

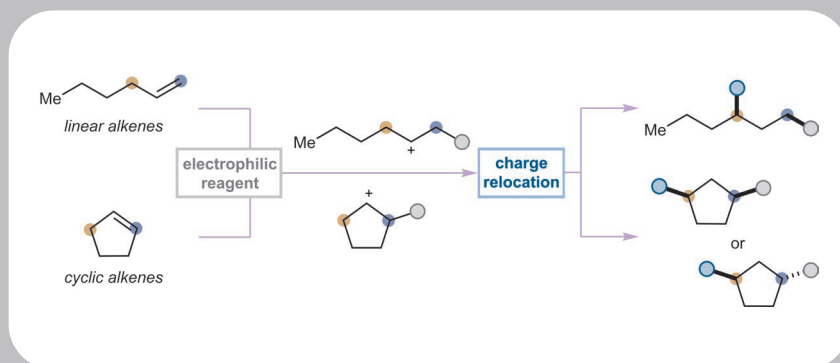
# Synform

People, Trends and Views in Chemical Synthesis

2024/06

## Stereodivergent 1,3-Difunctionalization of Alkenes by Charge Relocation

Highlighted article by B. R. Brutiú, G. Iannelli, M. Riomet, D. Kaiser, N. Maulide



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## Dear Readers,

This June issue of SYNFORM is kicked off by a Literature Coverage article introducing a ground-breaking contribution by the group of N. Maulide (Austria) who developed a versatile and elegant strategy to achieve the stereodivergent 1,3-difunctionalization of alkenes by taking advantage of charge relocation. The following article is a Young Career Focus interview with the 2024 Thieme Chemistry Journal Awardee Z. Zhang (USA) who discusses his personal and research interests, especially catalysis in organic chemistry. The next Literature Coverage article presents a work recently published in *Science* by the group of M. Powner (UK) presenting a compelling hypothesis on how pantetheine – a small molecule essential to all known life – could have been prebiotically and chemoselectively synthesized in water. The issue is wrapped up by a third Literature Coverage article covering the novel asymmetric synthesis of important S(IV) and S(VI) sulfur compounds, such as sulfoximines, sulfonimidoyl fluorides and sulfonimidamides, recently developed by the group of J. M. Lopchuk (USA).

Enjoy your reading!



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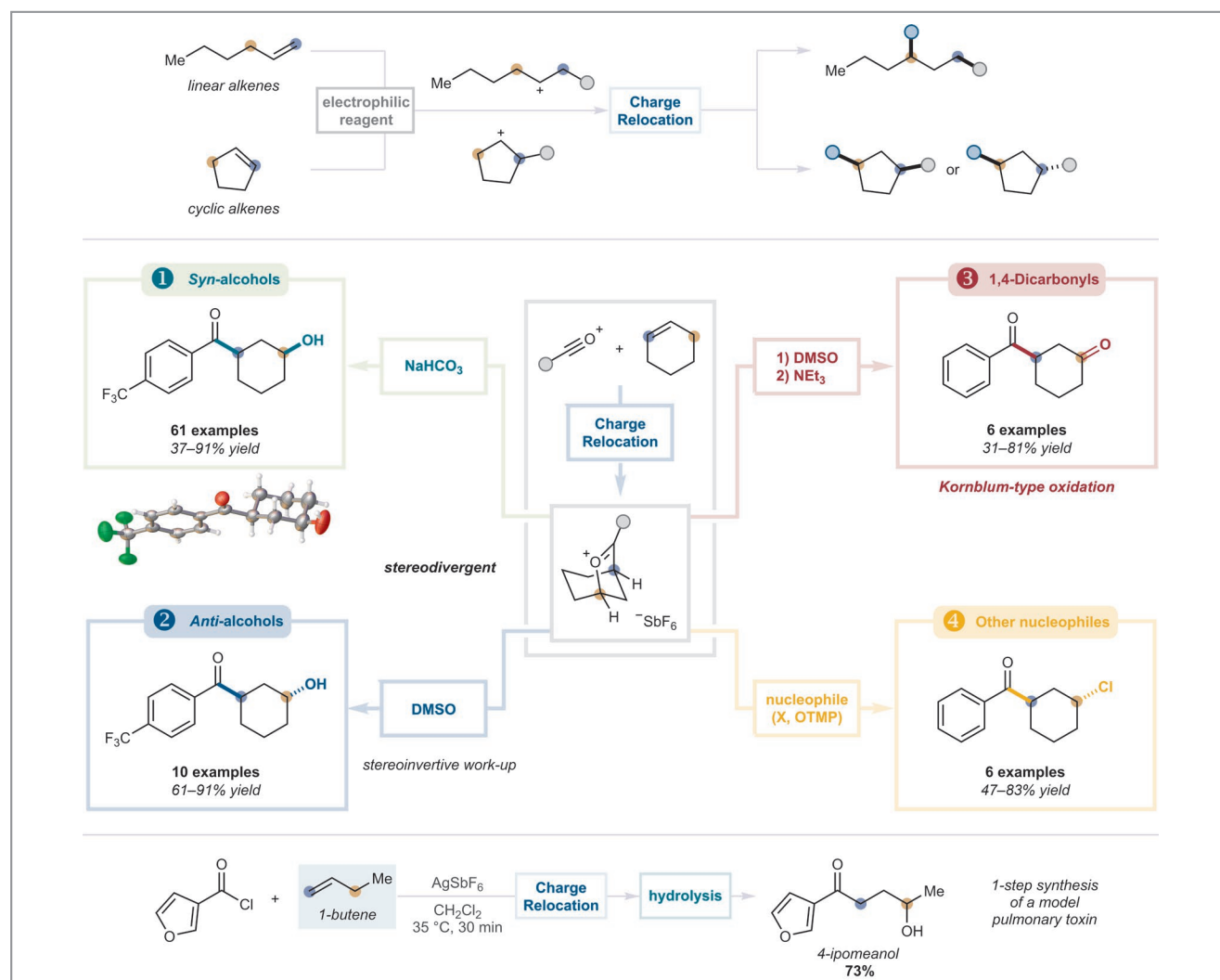
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# Stereodivergent 1,3-Difunctionalization of Alkenes by Charge Relocation

*Nature* **2024**, *626*, 92–97

Alkenes are one of the most basic, crucial and ubiquitous functional groups in organic synthesis and, as such, have long been of immense commercial importance, finding applications in, among other things, petrochemistry and the production of pharmaceuticals and fragrances. Among the many reaction modes accessible to alkenes (e.g., cycloaddition, oxidation, polymerization, metathesis, and others), alkene difunctional-

ization is arguably the most intuitive paradigm, serving as a textbook example of alkene reactivity in organic chemistry curricula around the world. Within the realm of alkene difunctionalization, 1,2-addition across the double bond and allylic functionalization are the most widely encountered reaction classes. In contrast, difunctionalization at positions remote from one another has been reported considerably less



**Scheme 1** Stereodivergent 1,3-difunctionalization of alkenes by charge relocation

frequently, and typically relies on carefully crafted substrates with directing groups and/or stabilizing features, all of which control the final site of bond formation.

“While an extensive body of work on remote functionalization using transition-metal catalysis can be found in the literature, such methods rely on a directing group that can stabilize the reactive intermediate in order to prevent common side-reactions such as  $\beta$ -hydride elimination,” said Professor Nuno Maulide, from the University of Vienna (Austria). “Our initial idea was born out of a consideration of the limitations of classical methods for alkene transformation. While the majority of known reactions only allow functionalization on the two alkene carbon atoms – or the allylic position – we sought to break this paradigm using the reactivity inherent to carbocationic species generated from the addition of electrophiles to alkenes.”

“Firstly, one cannot speak about electrophilic additions to alkenes without mentioning the extensive body of research on Friedel–Crafts-type reactions of alkenes,” continued Professor Maulide. “While Friedel–Crafts-type reactions have indeed been known to lead to a degree of functionalization at remote positions, a lack of regiocontrol for unbiased substrates invariably leads to a plethora of products and intractable mixtures – from elimination to mixtures of 1,2 and 1,3-functionalization products, resulting from unspecific addition of nucleophiles present in the reaction mixture.”

Aiming to funnel reactivity towards a single product, Professor Maulide and co-workers turned to a non-coordinating and non-basic counter anion, hexafluoroantimonate ( $\text{SbF}_6^-$ ). “Generating an electrophile in the presence of this anion led to a reagent that, after addition of the alkene, not only allows the resulting carbocation to persist, but enabled uninterrupted equilibration,” explained Professor Maulide. “By choosing an acylium ion as the electrophile and hexafluoroantimonate as the counteranion, we were able to generate a scenario in which the resulting positive charge relocates, through a series of hydride shifts, to a defined position, at which it is intercepted by the carbonyl oxygen, forming an oxocarbenium ion – our key intermediate.”

Professor Maulide outlined: “In exploring the possibilities for the synthesis of appealing products from the oxocarbenium intermediate, we relied on our experience with high-energy reactive intermediates, many of which we have similarly generated under mild conditions. Fortunately, we were able to identify a variety of complementary conditions that could be productively applied. While simple aqueous work-up leads to the formation of *syn*-configured 1,3-keto alcohols, we found dimethyl sulfoxide (DMSO) – in combination with tetrabutylammonium bromide (TBAB) – to be capable of affording the

isomeric *anti*-configured keto alcohols. Replacing TBAB with triethylamine, we gratifyingly found Kornblum-type oxidation to take place, directly forming 1,4-dicarbonyls (Scheme 1).”

“The appeal of this methodology lies not only in its conceptual beauty and simplicity, but also in the synthetic possibilities it opens up,” enthused Professor Maulide. He continued: “While established methods for alkene transformation require additional directing groups to enable selective reactions, our method works even with one of the simplest alkenes, 1-butene – a compound that was beyond the reach of all previous methods.”

Professor Maulide concluded: “Moving forward, we will expand the applications of feasible electrophilic reagents for the functionalization of alkenes as well as further investigate the bioactivity of 4-ipomeanol and the library of analogues we produced in a biological context.”



## About the authors



B. R. Brutiu

**Bogdan R. Brutiu** is from Arad (Romania) and earned his B.Sc. and M.Sc. degrees in chemistry from the University of Vienna (Austria). He is currently working as a final-year Ph.D. student in the group of Professor Maulide (University of Vienna). His research focus is on the chemistry of destabilized carbocations, C–C coupling reactions mediated by hydride transfer, isothiuronium salt reagents, and hypervalent iodine-mediated remote functionalization reactions. Also, he is a huge LEGO fan. He received the DOC Fellowship (Doctoral Fellowship Programme of the Austrian Academy of Sciences) in 2021.



Dr. G. Iannelli

**Giulia Iannelli** received her M.Sc. in pharmaceutical chemistry and technology in 2018 and her Ph.D. in 2022 from the University of Salerno (Italy) under the guidance of Professor Gianluca Sbardella and Professor Sabrina Castellano. Her doctoral work focused on the design, synthesis and biological evaluation of small-molecule modulators of epigenetic proteins. Currently, Giulia is a post-doctoral researcher in the laboratory of Professor Nuno Maulide in the University of Vienna (Austria), where she is working on the development of innovative synthetic transformations and the synthesis of complex structures with pharmaceutical relevance.



Dr. M. Riomet

**Margaux Riomet** studied chemistry at École Nationale Supérieure de Chimie de Paris (France) where she completed her Engineer Degree and M.Sc. degree in 2015 in partnership with Université Pierre et Marie Curie. In 2018, she obtained her Ph.D. under the supervision of Dr. Frédéric Taran at CEA Saclay (France). Her work was dedicated to the chemistry of iminosydones and their application in biology. After graduating, she joined the group of Professor Nuno Maulide at the University of Vienna (Austria) where she worked on the reactivity of short-lived carbocationic species. She then joined the team of Pro-

fessor Thomas Poisson and Professor Philippe Jubault in Rouen (France), focusing her research on photo-mediated transformations.



Dr. D. Kaiser

**Daniel Kaiser** completed his M.Sc. at the University of Vienna (Austria) in 2013 and received his Ph.D. in 2018, completing his studies under the supervision of Professor Nuno Maulide (University of Vienna). After a post-doctoral stay with Professor Varinder K. Aggarwal at the University of Bristol (UK), he returned to Vienna in 2020 to assume a position as senior scientist in the Maulide group. His current research focusses on the chemistry of destabilized carbocations and related high-energy intermediates.



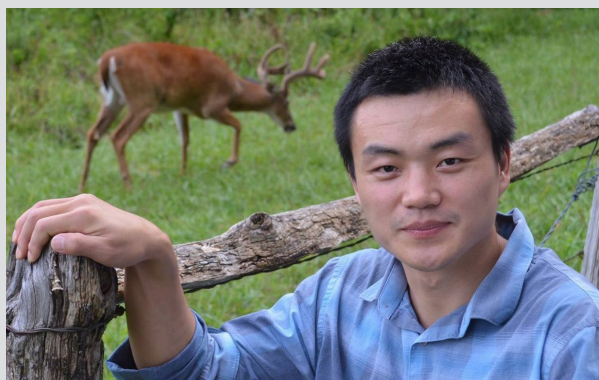
Professor N. Maulide

**Nuno Maulide** studied at the Instituto Superior Técnico (Portugal) and obtained his M.Sc. degree from the École Polytechnique (France). Following Ph.D. studies (Professor István Markó) at the Université catholique de Louvain (Belgium) in 2007, he moved to Professor Barry Trost's group (Stanford University, USA), before becoming Max-Planck Research Group Leader (MPI für Kohlenforschung, Germany) in 2009. In 2013, he moved to the University of Vienna (Austria), where he is Full Professor of Organic Synthesis and Adjunct PI at the Research Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences. His research involves unconventional reactivity in organic chemistry and the development of small-molecule tools for biochemical and medicinal applications.

## Young Career Focus: Professor Zuxiao Zhang (University of Hawai'i at Mānoa, 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 Zuxiao Zhang (University of Hawai'i at Mānoa, USA).

### Biographical Sketch



Prof. Z. Zhang

**Zuxiao Zhang** earned his Master of Science in organic chemistry from the Shanghai Institute of Organic Chemistry (P. R. of China), under the mentorship of Professor Guosheng Liu. Subsequently, he pursued his Ph.D. at the University of Florida, Gainesville, FL (USA), under the guidance of Professor William R. Dolbier Jr. In 2017, Zuxiao started a new chapter in his career as a postdoctoral research associate in the Nagib group at the Ohio State University, Columbus, OH (USA).

In 2021, Zuxiao returned to his homeland, joining the faculty at Zhejiang Normal University, Jinhua (P. R. of China) to start his independent research journey. Then he transitioned to the Chemistry Department at the University of Hawai'i at Mānoa (USA) in September 2023.

Zuxiao's research vision is anchored in three key directions: fluorine chemistry, radical chemistry, and asymmetric catalysis. His overarching objective is to develop innovative catalytic systems that harness both radical and polar reactivity, thereby enabling the selective functionalization of inert chemical bonds through multicomponent reactions. This endeavor not only facilitates the efficient synthesis of bio-relevant molecules, but also offers a robust platform for the late-stage functionalization of complex drug molecules.

### INTERVIEW

**SYNFORM** Which field of organic chemistry are you interested in the most and why?

**Prof. Z. Zhang** I'm most passionate about catalysis in organic chemistry. Catalysis holds a special place in my heart because it has the remarkable ability to transform seemingly impossible reactions into reality, and even convert waste into valuable products. Among the various forms of catalysis, I find photocatalysis particularly fascinating. It harnesses light as an external energy source, unlocking a whole new realm of possibilities for organic transformations. The idea of utilizing photons to drive chemical reactions is not only scientifically intriguing but also holds immense potential for sustainable and green chemistry practices. So, catalysis, especially photocatalysis, captivates me with its power to make transformative changes in organic synthesis while contributing to environmental sustainability.

**SYNFORM** Following that, what is the focus of your current research activity?

**Prof. Z. Zhang** My current research activity primarily revolves around the selective functionalization of inner chemical bonds, such as C–H, C–X, and C–O bonds. We're particularly interested in applying this selective functionalization approach within multicomponent reactions. By doing so, we aim to efficiently assemble complex molecules from simple starting materials. Additionally, we're exploring the application of these methodologies in the late-stage functionalization of drugs. This entails introducing specific functional groups into drug molecules at advanced stages of synthesis, which can significantly enhance their properties and efficacy. Overall, our focus lies in developing innovative strategies for targeted bond activation and functionalization to streamline the synthesis of complex molecules and facilitate drug development processes.



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

**Prof. Z. Zhang** In my perspective, organic chemistry maintains its pivotal role as the central science in modern times. The significance of organic chemistry stems from its profound impact on various aspects of life. Firstly, organic chemistry plays a crucial role in drug discovery and development. By harnessing the principles of organic synthesis, scientists can synthesize novel pharmaceutical compounds and optimize the efficiency of existing drugs, ultimately advancing healthcare and improving quality of life.

Furthermore, organic chemistry offers promising solutions to environmental challenges. Through innovative research and sustainable practices, organic chemists are devising methods to mitigate pollution, reduce waste, and develop eco-friendly alternatives to traditional chemical processes. By embracing green chemistry principles, organic chemists are pioneering pathways towards a more sustainable and environmentally conscious future.

In essence, the prospects of organic chemistry remain bright and multifaceted. Its applications extend far beyond the laboratory, impacting areas ranging from healthcare to environmental protection. As we continue to delve deeper into the intricacies of organic molecules and refine our synthetic methodologies, organic chemistry will undoubtedly continue to drive innovation and shape the world we live in.

**SYNFORM** Which difficulties are there for young upcoming chemists in your field? Do you have any tips?

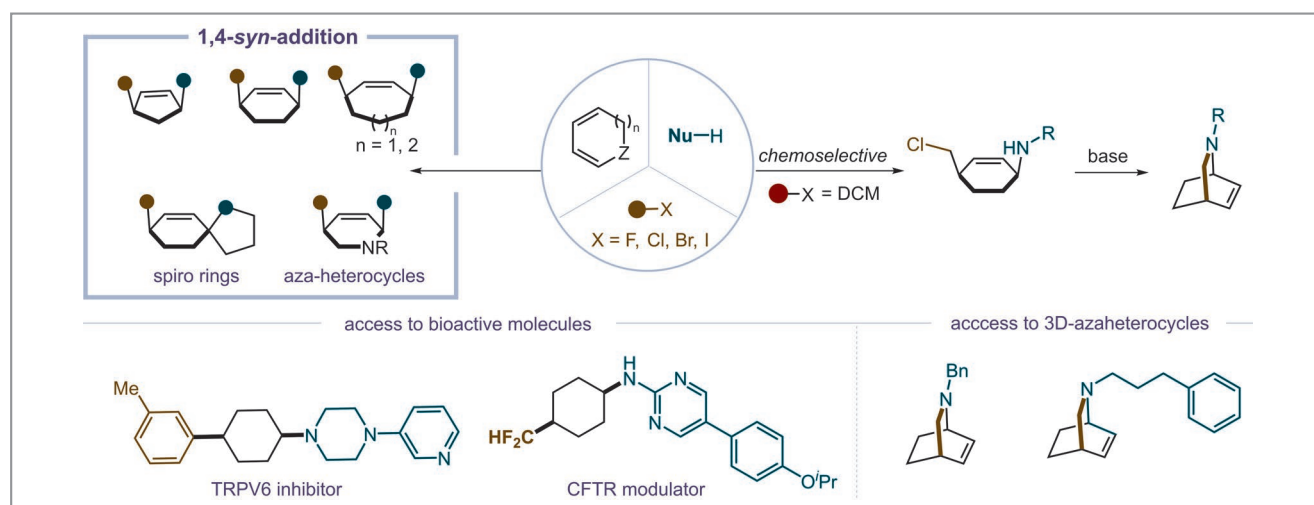
**Prof. Z. Zhang** In my field, young upcoming chemists often encounter challenges related to securing funding and grants to support their research endeavors. Additionally, identifying the specific problems they wish to solve within the vast landscape of chemistry can be daunting. However, there are several tips that can help navigate these difficulties.

Firstly, immersing oneself in the existing literature is crucial. By thoroughly digging into the literature within their area of interest, young chemists can gain valuable insights into current research trends, ongoing challenges, and potential gaps in knowledge. This knowledge serves as a foundation for identifying promising research directions.

Once a problem or area of focus has been chosen, perseverance is key. Research in chemistry, particularly when addressing complex problems, often involves trial and error. Young chemists should be prepared to encounter setbacks and obstacles along the way. However, maintaining persistence and resilience in the face of challenges is essential. Every failure provides an opportunity to learn and refine one's approach.

Furthermore, networking with peers, mentors, and established researchers can provide valuable support and guidance. Seeking out opportunities for collaboration and mentorship can help young chemists navigate the intricacies of their field and gain access to resources and funding opportunities.

In summary, while young chemists may face difficulties in securing funding and defining their research focus, dedication, perseverance, and a proactive approach to learning and networking can help overcome these challenges and pave the way for success in the field of chemistry.



**Scheme 1** Synthesis of 1,4-*cis*-disubstituted rings for the construction of complex bioactive molecules

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

**Prof. Z. Zhang** Our most significant achievement is the development of a robust protocol for 1,4-*syn*-addition of cyclic dienes, achieved through a hybrid palladium-catalyzed multicomponent reaction. Our mechanistic studies uncovered a crucial stepwise *anti*-alkene migration insertion, leading to exclusive formation of 1,4-*syn*-addition products (Scheme 1). This innovative approach allows for the efficient synthesis of diverse 1,4-*cis*-disubstituted ring systems, facilitating the construction of complex bioactive molecules. With its modularity and mild reaction conditions, this protocol holds great promise for organic synthesis and drug discovery.





# Prebiotically Plausible Chemoselective Pantetheine Synthesis in Water

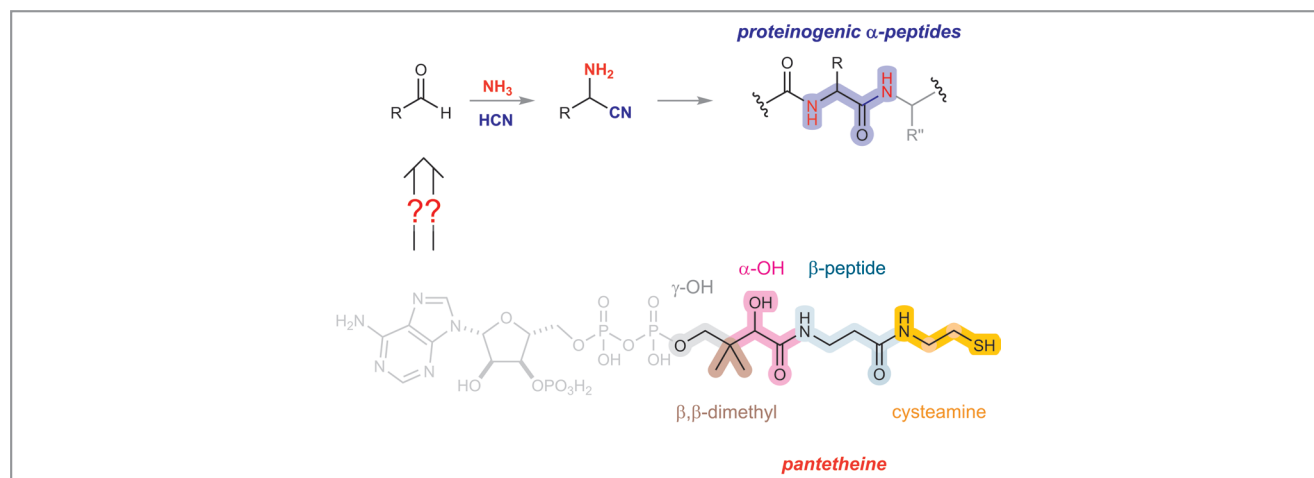
*Science* **2024**, *383*, 911–918

Pantetheine is the functional unit within coenzyme A (CoA). It is essential to all known life and, for example, is required in autotrophic carbon fixation pathways, energy metabolism, the citric acid cycle, and protein modification, as well as fatty acid, polyketide, isoprenoid, hemoglobin, cytochrome, and peptide biosyntheses. Therefore, not surprisingly, pantetheine is central to many different origins-of-life scenarios and may hold the key to uniting several 'leading' conceptual models for the origins of life, including the 'RNA-', the 'Peptide-', and the 'Thioester-World' hypotheses. But how and why pantetheine would emerge from prebiotic chemistry was a mystery, which was recently investigated by Professor Matthew Powner's group at University College London (UK). "The synthesis of pantetheine must be an important step toward understanding the origins and evolution of life, particularly the relationship between pantetheine, a structurally unique  $\beta$ -peptide, and proteinogenic  $\alpha$ -peptides (Scheme 1)," said Professor Powner to SYNFORM. "How and why both structures arose from the same chemical system must hold key clues to the underlying chemical selectivity required to build life, and so provides a unique opportunity to interrogate prebiotic chemistry."

The structural complexity of pantetheine has led some scientists to assume that 'simpler' thiols must have fulfilled pantetheine's essential role on the early Earth. However, pantetheine is strictly conserved across all domains of life, and the

(supposed) difficulty of pantetheine synthesis had not been tested. This work by Professor Powner's group demonstrates that pantetheine can be facily and selectively synthesized in high yield from hydrogen cyanide and its prebiotic products. Professor Powner emphasized: "Importantly, the pathway we outlined provides a chemical rationale for every element of pantetheine's unusual structure. The pathway reported not only begins from proteinogenic amino acid precursors, but also undergoes spontaneous differentiation from amino acid synthesis, such that pantetheine and amino acid precursors can both be selectively synthesized in the same multicomponent reaction. Moreover, our pathway blocks the synthesis of non-natural versions (i.e.,  $\alpha$ -homologues) of pantetheine."

The inspiration to seek to elucidate the chemical origins of pantetheine, biology's universal thiol cofactor, originated in the group's previous work. "We had demonstrated selective high-yielding prebiotic  $\alpha$ -peptide synthesis by employing prebiotic  $\alpha$ -aminonitriles, rather than amino acids as peptide building blocks (*Nature* **2019**, *571*, 546–549; *J. Am. Chem. Soc.* **2023**, *145*, 3121–3130)," explained Professor Powner, who continued: "We then went on to demonstrate that thiols, including CoA and pantetheine, catalyzed peptide–nitrile ligation in neutral water (*Science* **2020**, *370*, 865–869; *J. Am. Chem. Soc.* **2022**, *144*, 10151–10155). Our prior work demonstrated that nitriles are predisposed to yield proteino-



**Scheme 1** Uniting prebiotic peptide and cofactor syntheses to uncover the chemical roots of biological peptides

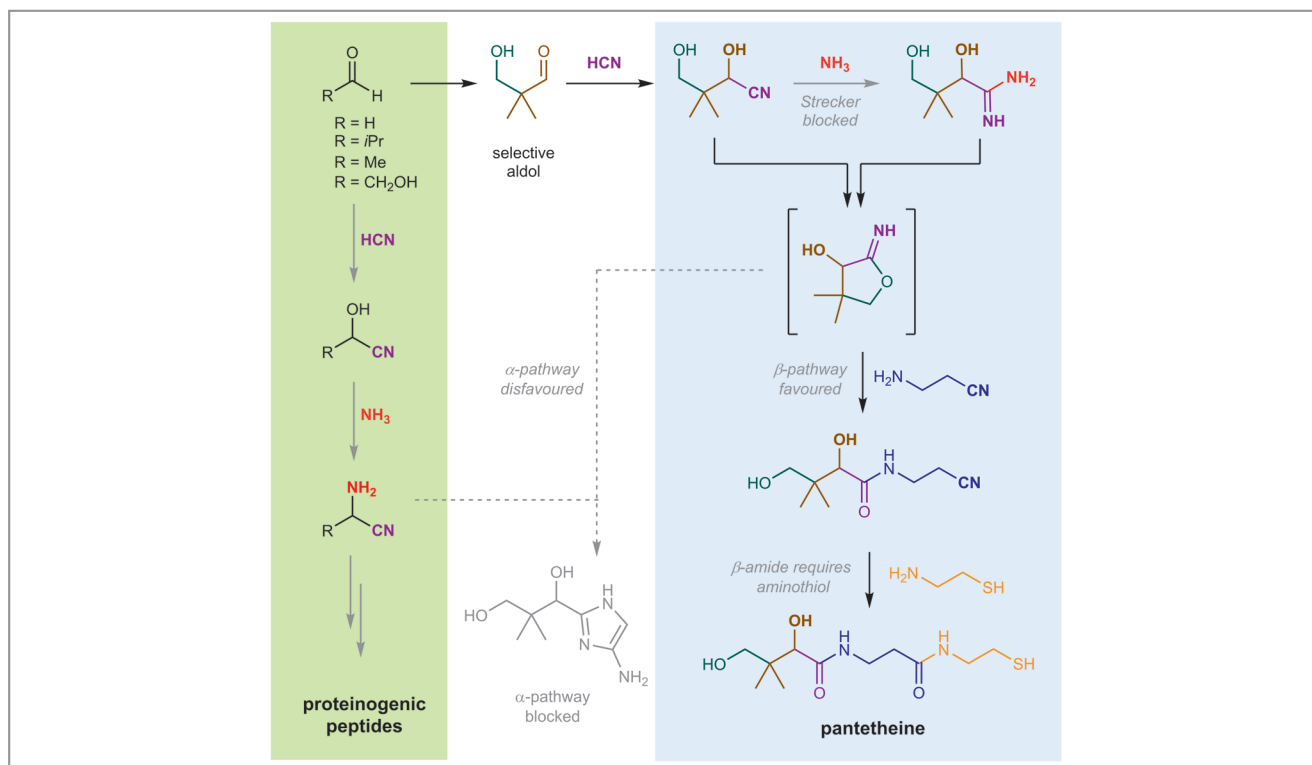
genic  $\alpha$ -peptides in water. However, we reasoned that if nitrile chemistry underpins the origins of biological peptides, then it must account for pantetheine, as well as proteinogenic peptides. In this work, we show that nitrile chemistry holds the key, through alternate mechanisms and reaction pathways to those that furnish  $\alpha$ -peptides, to unlocking selective pantetheine synthesis. The unification of predisposed  $\alpha$ -peptide and pantetheine syntheses further supports the thesis that the origins of biological peptides are underpinned by nitrile chemistry.”

The paper describes the first high-yielding, non-enzymatic syntheses of pantetheine in water, providing the first chemical rationale for its pantoate and  $\beta$ -alanine motifs (Scheme 2). Professor Powner said: “We demonstrate that  $pK_{\text{aH}}$  directed selective aminonitrile reactivity favours the canonical structure of pantetheine. Nitrile reactivity is essential for this selectivity, and remarkably, aminonitriles reverse the selectivity observed with amino acids. Therefore, whilst amino acids select against the synthesis of pantetheine, aminonitriles are highly selective for its synthesis.”

A selective (neutral pH) crossed-aldol reaction is shown to yield pantoic acid nitrile from prebiotic glycine and valine aldehyde precursors. Professor Powner told SYNFORM: “This

is a remarkably selective aldol reaction; isobutyraldehyde is observed to undergo selective aldol reaction with formaldehyde within a mixture of enolisable aldehydes. This is important for understanding the selective origins of pantoate and pantetheine. This hydroxymethylation establishes the control and intramolecular catalysis required to unleash the synthesis of pantetheine, providing a chemical rationale for the (biologically unusual  $\beta,\beta$ -gem-dimethyl) quaternary carbon of pantoic acid, as well as furnishing its  $\gamma$ -hydroxyl moiety. Installing this  $\gamma$ -hydroxyl is the key to the rest of the unfolding synthesis and has a domino effect on the subsequent reactions in the pathway to pantetheine.”

“No external activating agents are required for our synthesis of pantetheine, the latent activation of cyanide is employed for all amide bond formations,” remarked Professor Powner. He continued: “Moreover, pantoil-amide formation requires no external catalysis; the ideally poised  $\gamma$ -hydroxyl moiety of the pantoil structure is an intramolecular nucleophilic catalyst. This catalytic  $\gamma$ -hydroxyl moiety blocks aminonitrile formation, and therefore provides a highly selective chemical mechanism to differentiate proteinogenic aminonitriles from pantoic acid derivatives. This mechanism endows the iminolactone intermediate with a sufficient lifetime and



**Scheme 2** Divergent and chemoselective proteinogenic peptide and pantetheine syntheses by nitrile-mediated pathways in water

reactivity (even at extremely low concentration) to be intercepted by  $\beta$ -alanine nitrile, and chemo-specifically blocks synthesis of pantetheine analogues forming from (proteinogenic)  $\alpha$ -aminonitriles. Therefore, our synthesis is protecting-group-free, activating-agent-free, effective in water, and demonstrates a novel mechanism for peptide bond formation (and transamination) via intramolecular catalysis." According to Professor Powner, this has important implications for the widely voiced, but – as the authors argue within the manuscript – highly misguided opinion that water is detrimental to the synthesis of amides and other biological structures. This work highlights the importance of water as an essential element of prebiotic chemistry – the authors demonstrate that there is no ‘water paradox’, and that there is no problem associated with the synthesis of biological molecules in water. “These ‘problems’ appear to arise from the application of implausible, high-energy activating agents (e.g., EDC) to try to solve problems associated with the origins of life,” explained Professor Powner. He continued: “It is important to recognize the value of water, and in our work, we have developed bespoke chemical pathways and mechanisms appropriate to addressing synthesis in water and found these selectively deliver biological molecules.” Professor Powner concluded: “Our recent study demonstrates the development of new nitrile reactivity to solve a long-standing problem for the origins of life, the chemical synthesis of pantetheine.”

### About the authors



Dr. J. Fairchild

**Jasper Fairchild** grew up in the city of Plymouth in the south west of the UK. He received his MSci University of Nottingham (UK) in 2015, and then worked for Oxford Analytical Ltd for a short period. He decided to resume his studies at University College London (UCL, UK) under Professor James Anderson, synthesising luciferin analogues and earning an MRes in 2018. He remained at UCL to study prebiotically plausible chemoselective pantetheine syntheses and the photochemistry of thioacids under Professor Matthew W. Powner. He completed his PhD in 2024 and has stayed at UCL as an experimental officer.



Dr. S. Islam

**Saidul Islam** obtained his first-class MChem (chemistry with medicinal chemistry) at the University of Manchester (UK) in 2007. He stayed in Manchester to pursue doctoral studies in prebiotic chemistry with Professor John Sutherland FRS (University of Manchester, 2011), before moving to Queen Mary University of London (UK) as a research associate in organometallic chemistry and catalysis, working with Professor Igor Larrosa. Saidul then joined University College London (UK) as a postdoctoral research associate in organic chemistry, working with Professor Matthew Powner. He was appointed Lecturer at the Department of Chemistry, King's College London (UK) in 2022, where he is currently investigating the chemical origins of life on early Earth.



Dr. J. Singh

**Jyoti Singh** was born in Delhi, India. She completed her Bachelor's degree in chemistry from Ramjas College, Delhi University (India) in 2009, then obtained a dual Master's degree from the University of Delhi, India, and the Japan Advanced Institute of Science and Technology in 2015. She completed her PhD under the supervision of Prof. Henning J. Jessen at the University of Freiburg (Germany) in

2020. She is currently working as a postdoctoral research associate at University College London (UK) with Professor Matthew W. Powner. Her research focuses on investigating the origin of life question by exploiting the reactivity of nitriles with thiols.



*Assoc. Prof. D-K. Bučar*

**Dejan-Krešimir Bučar** obtained a BSc in chemistry under the supervision of Dr. Ernest Mestrovic at the University of Zagreb (Croatia) in 2004, and a PhD in chemistry from the University of Iowa (USA) in 2010, under the guidance of Prof. Leonard R. MacGillivray. He then started his independent research career as a Royal Society Newton International Fellow at the University of Cambridge (UK) in 2011, where he was kindly hosted

by Prof. William Jones. While in Cambridge, he was also a Bye-Fellow at Sidney Sussex College (UK). He joined the Department of Chemistry at University College London (UK) in 2013, as UCL Excellence Fellow and lecturer. His research interests mainly evolve around molecular cocrystals and their applications.



*Prof. M. W. Powner*

**Matthew W. Powner** obtained a Master's degree in chemistry at the University of Manchester (UK) in 2005, and completed a medicinal chemistry internship at AstraZeneca, Alderley Park. He then gained a PhD in organic chemistry, working with Prof. John Sutherland, at Manchester in 2009. He continued his research as an EPSRC Doctoral Prize postdoctoral fellow in Manchester, before being awarded a Harvard Research Fellowship to work with Nobel laureate Prof. Jack Szostak at Massachusetts General Hospital (USA). He joined University College London (UK) in 2011, where he is currently Professor of Organic Chemistry. He has been awarded various prizes and fellowships, including the RSC Harrison-Meldola Memorial Prize (2019) and was a Blavatnik Award Honoree (2021). His research interests include the chemical origins of life, peptides, and nucleic acids.

# Asymmetric Synthesis of Sulfoximines, Sulfonylimidoyl Fluorides and Sulfonylimidamides Enabled by an Enantiopure Bifunctional S(VI) Reagent

*Nat. Chem.* **2024**, *16*, 183–192

Sulfur in its various oxidation states represents a key element in a range of important chemophores in the natural and industrial worlds. According to Professor Justin M. Lopchuk at the H. Lee Moffitt Cancer Center and Research Institute (USA), the higher-order S(IV) and S(VI) functionalities – such as sulfoxides, sulfones and sulfonamides – have historically dominated the sulfur-containing pharmaceutical, agrochemical, and materials landscape. “Despite the successful applications of the previously mentioned S(IV) and S(VI) groups, other less common sulfur-containing sulfonylimidoyl functionalities exist that have been, until recently, largely overlooked in the realm of chemical discovery,” said Professor Lopchuk to SYNFORM, adding: “Sulfoximines, sulfonylimidamides, and sulfonylimidoyl fluorides (Figure 1) are aza-derivatives of sulfonyls and are among the underrepresented S(VI) groups – each providing unique structural and physicochemical properties to be exploited for a variety of applications. As drug discovery programs begin to seek alternative chemical spaces with increasing three-dimensionality and complexity, sulfonylimidoyl groups offering additional spatial vectors and a stereogenic S-center will become more attractive if synthetic methodologies permit their use.”

Drawing inspiration from highly efficient SuFEx chemistry and modular sulfonyl reagents, Professor Lopchuk's group sought to develop a chiral bifunctional reagent platform to address the asymmetric control of the sulfur stereocenter in sulfonylimidoyl groups. Professor Lopchuk said: “During the discovery phase, we prioritized synthetic practicality, feasibility, and bench stability of the reagent. Ideally, the source of chirality (both enantiomers) would be either available directly from the commercial chiral pool or derived from it with minimal chemical modifications. The widely available (*R*)- and (*S*)-*tert*-butyl sulfonylamides (<\$1/g) were chosen as the starting building blocks based on factors such as financial feasibility, the stereogenic stability of *tert*-butyl sulfonyls, and known activation methods of *tert*-butyl S(VI) derivatives for further S-functionalization. We initially believed reagent stability would be an additional feature of the sulfonylimidoyl fluoride SuFEx design; however, the choice of the *N*-protecting group directly correlated to and had an impact on the stability. Elec-

tron-withdrawing protecting groups (Boc, Bz, Piv) provided increased stability, while introducing an additional electrophilic center. Selective addition to sulfur with carbon nucleophiles turned out to be synthetically challenging.”

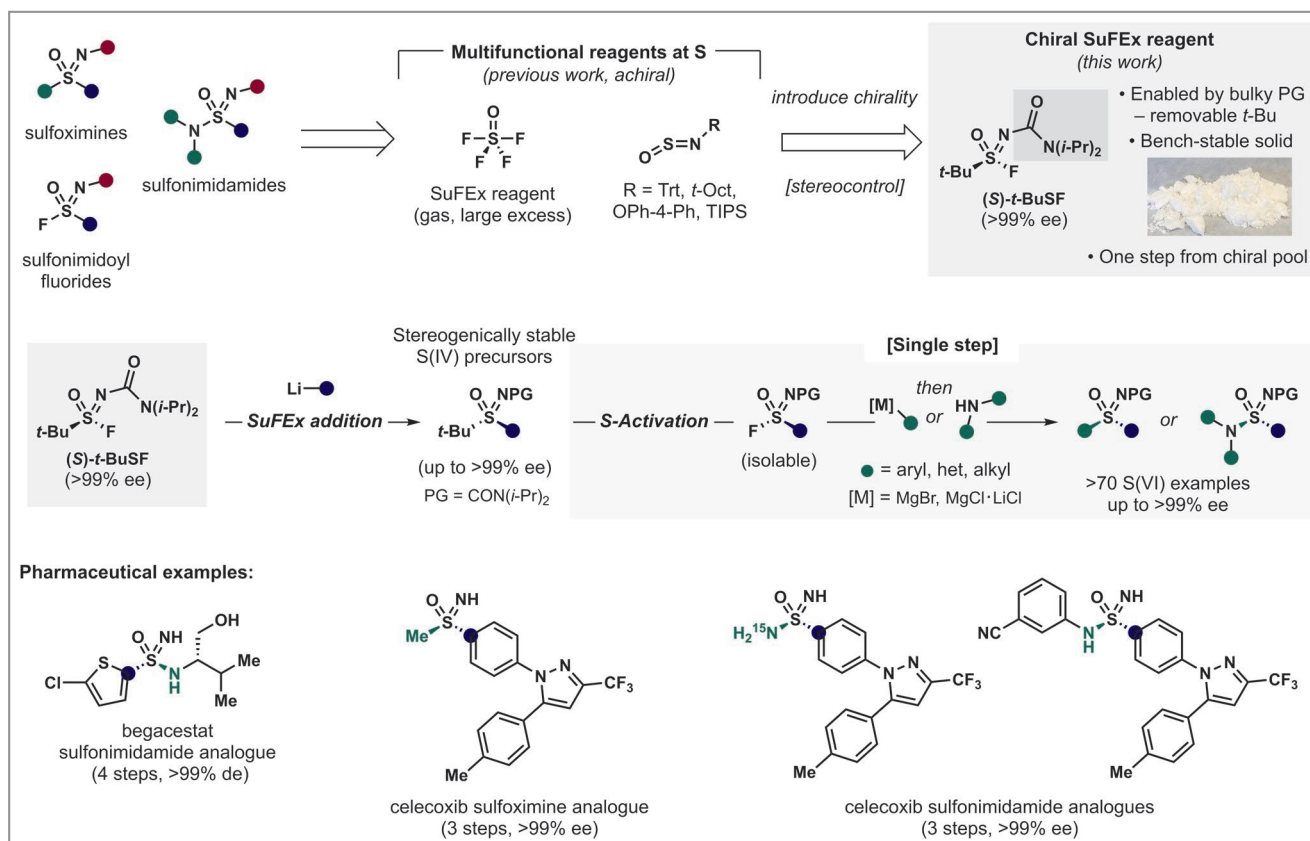
Attempts to activate the S–F bond using the previously mentioned protecting groups were unfruitful. Therefore, the authors' final design hinged on increasing the electronic and steric bulk around the carbonyl protecting group. “Dimethyl and diethyl carbamoyl groups were evaluated, both showing notably increased stability relative to their acyl and carbamate counterparts, and, to our delight, increased SuFEx selectivity with phenyl lithium,” explained Professor Lopchuk. He continued: “By further increasing the steric bulk with an *N,N*-diisopropyl carbamoyl function, we obtained a solid and crystalline sulfonylimidoyl urea with markedly improved stability and exclusive SuFEx selectivity using organolithiums. The perfect balance of electronics and sterics allowed for the development of the bench-stable (>1 year) and selective chiral SuFEx reagent ***t*-BuSF**.”

A new sulfonylimidoyl *N*-protecting group that provides stability under a variety of conditions was therefore discovered, enabling the initial S(VI) transfer between a wide range of organolithium reagents (>30 examples, 95% to >99% ee) including aryl, heteroaryl, and alkyl – with many gram-scale examples. Professor Lopchuk remarked: “The resulting *tert*-butyl sulfoximines are stereogenically stable intermediates that were rapidly diversified to sulfonylimidoyl fluorides, sulfoximines or sulfonylimidamides by a novel redox-neutral S-activation strategy in a single step (or even stepwise), without loss of enantiopurity (>30 examples, >99% ee). Furthermore, ***t*-BuSF** was applied to the enantiopure synthesis of five pharmaceutical targets with improvements in overall step-count, yield and enantiopurity.”

The authors believe that the utility and practicality of ***t*-BuSF** warrant its adoption and wide implementation in organic chemistry research, for future investigations of the unique properties of, *but not limited to*, sulfoximines, sulfonylimidoyl fluorides, and sulfonylimidamides. Professor Lopchuk concluded: “The significant improvements in overall synthetic efficiency of this method over the current state of the art, the

stability of our reagent and intermediates, and the wide-ranging implications to fields and areas of chemical research other than medicinal chemistry, such as chemical biology, organocatalysis, photochemistry, electrochemistry, organometallic chemistry, and materials chemistry, make this a highly valuable reagent platform for the scientific community.”

*Matters female*



**Scheme 1** A chiral SuFEx reagent platform developed for the asymmetric synthesis of sulfonimidoyl functionalities



## About the authors



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**Shun Teng** obtained his BSc in pharmaceutical science from Wuhan University (P. R. of China) in 2018. After a rotation in the chemistry department, he began his graduate studies at Lee Moffitt Cancer Center and Research Institute (USA) under the supervision of Prof Justin M. Lopchuk in 2020. His research focused on asymmetric synthesis of sulfur-containing compounds. In 2023, he received his PhD in chemistry and moved back to

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**Zachary Shultz** received his PhD in chemistry from the University of South Florida (USA) in 2019 under the guidance of Professor James Leahy where he focused on the total synthesis of cannabinoids and marine natural products. After completing his PhD, he joined Dr. Justin Lopchuk's group at H. Lee Moffitt Cancer Center and Research Institute (USA) as a postdoctoral fellow, developing new practical synthetic methodologies

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Prof. J. M. Lopchuk

**Justin M. Lopchuk** received a dual BS degree in chemistry and biology from Muhlenberg College in Allentown, Pennsylvania (USA). His PhD studies were conducted at Dartmouth College (USA) in the laboratory of Prof. Gordon Gribble with a focus on heterocyclic chemistry and the synthesis of indole-containing natural products. He completed postdoctoral work on the synthesis of diterpenoid natural products and strain-release

functionalization at The Scripps Research Institute in La Jolla, California (USA) under the guidance of Prof. Phil Baran. In 2017, he began his independent career as an Assistant Professor in the Department of Drug Discovery at Moffitt Cancer Center (USA) and was promoted to Associate Professor with tenure in 2023. His group focuses on the development of new methods for C–N, C–S, and C–C bond formation, the design of new covalent reactive groups, the total synthesis of bioactive natural products, and the structure-based drug design of small molecule inhibitors and PROTACS.

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— Literature Coverage

### Congested C(sp<sup>3</sup>)-Rich Architectures Enabled by Iron-Catalysed Conjunctive Alkylation

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(by R. Rasappan and co-workers)

#### **Synlett** Account: Stereogenic $\pi$ -Conjugated Macrocycles: Synthesis, Structure, and Chiroptical Properties Including Circularly Polarized Luminescence

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#### Publication Information

Synform will be published 12 times in 2024 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

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