potential of a transformation that could easily access carbocations directly from C–H bonds and what sort of impact that could have on facilitating late-stage functionalization of drug compounds,” explained Professor Musacchio. She continued: “Due to the unique properties of fluorine on a compound’s lipophilicity, conformation, and metabolic stability, Yayla and Lall were particularly excited by the platform’s potential to establish a robust and mild C(sp³)–H fluorination with all commercially available reagents. So we decided to team up! Also, Dr. Yayla and I are good friends from

graduate school, so it was a dream come true to get to work with her in a professional setting!”

Professor Musacchio pointed out that in some respects, the field of C(sp³)–H fluorination is quite mature and that elegant work by Paquin and Sammis,⁵ Lectka,⁶ Britton,⁷ and Chen⁸ utilized electrophilic fluorinating reagents to target many C(sp³)–H bonds, providing an array of options with this class of reagents. “However, if you need a general C–H fluorination method that can engage nucleophilic fluoride reagents, only one synthetic strategy was available before: the P450-inspired system developed by Groves and team at Princeton University (USA).⁹ Practicing chemists have far fewer options with nucleophilic fluoride. Fluorination chemists are very aware of the advantages and disadvantages of nucleophilic and electrophilic fluorine reagents,” said Professor Musacchio. She continued: “For example, the high reactivity of electrophilic fluorine reagents can’t be beaten, but if we can coax fluoride sources to act on its (weakly) nucleophilic properties,



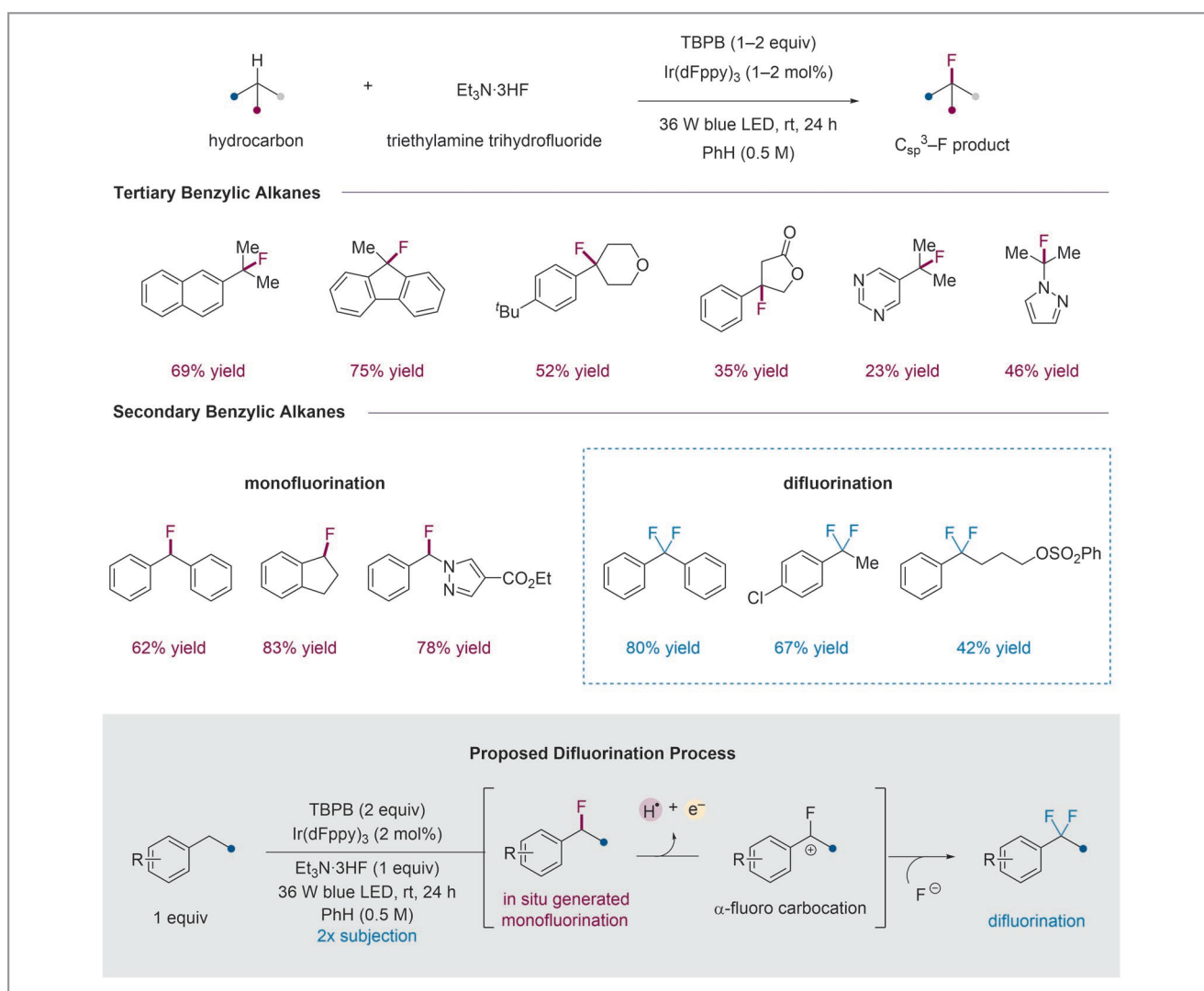
Scheme 2 Proposed photocatalytic cycle for the [HAT + RPC] process with a few highlighted drug compounds

it can open up the door to practical advantages such as greater solubility, non-oxidizing reagent, and potential radiolabelling applications with fluorine-18.”

The larger picture, however, is the general strategy taken to ‘dismantling’ a C(sp³)-H bond. “Back when we started in 2019, we already knew this was the problem we wanted to tackle,” said Professor Musacchio. She explained: “The most common way to access a carbocation intermediate is from an existing functional group: alkyl halide, olefin, protected alcohol, epoxide, etc., but there are very few ways to access carbocations directly from C(sp³)-H bonds, especially under mild conditions, with mild reagents and oxidants. Indeed, when you look at the field of C-H functionalization, the majority

of new methods rely on alkyl radical or metal alkyl intermediates. We wondered if we could leverage the high reactivity of a carbocation intermediate for C-H functionalization, we just had to figure out how to get there.”

The key for the group to getting the chemistry to work was finding the right oxidizing agent that could generate an active HAT reagent. They looked at several different reagents and then narrowed in on peroxides: carbon-based peroxides are fairly mild oxidants. When they tested *tert*-butyl peroxybenzoate (TBPB), the group immediately observed fluorinated product for their model substrate. “From there, investigating various reducing photocatalysts led us to Ir(dFppy)₃, which is reducing but also has enough oxidizing power to mediate



Scheme 3 Monofluorination and difluorination of simple compounds

the radical-polar crossover step (radical oxidation),” remarked Professor Musacchio. She continued: “This is the beauty of the reaction – the oxidation of the carbon radicals is not all that hard, so we could get away with using a mildly oxidizing photocatalyst (Scheme 2). This is the key advantage our chemistry has over other C–H fluorination reactions that utilize Select-Fluor (which is a strong oxidant).”

Professor Musacchio revealed that the difluorination from Figure 6 of the original paper (see Scheme 3) was actually an unexpected finding. “We had started our investigations by fluorinating tertiary benzylic hydrocarbons, but when we moved to secondary benzylic hydrocarbons, we found difluorination products along with the expected monofluorination product,” she said. Although excited that their platform could be extended to difunctionalization of methylene sites, the group was surprised. Their first instincts were the second [HAT + RPC] sequence would be less favorable due to the inductive effects of the fluoride. “However, we found it difficult to prevent the difluorination from occurring on simple substrates and ultimately had to adjust the equivalents of our system to make the fluoride the limiting reagent to selectively obtain monofluoro products,” said Professor Musacchio, who added: “However, on complex substrates, we did not observe the same issue.”

For secondary benzylic substrates, a second subjection of the crude reaction mixtures (after an aqueous base wash) to the [HAT + RPC] protocol afforded good yields of the *gem*-difluoro products.

“The finding of the difluorination has definitely opened up a new area of research in my lab – exploring the reactivity of α -halo carbocations,” said Professor Musacchio. She went on: “We’ve found a way to generate these less explored intermediates under mild conditions and expect this to result in several new methods.”

The group is really excited to continue developing this chemical toolbox as a robust *unified* C–H functionalization platform that can engage other nucleophiles, especially given the high applicability to drug compounds the fluorination seemed to have. Professor Musacchio said: “We do a little teaser of this at the end of our paper and show that already many other nucleophile types can react in the photochemical formal hydride abstraction – arenes via Friedel–Crafts reactions, nitrogen nucleophiles to give a C–H azidation and the Ritter reaction, alcohols for etherification reactions, and carboxylic acids for esterifications. Additionally, we envision this could be a powerful strategy for making saturated heterocycles through intramolecular trapping of pendant nucleophiles. The possibility of teaming up with a radiolabelling expert to apply this to fluorine-18 efforts is also on the horizon.

And of course, we aim to extend the [HAT + RPC] strategy to aliphatic substrates. We are currently redesigning our hydrogen-atom transfer reagents so as to functionalize aliphatic methylene sites, which would be a great accomplishment.”

Professor Musacchio concluded: “Lastly, we would like to acknowledge similar work that was recently published from the Doyle group.¹⁰ Throughout the development stages, Prof. Doyle and I became aware our teams were working on related mechanistic questions. We communicated regularly, sharing progress with each other along the way and were able to time the release of the work within a few weeks of each other. Her team performed some excellent work establishing that methyl radical is their operative hydrogen-atom abstractor in the [HAT + RPC] design. She proved to be a great mentor to our young team throughout this process, for which we are grateful.”

Patricia Z. Musacchio

About the authors



Y. Zhang

Yufei Zhang was born in Anhui Province, P. R. of China. She joined the research group of Prof. Hongyu Zhang’s lab in 2014 while working to obtain her Bachelor of Science from Jilin University (P. R. of China). Her research involved the synthesis and performance research of organic photoelectric materials. Currently, she is a graduate student in the chemistry and biochemistry department in Worcester Polytechnic Institute. She joined the research group of Prof. Patricia Z. Musacchio in 2020. Her current research interests include C(sp³)-H functionalization.



N. Fitzpatrick

Nicholas Fitzpatrick was born in Philadelphia, PA (USA) and completed his B.S. in chemistry at Wilkes University in Wilkes-Barre, PA (USA), where he worked under Dr. Megan Youmans and Dr. Amy Bradley. He currently lives in Worcester, MA (USA) where he is working towards his PhD in organic chemistry under the guidance of Prof. Patricia Z. Musacchio. His studies focus on the use of photoredox

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catalysis to perform C(sp³)-H functionalizations to forge new C-O and C-C bonds.



Dr. M. Das

Mrinmoy Das was born in West Bengal (India) and completed his B.Sc. from Ramakrishna Mission Vidyamandira, Belur Math (India). He went for his M.Sc. at Indian Institute of Technology, Kanpur (India) under the supervision of Prof. Jitendra K. Bera. Then he moved to Singapore for his doctoral training in organic synthesis with Prof. Liu Xuewei at Nanyang Technological University. He moved back to India and start working as a research associate with Prof. Indu Bhusan Deb at CSIR-Indian Institute of Chemical Biology. Currently, he is working as a postdoctoral fellow with Prof. Patricia Z. Musacchio at Worcester Polytechnic Institute (USA). His current research is focused on the development of novel synthetic methodologies towards C-N bond formation through photoredox catalysis.



I. Bedre

Ishani Bedre was born in Winchester, MA (USA). She is a junior undergraduate, majoring in biochemistry with a minor in psychology, at Worcester Polytechnic University in Worcester, MA (USA). In 2020, she joined Prof. Patricia Z. Musacchio's group at the same university, where she began to research photocatalyst-mediated synthesis. She is currently working on developing a new strategy for targeting specific amino acids in proteins for selective bioconjugation efforts.



Dr. H. Yayla

Hatice (Hattie) Yayla was born and raised in Oslo (Norway). She completed her B.A. in chemistry at Wellesley College (USA) and carried out her PhD work with Prof. Rob Knowles at Princeton University (USA). In 2016, she joined Pfizer as a medicinal chemist. She is currently a Principal Scientist in a synthesis technology group supporting Medicine Design at Pfizer located in Groton, CT (USA).



Dr. M. S. Lall

Manjinder S. Lall was born in London (UK) and grew up in Calgary (Canada). Manj received his B.Sc. degree from the University of Calgary in 1995. He completed his Ph.D. in organic chemistry at the University of Alberta (Canada) in 2000, under the supervision of Prof. John Vederas. In 2000, he moved to the USA to undertake postdoctoral studies at The Scripps Research Institute in La Jolla (USA), under the guidance of Prof. Dale Boger. Manj is now an Associate Research Fellow at Pfizer located in Groton, CT (USA), and has worked at Pfizer for 20 years in various lines including medicinal chemistry, process chemistry and ADME Sciences. He has held membership to the American Chemical Society for 26 years and serves as a committee member for the ACS Green Chemistry Institute Pharmaceutical Roundtable. His research interests consist of organic synthesis, medicinal chemistry, photochemistry, biocatalysis, and late-stage lead diversification.



Prof. P. Z. Musacchio

Patricia Z. Musacchio is originally from Sandy, Utah (USA) and is currently an Assistant Professor at Worcester Polytechnic Institute in central Massachusetts (USA). Her group specializes in developing new organic transformations that expedite the synthesis of valuable small molecules. She obtained her undergraduate degree from the University of Texas, Austin (USA) where she worked in the area of total synthesis with Prof. Stephen F. Martin. To pursue her passion in organic chemistry, Patti then went to Princeton University (USA) to study with Prof. David W. C. MacMillan for her graduate work where she developed a silyl radical-mediated cross-electrophile coupling with metallaphotoredox catalysis. Afterward, she joined Prof. F. Dean Toste's group at U.C. Berkeley (USA) for her postdoctoral studies.

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Remote Steric Control for Undirected *meta*-Selective C–H Activation of Arenes

Science **2022**, *375*, 658–663

According to Dr. Laurean Ilies, from the RIKEN Center for Sustainable Resource Science (Saitama, Japan), a major goal of modern synthetic chemistry is the creation of organic molecules in the most straightforward and efficient manner possible. “For this purpose, the use of a metal catalyst to directly introduce functionality into a simple or complex organic molecule (transition-metal-catalyzed C–H activation) has received much attention,” said Dr. Ilies. “However, a serious problem arises: even simple organic molecules have many C–H bonds, and steering the catalytic species towards the desired site is difficult. This problem is familiar even to students of introductory basic organic chemistry, who often encounter questions about *ortho/meta/para* selectivity in the reaction of arenes.” The research described in a recent article published in *Science* by the Ilies group provides a new solution to the selectivity problem. Inspired by the lock-and-key model of enzymatic catalysis, the authors designed a new catalytic system which creates a molecular pocket that fits an arene substrate only in a determined orientation, thus controlling the selectivity. They demonstrated this concept for the *meta*-selective functionalization of simple arenes such as alkylbenzenes, anilines, and phenols, and for the late-stage selective functionalization of complex drug molecules.

“It can be said that the seeds of this project were planted more than 10 years ago, when I was an assistant professor at the University of Tokyo in Japan (working with Prof. Eiichi

Nakamura), and Sobi Asako was a Ph.D. student in the same group (2009–2014),” said Dr. Ilies. He continued: “We were working on iron-catalyzed functionalization of C–H bonds,¹ and found that the key to controlling these reactions was the use of a rather complicated ‘directing group’: an organic group (in this case an amide bearing 8-aminoquinoline) that must be installed onto the substrate to coordinate the metal catalyst and facilitate reactivity and selectivity.”

In 2018, Dr. Ilies started a new research group at RIKEN, and one major idea was to get rid of the directing group and achieve a more general strategy for the selective functionalization of various organic molecules. But despite many attempts, success was elusive. “Dr. Asako was at that time assistant professor at Okayama University (Japan), working on a different chemistry (molybdenum catalysis and organosodium chemistry), but I convinced him to join the new team at RIKEN,” remarked Dr. Ilies. By chance, also in 2018 the late Prof. Daisuke Uemura, whom Dr. Ilies knew from his student days when they were playing tennis together, asked them to write a book on C–H activation. “While building up the laboratory there was plenty of time to think about the contents of the book, and to analyze in more depth the unsolved problems in C–H activation and the known strategies in the literature,” explained Dr. Ilies. He continued: “At this point I would like to acknowledge Dr. Takumi Yoshida, the first member of the Ilies team, who brought significant contributions both to the

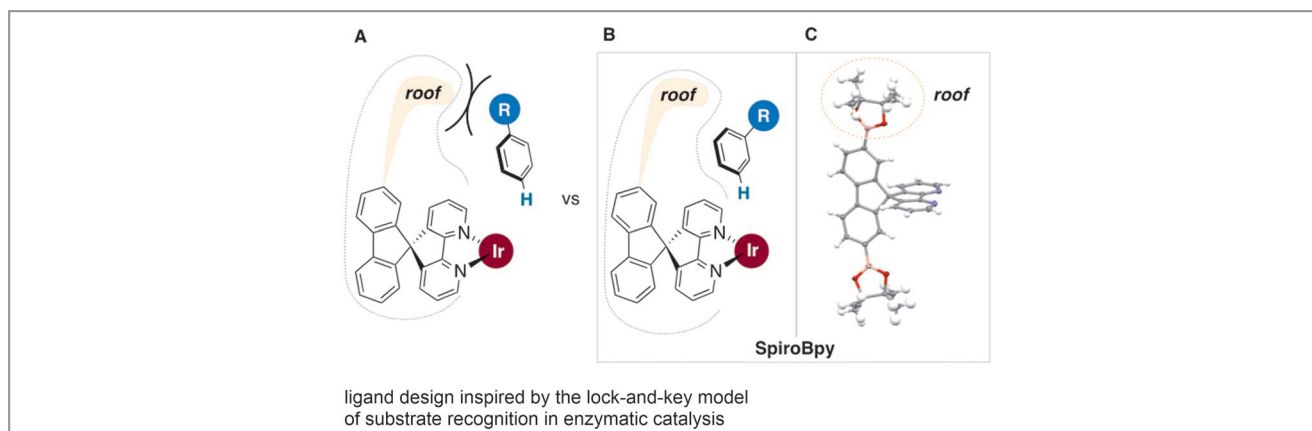
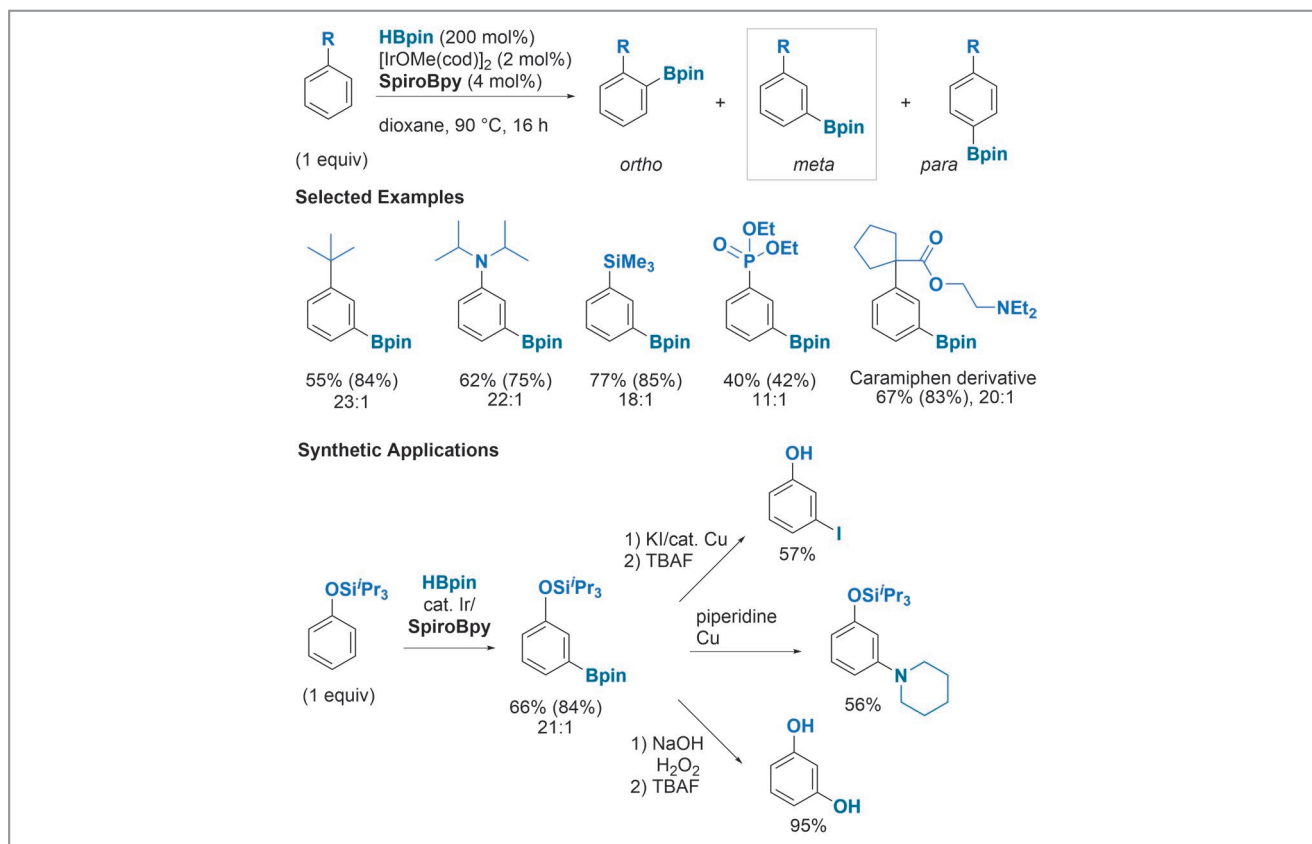


Figure 1 The design of the spirobipyridine (SpiroBpy) ligand

book, and to preliminary ligand designs and trials.” By 2019, the book was ready,² the laboratory was functional, and Dr. Asako was using his skills in molecular modeling and DFT calculation to come up with the first ligand design. Dr. Ramadoss joined the group and tried making this initial ligand, but the synthesis turned out to be quite challenging. Dr. Asako recalls: “After struggling for a while with little progress, a eureka moment came unexpectedly from my work on a different project, molecular modeling of some gigantic hollow molecules (resembling an enzyme). Thus, I designed the bifunctional spirobipyridine (SpiroBpy) ligand for remote steric control (Figure 1). The spirobipyridine has been used for materials science and its synthesis was known, but surprisingly it has never been used for catalysis despite the prevalence of 2,2'-bipyridine as a useful ligand. The idea was to attach a molecular ‘roof’ to the spirobipyridine and create a molecular pocket that allows the substrate to approach the catalytic center only in the *meta* orientation (Figure 1, B). Importantly, this ‘roof’ is placed remotely from the coordination site, rather than in its proximity

as with conventional bulky ligands, enabling both selectivity control and high reactivity.” Dr. Ramadoss made the first spirobipyridine ligand having a phenyl group as the ‘roof’, and initial studies showed that selective reaction of *tert*-butylbenzene through remote steric control is indeed possible. After spending a long time trying various organic groups as the ‘roof’, they found out that using a boronic ester group (Bpin) is the best choice (Figure 1, C), probably because this moiety gives a planar alignment in the transition state to effectively block the *para* approach of the substrate. Dr. Ilies commented: “Incidentally, at the same time, mechanistic studies suggested that *in situ* borylation of the ligand may be the key for achieving selectivity for a different project, the borylation of fluoroarenes.³ Finally, in 2021, Dr. Jin joined the group and helped to complete the project, notably the synthetic applications of the reaction for late-stage functionalization of drug molecules and the synthesis of phenol derivatives.”

The optimized reaction is shown in Scheme 1. Initial studies focused on alkylbenzenes, because these simple sub-



strates lack functionality capable of strong electronic interactions, and therefore their selective activation through other methods is difficult. “The strategy proved quite general, and important classes of molecules, such as anilines and phenols, could be selectively borylated at the meta position,” revealed Dr. Ilies, who continued: “It should be noted that such selectivity had not yet been achieved by any other method: electron-rich arenes react under electrophilic substitution conditions at the ortho and para positions, and functionalization of the meta position of phenol or aniline compounds is an undergraduate-level organic chemistry problem that requires multiple steps.”

According to the authors, this reaction has the potential to efficiently produce molecules of interest for medicinal chemistry, materials science, etc., and to create new, unexplored chemical space for drug discovery or the development of functional materials. “The remote steric control strategy can in principle be applied to other C–H activation reactions, and the ligand ‘roof’ can be designed to fit a substrate in various orientations to target different C–H bonds,” said Dr. Asako. Dr. Ilies concluded: “There are many more possibilities to be explored in addition to C–H activation: thinking about the prevalence of bipyridine in catalysis, spirobipyridine ligands are expected to be effective for various other catalytic reactions. The Ilies group is actively working on these developments at the moment.”

Mattias Farnok

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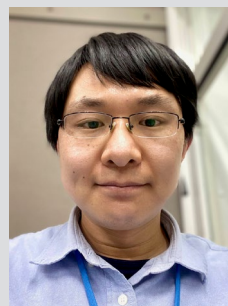
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About the authors



Dr. B. Ramadoss

Boobalan Ramadoss was born and grew up in Chengalpattu, India. After completing a BSc (2008) in chemistry from Rajeshwari Vedachalam Government Arts College, Chengalpattu (India), he obtained an MSc (2010) from Gurunanak College, Chennai (India). After that he received his MPhil (2013) in organic chemistry from the University of Madras (India) under the guidance of Dr. A. K. Mohanakrishnan. He received PhD (2018) for his work on C–H bond activation under the supervision of Prof. Chien-Hong Cheng from National Tsing Hua University, Hsinchu (Taiwan). In 2018 he was appointed as a postdoctoral researcher at RIKEN with Dr. Laurean Ilies’s team (Japan). His research interest mainly focuses on C–H functionalization reactions and C–C bond formation using metal catalysis.



Dr. Y. Jin

Yushu Jin was born in Nanjing (China) and grew up in Shanghai (China). He received his MSc in 2015 and PhD in 2018 from Kyushu University (Japan) under the supervision of Prof. Ryoichi Kuwano. In 2015, he was a visiting researcher in Prof. John F. Hartwig’s group at University of California, Berkeley (USA). In 2018, he joined Prof. Nobuharu Iwasawa’s group at Tokyo Institute of Technology (Japan) as a postdoctoral fellow. In 2021, he moved to Prof. Laurean Ilies’s group at RIKEN (Japan) as a postdoctoral researcher. His research has focused on transition-metal-catalyzed reactions, including asymmetric hydrogenation, CO₂ fixation, and C–H functionalization.



Dr. S. Asako

Sobi Asako was born in Yokohama (Japan). He obtained his PhD in 2014 from the University of Tokyo, Japan (advisor: Prof. Eiichi Nakamura), where he developed iron-catalyzed C–H functionalization reactions. In the same year, he was appointed assistant professor at Okayama University (Japan) in

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the group of Prof. Kazuhiko Takai, where he started exploring organosodium chemistry using sodium dispersion and molybdenum chemistry for the development of diazo-free reactions using unconventional stable precursors such as carbonyl compounds and cyclopropanes. In 2019, he moved to RIKEN Center for Sustainable Resource Science as a senior scientist to further pursue research along these lines. His research interests cover the exploration of sustainable organic synthesis and the design of conceptually new catalysts for challenging transformations.



Dr. L. Ilies

Laurean Ilies was born and grew up in Transylvania (Romania). He received his BSc (2004), MSc (2006) and PhD (2009) from the University of Tokyo, Japan (advisor: Prof. Eiichi Nakamura), working on the development of new synthetic methods for conjugated heterocyclic compounds and their applications in materials science. In 2009, Laurean was appointed assistant professor at the University of Tokyo (Japan), and in 2014 he was promoted to associate professor. During this time, he mainly investigated catalysis with Earth-abundant metals, especially iron, for C–H functionalization. In 2018, Laurean was appointed team leader at RIKEN, running a research group focused on the development of new synthetic methodologies for C–H functionalization, catalysis with Earth-abundant metals, and organosodium chemistry.

Enantioselective Cu(I)-Catalyzed Borylative Cyclization of Enone-Tethered Cyclohexadienones and Mechanistic Insights

Nat. Commun. **2022**, *13*, 854

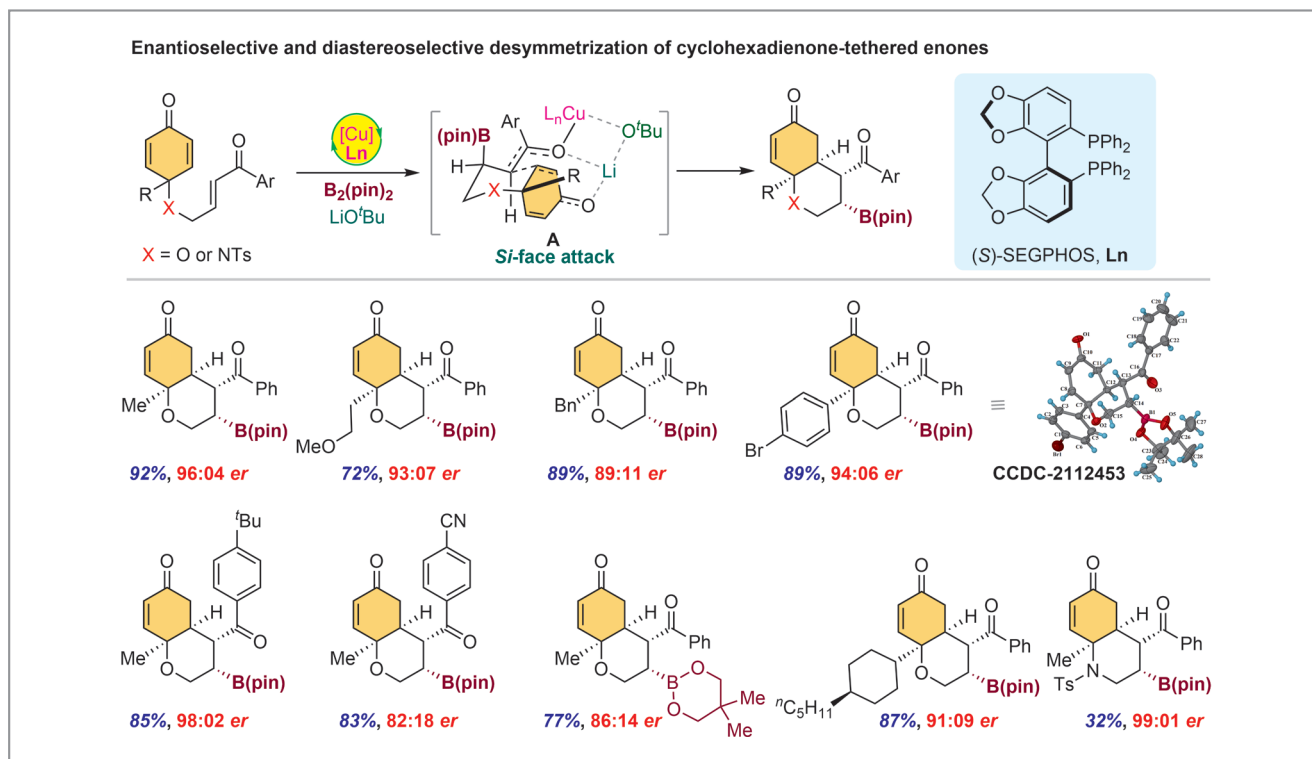
Dr. Rambabu Chegondi's research group at CSIR-Indian Institute of Chemical Technology (IICT) in Hyderabad (India) focuses on the development of new synthetic strategies with broad applications in organic synthesis. In particular, the design of new enantio- and diastereoselective desymmetrization methods for prochiral-1,3-diones, cyclohexa-2,5-dienones, and other C_2 -symmetric substrates to access complex molecules with multiple stereogenic centers are major research goals in the group.

Dr. Chegondi said: "Over the last decade, the enantioselective desymmetrization of prochiral cyclohexadienones has emerged as the most powerful and convenient strategy for the rapid construction of highly functionalized bicyclic frameworks in a single operation. We have also been developing enantioselective transition-metal-catalyzed cyclizations of enone-tethered cyclohexadienones." In 2018, the Chegondi research group disclosed the Rh-catalyzed reductive cyclization of C_2 -symmetric cyclohexadienones using simple (*R*)-BINAP as a chiral ligand to afford *cis*-hydrobenzofurans and *cis*-hydroindoles in high yields with up to >99% ee [*ACS Catal.* **2018**, *8*, 1440–1447]. In the following year, they disclosed a highly diastereoselective desymmetrization of enone-tethered cyclohexadienones via cascade annulation triggered by Lewis acid catalyzed Friedel–Crafts alkylation to construct bridged polycyclic indoles with highly divergent and challenging architecture [*ACS Catal.* **2019**, *9*, 10012–10019]. According to Dr. Chegondi, "Recently, copper has become a highly efficient and cost-effective catalyst for borylative addition to various functionalities using diborane reagents. Several reactions have been reported on tandem borylcupration of carbonyls, imines, alkenes, and alkynes, followed by trapping with external electrophiles. However, copper-catalyzed borylative cyclization of alkene-tethered electrophiles has been rarely studied."

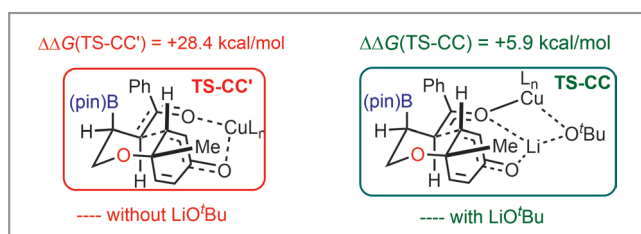
The work published in the title article started when Dr. Chegondi discussed with his students the possibility of an enantioselective Cu(I)-catalyzed β -borylation, followed by Michael addition on prochiral enone-tethered 2,5-cyclohexadienones to form *cis*-hydrobenzopyrans. Dr. Chegondi said: "The catalytic asymmetric borylation of conjugated carbonyls followed by stereoselective intramolecular cascade cyclizations with in situ generated chiral enolates is extremely rare."

Discussing the challenges of the enantioselective Cu(I)-catalyzed β -borylative cyclization of enone-tethered cyclohexadienones, he added: "However, the major challenges of this reaction are the chemoselective 1,4-addition of nucleophilic boron on three different enone functionalities within the starting substrate and the diastereoselective C–C bond formation."

Dr. Chegondi recalls that the group started this investigation with an effort to conduct an elaborate optimization to enable the enantioselective Cu(I)-catalyzed β -borylation/Michael addition on prochiral enone-tethered 2,5-cyclohexadienones. Eventually, the $Cu(MeCN)_4PF_6/(S)$ -SEGPLHOS catalytic system – using precisely 2.0 equiv of *t*-BuOLi at low temperature – proved to be the best conditions for this method to afford *cis*-hydrobenzopyran scaffolds in excellent stereoselectivity and yields (Scheme 1). "This enantioselective borylative cyclization is tolerated for electronically and sterically diverse substituents at the quaternary prochiral carbon center, as well as at the aryl ring of the tethered enone. This reaction is also compatible with *N*-Ts-linked cyclohexadienones, providing moderate yields and excellent enantioselectivity. The absolute stereochemistry of the four contiguous chiral centers was assigned by X-ray crystallography," said Dr. Chegondi, who added that to make the reaction even more useful, they sought to evaluate the one-pot sequential borylative cyclization/oxidation process. "The Cu-catalyzed borylation of enone under standard reaction conditions, followed by the sequential addition of the sodium perborate oxidizing agent in the same flask, afforded the β -alcohol product via the β -borylation intermediate," said Dr. Chegondi. "All reactions proceed with complete retention of stereochemistry from the C–B bond to the C–O bond in a highly enantioselective fashion, affording the corresponding products in similar yields and enantiomeric ratios." Additionally, Dr. Chegondi recalls that his group investigated the sequential borylative cyclization/oxidation in the absence of base, under standard conditions: "Interestingly, the transformation on the substrate produced the fused dioxane product via conjugate borylation/oxidation/oxa-Michael addition, instead of the C–Michael adduct, with moderate enantioselectivity. At that point, it was evident that the absence of base (*t*-BuOLi) had a significant effect on the enantioselectivity."



To gain further insights into the role of *t*-BuOLi via computational studies, Dr. Rambabu contacted his friend and colleague, Dr. Kumar Vanka. After a few rounds of discussion, Dr. Vanka and his student started investigating the role of the base in the reaction. Density Functional Theory (DFT) calculations revealed that the absence of base led to a pathway for which the activation barrier needed was 22.5 kcal/mol higher with respect to the C–C cyclization step (Figure 1). Dr. Vanka acknowledged that the reviewer's suggestions were helpful to unveil the complete mechanistic pathway, as indicated in the supporting information of the title paper.



Dr. Chegondi concluded: “We have developed the enantioselective Cu(I)-catalyzed β -borylation/Michael addition of prochiral enone-tethered 2,5-cyclohexadienones. The reaction proceeds via 1,4-borocupration at the enone, followed by *Si*-face attack of the chiral enolate on the cyclohexadienone ring, via a chair-like transition state. DFT calculations explained the requirement of the excess base, which leads to the formation of the more favorable chiral lithium enolate, that undergoes C–C bond formation in the key desymmetrization step. One-pot sequential borylation/cyclization/oxidation afforded the corresponding alcohols without affecting the yield and enantioselectivity. This asymmetric desymmetrization strategy has broad substrate scope and generates highly functionalized bicyclic enones bearing four contiguous stereocenters with excellent yield, enantioselectivity, and diastereoselectivity, thereby offering new prospects in the rapid synthesis of highly functionalized structural motifs. The synthetic utility of this reaction has been demonstrated with a gram-scale reaction and further chemoselective transformations on the product.”

Kumar Vanka

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Rambabu Chegondi received his M.Sc. degree from the University of Hyderabad (India) and completed his Ph.D. in organic chemistry from the Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad (India) under the supervision of Dr. S. Chandrasekhar. In 2009, he joined the group of Prof. Paul R. Hanson at The University of Kansas (USA) as a postdoctoral researcher. After returning from the USA, he started his independent research career at CSIR-IICT, Hyderabad. He is currently working as a Senior Scientist and his research interests focus on the development of new catalytic enantioselective desymmetrization methods and their application towards the synthesis of biologically important complex molecules.



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Sandip B. Jadhav completed his B.Sc. and M.Sc. degrees from Savitribai Phule Pune University, Maharashtra (India). After his Master's degree, he was awarded a UGC-JRF fellowship in 2016. He joined CSIR-IICT, Hyderabad as a Ph.D. student under the supervision of Dr. Rambabu Chegondi in 2017. His current research interests include enantioselective and diastereoselective desymmetrization of prochiral cyclohexadienones to access bicyclic scaffolds with contiguous stereocenters.



S. Maurya

Sundaram Maurya completed his B.Sc. Honors (Chemistry) from Acharya Narendra Dev College, University of Delhi, New Delhi (India). After completing M.Sc. in organic chemistry from Hindu College, University of Delhi, he joined CSIR-IICT (India) as a Ph.D. student under the supervision of Dr. Rambabu Chegondi in July 2019. His current research interest focuses on the enantioselective desymmetrization of 2,2-disubstituted cyclic 1,3-diones via remote functionalizations.



Dr. J. B. Nanubolu

Jagadeesh Babu Nanubolu received his integrated B.Sc. and M.Sc. degrees in chemistry from Sri Sathya Sai Institute of Higher Learning, Puttaparthi (India) in the years 1998–2003. Later, he joined the School of Chemistry, University of Hyderabad (India) for his doctoral program funded by UGC and obtained his Ph.D. under the supervision of Prof. Ashwini Nangia in 2008. He moved to University of Nottingham (UK) in 2009 for postdoctoral research funded by the EPSRC and worked with Dr. Jonathan Burley. He returned to India in 2011 and joined the CSIR-IICT. He is currently working as a Senior Scientist in the Center for X-ray Crystallography, Department of Analytical & Structural Chemistry, CSIR-IICT. His research areas of interest include crystal engineering and development of new solid forms of drugs, polymorphism, pharmaceutical co-crystallization and structure–property correlations.



Dr. K. Vanka

Kumar Vanka completed his undergraduate studies (B.Sc.) at the Indian Institute of Technology, Kharagpur (India), and then received his M.Sc. and Ph.D. degrees in computational chemistry under the guidance of Professor Tom Ziegler at the University of Calgary (Canada). This was followed by a postdoctoral stint at the University of Kansas (USA), under Professor Ward Thompson. He has been a scientist at the National Chemical Laboratory (CSIR-NCL), India, since December of 2007 and is currently a Principal Scientist there. His research interests include computational studies into reaction mechanisms relevant to organic, inorganic and organometallic chemistry, as well as investigations into the origins of life on earth and in the universe.

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interest focuses on interstellar chemistry as well as to provide computational insights to address important, fundamental questions about the origin of life.

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