

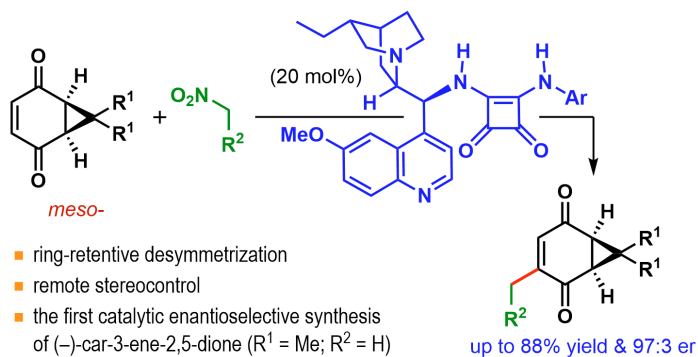
Synform

People, Trends and Views in Chemical Synthesis

2024/07

SYNLETT Best Paper Award 2023: Catalytic Enantioselective Desymmetrization of *meso*-Cyclopropane-Fused Cyclohexene- 1,4-diones by a Formal C(sp²)-H Alkylation

Highlighted article by S. Ray, S. Mukherjee



Contact

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Dear Readers,

In this July issue of SYNFORM, we celebrate the first of the two 2023 Best Paper Award winners. Professor Santanu Mukherjee and Sayan Ray from the Indian Institute of Science, Bangalore (India), who are the recipients of the SYNLETT Best Paper Award 2023 for their article “Catalytic Enantioselective Desymmetrization of *meso*-Cyclopropane-Fused Cyclohexene-1,4-diones by a Formal C(sp²)-H Alkylation” (*Synlett* **2023**, *34*, 863–867), are featured in an interview that provides background information on their award-winning research, as well as current research activities ongoing in the group. The SYNTHESIS Best Paper Award 2023 winners – Professor Takaaki Sato and co-authors – will be featured in the August issue. This July issue features three more articles, starting with a Young Career Focus interview with F. F. Mulks (Germany) – a 2024 Thieme Chemistry Journals Awardee. The next Literature Coverage article covers an intriguing piece of research recently published by the group of J. J. Weigand (Germany) on the synthesis of π -conjugated 1,3-azaphospholes from alkynes, which exploits a [3+2]-cycloaddition and reductive aromatization sequence. The issue is closed by a second Literature Coverage article stemming from a collaboration among the groups of M. J. Koh, X. Zhang (both in Singapore) and P. L. Holland (USA), who jointly developed an approach to congested and C(sp³)-rich architectures utilizing an iron-catalyzed conjunctive alkylation reaction.

Enjoy your reading!



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Contact

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

SYNLETT Best Paper Award 2023: Catalytic Enantioselective Desymmetrization of *meso*-Cyclopropane-Fused Cyclohexene-1,4-diones by a Formal C(sp²)-H Alkylation

Synlett **2023**, *34*, 863–867

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 Santanu Mukherjee and Sayan Ray, from The Indian Institute of Science, Bangalore (India), are the recipients of the SYNLETT Best Paper Award 2023. The authors are recognized for their extremely elegant and highly enantioselective approach to desymmetrize bicyclo[4.1.0]heptenes. The organocatalytic reaction features the use of nitroalkanes as source of alkyl groups in a C(sp²)-H alkylation. The method is applied in the first enantioselective synthesis of 3-carene-2,5-dione.

SYNFORM spoke with Professor Santanu Mukherjee, 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



From left: Prof. S. Mukherjee and S. Ray

Santanu Mukherjee is a Professor in the Department of Organic Chemistry at the Indian Institute of Science, Bangalore (India). He obtained his M.Sc. (Chemistry) in 2002 from the Indian Institute of Technology, Kanpur (India) and Ph.D. in 2006 working with Prof. Albrecht Berkessel at Universität zu Köln, Germany. After working as a postdoctoral fellow with Prof. Benjamin List at Max-Planck Institut für Kohlenforschung in Mülheim an der Ruhr, Germany (2006–2008) and with Prof. E. J. Corey at Harvard University, USA (2008–2010), he started his independent career at Indian Institute of Science, Bangalore in 2010. His

research interests revolve around various aspects of asymmetric catalysis, with a particular emphasis on desymmetrization and their application to complex targets.

Sayan Ray was born in Kolkata, West Bengal, India. He had his early education from Baruipur High School, West Bengal. He received his B.Sc. (Chemistry Hons.) in 2016 from Dinabandhu Andrews College, Garia, Kolkata (Calcutta University, India) and his M.Sc. (Organic Chemistry) in 2018 from the Indian Institute of Technology, Bhubaneswar (India). In August 2018, he joined the Department of Organic Chemistry, Indian Institute of Science, Bangalore (India), as a Ph.D. student under the supervision of Prof. Santanu Mukherjee. His research interests include the development of organocatalytic enantioselective desymmetrization strategies for the synthesis of ladderane-based natural products and unnatural analogues. He is a recipient of the Prime Minister's Research Fellowship (PMRF) of the Ministry of Education, Government of India.

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. S. Mukherjee The direct introduction of an alkyl chain into a C(sp²)-H bond is in itself a challenging transformation. Carrying out this reaction in an enantioselective fashion is an even more significant challenge. We have demonstrated the feasibility of this transformation for different classes of substrates (i.e., prochiral and *meso*) during the past decade.

In this paper, we have applied this reaction to yet another class of substrates – namely, *meso*-cyclopropane-fused cyclohexene-1,4-diones. Due to the strained nature of cyclopropanes, desymmetrizations of these *meso*-bicyclo[4.1.0]heptane derivatives are commonly associated with the opening of the cyclopropane ring. Here, we showed, for the first time, that ring-retentive enantioselective desymmetrization of *meso*-bicyclo[4.1.0]heptane derivatives is possible.

As described below, the actual objective of this research is to verify the viability of applying this C(sp²)-H alkylative desymmetrization to an exciting class of complex targets. We could eventually achieve these targets.

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

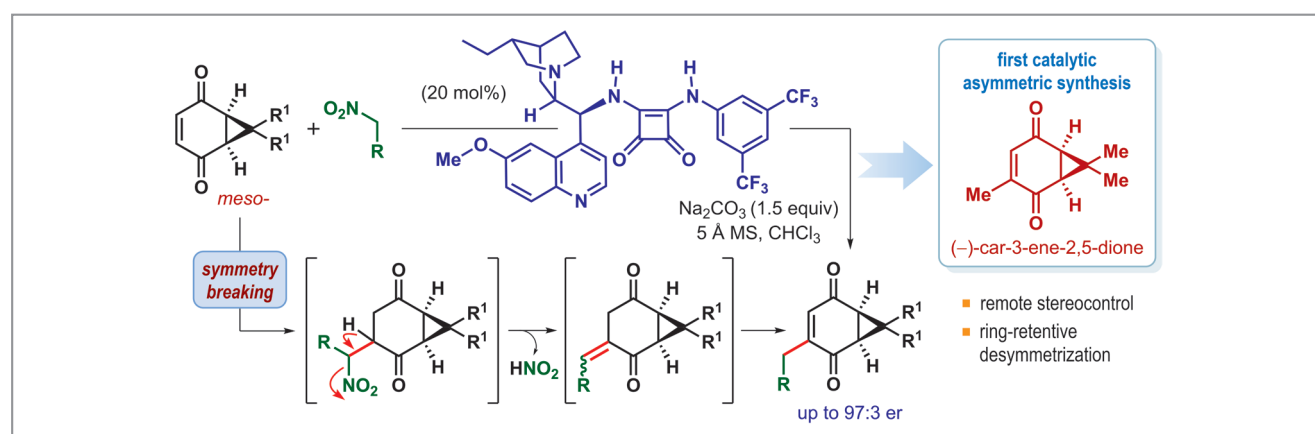
Prof. S. Mukherjee This research program of enantioselective C(sp²)-H alkylative desymmetrization started (somewhat serendipitously) in our lab about a decade ago. After the initial efforts to understand the mechanism of this reaction

and explore its generality, we began looking for its application to complex targets. Ladderane phospholipids and their fascinating structures have been an inspiration since I came across them during my Ph.D. days. There is nothing more exciting than applying our own reaction to such attractive and rarely studied targets. That's when my Ph.D. student Sayan came on board and took up the challenge. We decided to use these *meso*-cyclopropane-fused cyclohexene-1,4-diones as our model substrate because of their loose structural resemblance to the cyclobutane-fused cyclohexane core found in [3]-ladderanol. These symmetrical compounds initially formed the basis of our entire catalyst design and optimization for C(sp²)-H alkylative desymmetrization, which was then translated to a [3]-ladderanol precursor. During this study, we realized that the ring-retentive desymmetrization of the *meso*-cyclopropane-fused cyclohexane core has never been explored, and a successful C(sp²)-H alkylative desymmetrization led to the first catalytic enantioselective synthesis of car-3-ene-2,5-dione – a natural product (Scheme 1).

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

Prof. S. Mukherjee After successfully achieving the enantioselective total synthesis of [3]-ladderanol, we turned our attention to more challenging [5]-ladderanoic acid – once again through the application of our C(sp²)-H alkylative desymmetrization reaction. We have recently completed this synthesis and hope to report it soon!

In the meantime, our research program on enantioselective desymmetrization grew beyond C(sp²)-H alkylation. In the last few years, we have developed an efficient catalytic



method for enantioselective de novo construction of centrally and axially chiral arenes using dienamine catalysis. We are currently working on overcoming the limitations of this method and applying it to the enantioselective synthesis of other classes of chiral arenes.

Besides organocatalytic enantioselective desymmetrization, our research group has been working on asymmetric allylic, allenyl, and propargylic substitution reactions using transition-metal catalysis. Having developed expertise in organocatalysis and transition-metal catalysis, our long-term goal of combining these two classes of catalysis in a cooperative manner is finally yielding fruit!

We constantly look to apply our reactions to complex natural products and bioactive targets.

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

Prof. S. Mukherjee The field of organic synthesis has been witnessing explosive growth during the past two decades. Besides the maturation of the existing research areas, 'new' research directions in catalysis have emerged with rapid and exciting developments – not just catalysts and ligands, but also methods and concepts. These discoveries have transformed the thought process of synthetic organic chemists. More importantly, many of these developments are inspired by the potential of their real-life applications, which makes this growth even more exciting.

Organic synthesis is all about selectivity – all sorts of it. Rapid and economical synthesis of targets has been, and will continue to be, the ultimate motivation behind any discovery and development.

As long as small molecules remain a significant component of the pharmaceutical and agrochemical industries, organic synthesis will continue to play a key role in the timely delivery of these products to their end users.

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

Prof. S. Mukherjee Nothing is more satisfying than receiving appreciation for a specific work for its merit by experts in the field. Our work was selected by the members of the Editorial Board of SYNLETT, each of whom is a renowned synthetic organic chemist and expert in their field. From this perspective, this award means a lot to us. This is a wonderful recognition for our work and also a huge encouragement for me, my student Sayan, and our research group in general. The effort behind this work may not be evident from the paper itself, which makes this award even more special for us!



Young Career Focus: Dr. Florian Mulks (RWTH Aachen University, Germany)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Florian Mulks (RWTH Aachen University, Germany).

Biographical Sketch



Dr. F. Mulks

Florian F. Mulks studied chemistry at the University of Heidelberg (Germany), where he received his doctorate in 2018 under the supervision of Stephen Hashmi. He spent postdoctoral periods in the groups of Prof. Faraji at RUG Groningen (the Netherlands), Eva Hevia at the University of Strathclyde, Glasgow (UK), and at the University of Bern (Switzerland). He then received a Feodor Lynen Fellowship from the Alexander von Humboldt Foundation for research with Mookie Baik and Guy Bertrand at KAIST, Daejeon (South Korea) and UC San Diego (USA). In early 2022, he returned to Germany to begin his independent research associated with the chair of Carsten Bolm at the RWTH Aachen University, supported by the Alexander von Humboldt Foundation through a Feodor Lynen Return Fellowship. Later in 2022, the Fonds der Chemischen Industrie began supporting his group with a Liebig Fellowship. His group currently studies dicationic organic and main group Lewis acids, their coordination chemistry, and concepts for rationalising organic and main group chemistry.

INTERVIEW

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

Dr. F. Mulks I am very interested in new types of organic compounds to gain a deeper understanding of the underlying design principles and to explore their potential applications. This involves exploring the chemical limits of carbon, determining the properties of such compounds, and establishing general concepts from observations. Research that expands our knowledge of the fundamental properties and reactivity of carbon in molecules, such as creating unusual charge and valency situations, has the potential to push the research frontier into unknown territory. Such work creates metaphorical outposts that serve as starting points for deeper exploration of new and exciting areas. The potential applications of organic compounds in surprising domains are vast and unknown. For example, they can replace metals in high-performance semiconductors and OLEDs. Such research is ultimately driving the replacement of finite and hazardous materials with renewable organic compounds in a wide range of applications.

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

Dr. F. Mulks Our current research activities are two-fold: Our group studies supercharged carbon compounds to open new perspectives in organic chemistry. We borrow strategies from coordination chemistry to stabilise highly charged carbon centres in unusual coordination geometries. Such compounds push the boundaries of carbon chemistry. We tweak the valence and electronic structure of carbon compounds to replace toxic and rare elements in catalysis. We are excited to see what we will find as we delve deeper into the realm of highly charged, unusual valence compounds of carbon. In our second major research stream, we use electronic struc-

ture theory and statistical tools to analyse and conceptualise chemical reactivity. The concepts we use to understand and teach chemistry need to keep pace with our deepening understanding of the matter to fuel our progress and keep us human chemists competitive with machine tools. Our multifaceted research philosophy enhances our comprehension of fundamental chemical processes and propels us towards pioneering solutions with tangible applications.

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

Dr. F. Mulks Organic chemistry is at a pivotal point in its history. Organic chemistry as a traditional, hands-on field is being reinvented in the context of the era of artificial intelligence and high-end machines that can provide tremendous assistance in both planning and carrying out syntheses. Chemists of the future will work even more closely with machines than they do today. We will find ways to follow our passion that work efficiently with the coming technological advances and ensure that our progress stays on track. We will find ways to create and store our data that empower both humans and machines. We will find ways to identify and correct rogue data. The organic chemists of the future will feed research ideas to machines and work closely with them to solve problems. I am confident that a vibrant and creative future awaits the field. If we can delegate more and more mundane tasks to our electronic helpers, we can focus on what really matters: awesome ideas and experiments.

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

Dr. F. Mulks It can be difficult to pursue important ideas if they stray far from current trends. The temptations of an easier peer-review process and quick citations encourage a focus on fashionable research topics. Younger scientists, in particular, may prioritize safe successes over following original ideas. However, it is important to persevere with these ideas as they are necessary for progress. You will eventually discover ways to position your work within contemporary literature. We have a unique opportunity to make a lasting impact on the world. Although other options may seem safer for our careers, we owe it to humanity and our idealistic past selves to take risks and pursue our best ideas.

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

Dr. F. Mulks The launch of the independent group in 2022 was my career highlight. Initially, I enjoyed developing my ideas independently, but I am very pleased to see the group growing. As it does, so does our research and the scope of our interests through the added interests of new members. Regarding our research, our exploration of highly charged carbon molecules began with base-stabilised diaminocarbo-dications (Figure 1). We discovered that these compounds are easy to handle and can be synthesised on a large scale, making them promising as Lewis acids and organocatalysts (refer to: *Chem. Eur. J.* **2023**, *29*, e202302089 and *Molbank* **2023**, *2023*, M1710). This marks the turning point where our research transitions from basic science to practical application. I cannot wait to see where the journey of these acids and the journey of our group takes us.

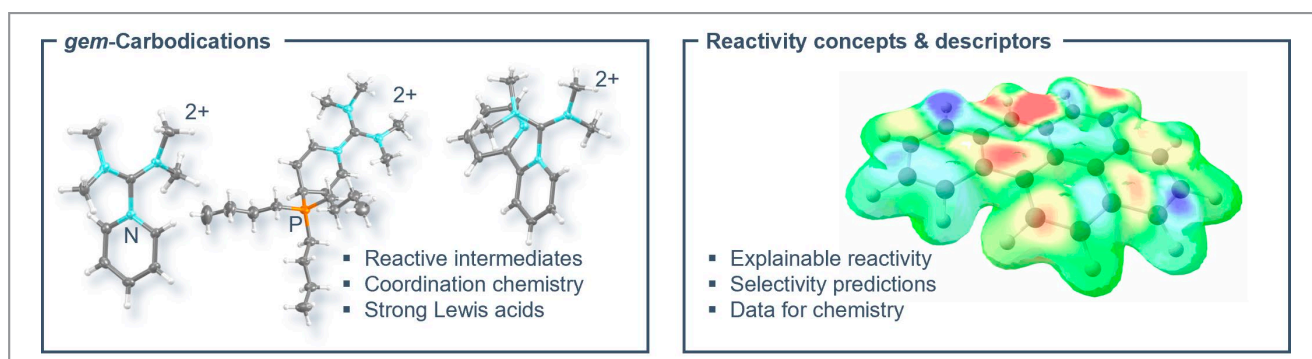


Figure 1 Schematic overview of the main research interests of F. Mulks' research group. Figures are in part used from the following Open Access (CC BY) publications [*Chem. Eur. J.* **2023**, *29*, e202302089; *Molbank* **2023**, *2023*, M1710].

SYNFORM *Could you tell us something about yourself outside the lab, such as your hobbies or extra-work interests?*

Dr. F. Mulks My brain enjoys painting very much. It induces a meditative state of deep focus. Spending a longer evening in a creative flow-state provides an incomparable feeling of transcendent light-heartedness and contentment. Despite their differences, creative arts and chemistry are both amazing retreats and great teachers. Working in research labs for a long time can make us cautious perfectionists. Safety is often prioritised when conducting experiments, which is important. However, this mindset can lead to procrastination when it comes to creative tasks such as writing. Engaging in activities such as painting can help break down some of the mental barriers that years of research may have established. Working with paints requires unrestricted experimentation. If the first attempt does not work, simply paint over it and try again. Rinse and repeat.

Note: DeepL was used in editing this document.

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

Convenient Access to π -Conjugated 1,3-Azaphospholes from Alkynes via [3+2]-Cycloaddition and Reductive Aromatization

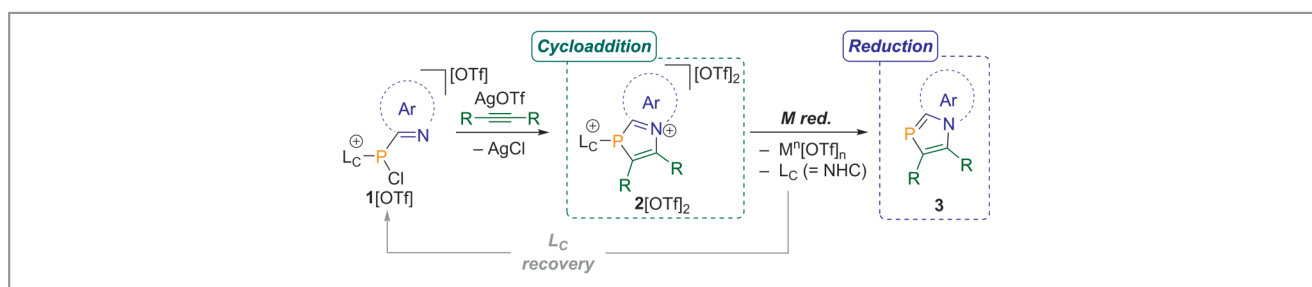
Chem **2024**, *10*, 644–659

The chemistry of phosphorus-containing heterocycles is well established and in recent years a significant number of *P*-heterocycles have been successfully used in various applications related to organic semiconductors, such as OLEDs, OPVs and OFETs, or as ligands in transition-metal complexes. A recent article in *Chem* from the group of Professor Jan J. Weigand at the Technische Universität Dresden (Germany) describes a new method for the synthesis of annelated 1,3-azaphospholes (**3**) in a two-step procedure from a conveniently accessible phosphorus building-block. The described method provides access to a wide range of compounds, which allows study of their physical and chemical properties. “Initially, 1,3-dipolar triflatophosphanes are formed that readily engage in ‘click-type’ [3+2]-cycloaddition reactions with alkynes to afford 1,3-azaphospholium cations **2**[OTf]₂ as their respective triflate salts,” said Professor Weigand. He continued: “Subsequent reduction reactions lead to the formation of 1,3-azaphospholes (**3**, Scheme 1), a substance class that was only accessible to a limited extent due to inconvenient synthetic access pathways. Interestingly, the imidazoliumyl substituent is reductively cleaved to yield an *N*-heterocyclic carbene as the leaving group, an approach that we have developed in our group over the past years (*J. Am. Chem. Soc.* **2023**, *145*, 10364–10375).”

The Weigand group’s approach originates from a previous contribution in which highly electrophilic fluorophosphonium ions with a donor atom in the 3-position were used as frustrated Lewis pairs for the activation of small molecules (*Chem. Eur. J.* **2021**, *27*, 13709–13714). Professor Weigand explained: “We adapted this method slightly to phospheni-

um ions, which in turn led to the formation of phosphorus ring systems with tri-coordinate phosphorus atoms. During our investigations, we noticed that due to the coordination of one triflate anion, triflatophosphanes are the reactive species in the cycloaddition reactions. After standard electrochemical screening of a model compound, it was determined that the cycloaddition products could be reduced to afford neutral 1,3-azaphospholes (**3**). Due to convenience and ease of handling, we used zinc dust in most of our syntheses.”

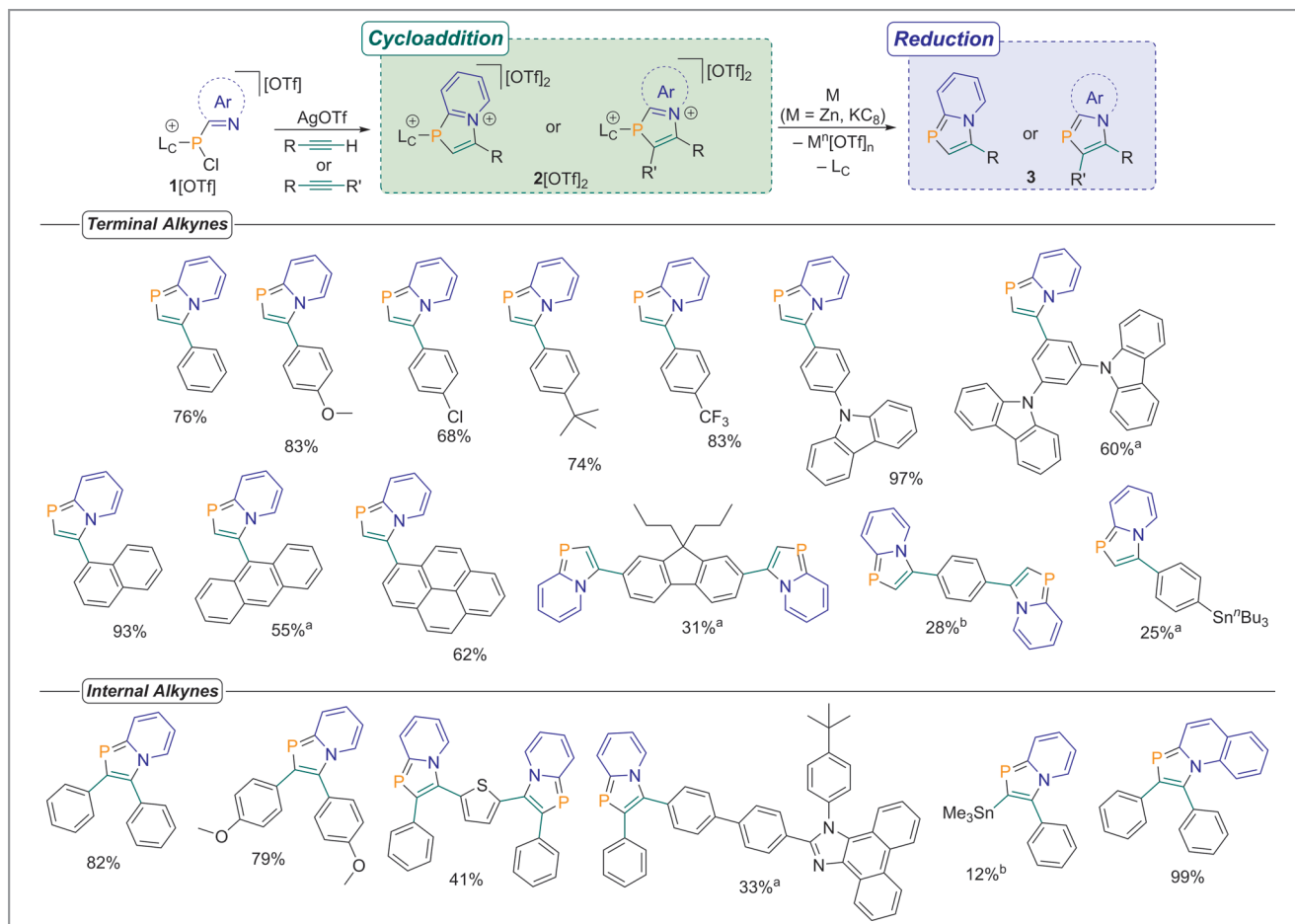
What particularly stands out with this approach is its convenience and scope (Scheme 2). “The range of usable alkynes has been expanded to 19 derivatives, achieving yields of up to 99%. Typically, such 1,3-azaphospholes are prepared either from phosphalkynes or other phosphorus building-blocks, both of which have lacked sufficient scope and have only been scarcely explored in recent years,” remarked Professor Weigand. He went on: “Furthermore, we believe that the simplicity of this approach will appeal to a large segment of the research community, as the main precursors can be synthesized from readily available starting materials using common Schlenk techniques in quantitative yields (*J. Am. Chem. Soc.* **2010**, *132*, 16321–16323). The range of potential alkynes is undoubtedly vast.” Professor Weigand concluded: “We aim to establish 1,3-azaphospholes as a new and promising substance class and have therefore investigated some fundamental structure–property relationships, deriving some general design rules to influence their optoelectronic properties. Given the expanded scope behind our method, we anticipate that these compounds can be specifically adapted targeting



Scheme 1 Two-step synthesis of 1,3-azaphospholes (**3**) involving a 1,3-dipolar cycloaddition of **1**[OTf] with alkynes in the presence of AgOTf to form azaphospholium salts **2**[OTf]₂, which are subsequently reduced to yield 1,3-diazaphospholes (**3**).

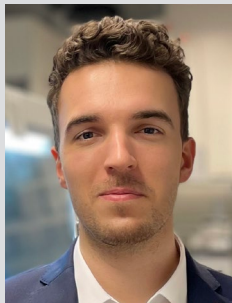
favorable optoelectronic characteristics, potentially making them suitable for innovative applications including organic semiconductors, OLEDs, OPVs, and OFETs.”

Mattias Forsell



Scheme 2 Scope of 1,3-azaphospholes (**3**) prepared using the described method. ^a Yield from crude starting material. ^b Yield from **1[OTf]**.

About the authors



J. Fidelius

Jannis Fidelius received his B.Sc. in chemistry from the Dresden University of Technology (Germany) in 2017 under the supervision of Prof. Dr. Peter Metz. He then completed his M.Sc. degree in Dresden in 2019. He is currently pursuing his Ph.D. under the supervision of Prof. Dr. Jan J. Weigand, focusing on the development of novel methods for the synthesis of phosphorus-containing ring systems and their application as novel molecular materials, with a special focus on optoelectronic properties.



Dr. K. Schwedtmann

focusing on reactive phosphorus compounds and sustainable phosphorus chemistry.

Kai Schwedtmann received his diploma degree from the WWU Münster (Germany) in 2012 and started his Ph.D. studies under the supervision of Prof. Jan J. Weigand. In 2013, he moved to TU Dresden (Germany), where he received his Dr. rer. nat. in 2016. During his Ph.D. studies, he was a visiting researcher in the group of Prof. Neil Burford in 2014 at the University of Victoria (Canada). Today, he is senior researcher at TU Dresden,



Prof. J. J. Weigand

Jan J. Weigand obtained his diploma in chemistry in 2002 and his Dr. rer. nat. in 2005 from the LMU in Munich (Germany). Awarded the Bavarian Culture Prize in 2005, he received a Lynen Scholarship from the Alexander von Humboldt (AvH) Foundation for postdoctoral research at Dalhousie University in Halifax (Canada). He returned to Germany with a Lynen Return Fellowship and began his habilitation at WWU Münster in 2007 under the supervision of Prof. Hahn. Shortly thereafter, he was awarded the Liebig scholarship of the Fonds der Chemischen Industrie (FCI), allowing him to start his independent career in 2008. In April 2010, he became a fellow of the prestigious Emmy Noether research program awarded by the DFG, and received the Wöhler Young Scientist Research Award. In July 2012, he was granted an ERC Starting Grant by the European Council (EC). Since January 1, 2013, he has been a full professor at TU Dresden (Germany). His research focuses on molecular inorganic and phosphorus chemistry, including the development of sustainable methods for extraction, technical applications, and novel recycling strategies. This encompasses innovative catalyst systems for use in the petrochemical industry and resource conversion into biogenic and fossil residues. In 2023, he received Reinhardt Koselleck funding from the DFG for the project 'Blueprint for a Modern Sustainable Phosphorus Chemistry'.

Congested C(sp³)-Rich Architectures Enabled by Iron-Catalyzed Conjunctive Alkylation

Nat. Catal. 2024, 7, 321–329

Transition-metal-catalyzed cross-coupling has become a staple synthetic method for forming carbon–carbon bonds in the pharmaceutical industry. However, advancements in this field are largely focused on reactions involving sp² carbons. Comparatively, sp³-hybridized substrates are less reactive due to their resistance to oxidative addition during cross-coupling (Figure 1a). Due to the prevalence of densely functionalized sp³ environments in biologically active natural products, methods for assembling congested cores are urgently needed, particularly those that construct multiple sp³–sp³ (alkyl–alkyl) bonds. “A catalytic process that assembles multiple alkyl–alkyl bonds to afford densely substituted entities

would empower users to access medicinally valuable but synthetically elusive C(sp³)-rich building blocks with sterically crowded stereocenters,” stated Professor Ming Joo Koh from the National University of Singapore.

Three-component conjunctive cross-coupling reactions represent a highly promising approach for creating vicinal C(sp³)-C(sp³) linkages via dialkylation of readily available alkene precursors. Nevertheless, there are currently only a few regioselective dialkylation methods that yield uncongested adducts containing tertiary carbon centers, and none of these methods utilize iron for catalysis (Figure 1b). “The main reason is that during the reaction process, alkyl–iron intermediates

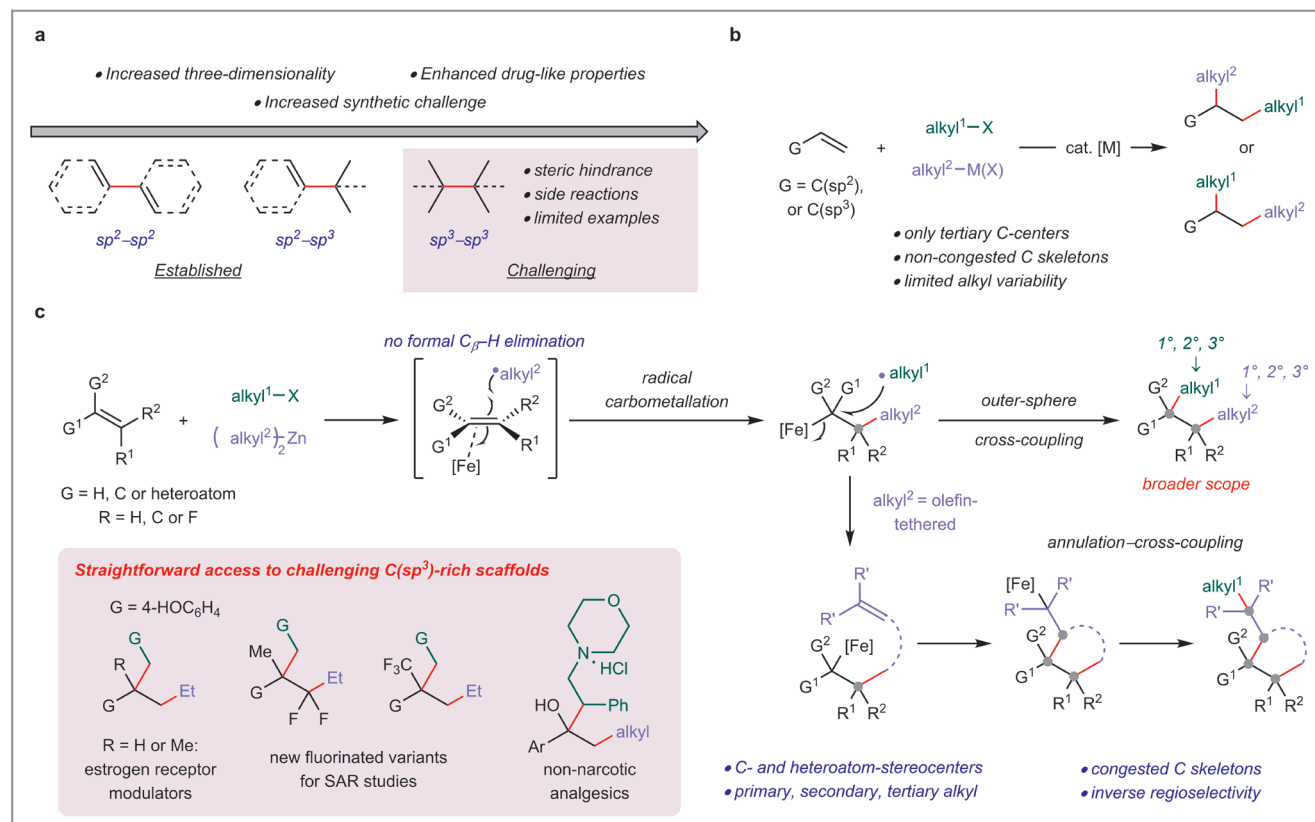


Figure 1 Development of an iron-catalyzed strategy for conjunctive alkylation. a, Challenges in constructing C–C bonds by cross-coupling. b, Previous catalytic approaches in conjunctive alkylation. c, Reaction design leveraging iron-catalyzed alkyl-radical-transfer-cross-coupling cascades to access complex C(sp³)-rich building blocks.

that contain C_β-H bonds are formed, which are unstable and prone to undergo undesired C_β-hydride elimination," Professor Koh explained.

Recently, the groups of Professor Koh, Dr. Xinglong Zhang (Institute of High Performance Computing, Agency for Science, Technology and Research (A*STAR), Singapore) and Professor Patrick Holland (Yale University, USA) described an earth-abundant (terpyridine)iron-catalyzed strategy for the dialkylation of olefins using C(sp³)-Zn nucleophiles and sp³-hybridized electrophiles (Figure 1c). "This catalytic system can form two alkyl-alkyl bonds, allowing primary, secondary, and even tertiary alkyl units to be installed on either olefinic carbon, offering access to a much wider range of products and new chemical space," asserted Professor Koh. He continued: "To highlight new synthetic opportunities from this reaction, we demonstrate the rapid synthesis of sterically congested bioactive compounds and fluorinated carbocycles with multiple contiguous stereocenters that can serve as precursors of pharmaceutically relevant organofluorides."

"This catalyst system has great generality, providing access to many C(sp³)-rich building blocks bearing tertiary or quaternary centers. These include stereocenters substituted

with boron, nitrogen, oxygen, silicon, sulfur, phosphorus, and fluoroalkyl motifs, each with unique electronic and steric properties," said Dr. Tongde Tan, the first author of this paper. He continued: "Even sterically demanding di- and tri-substituted olefins could undergo reaction to deliver products with crowded sp³-sp³ carbon skeletons."

Professor Koh told SYNFORM: "This reaction mechanism offers a unique pathway for dialkylation of olefins through stepwise iron-mediated radical carbometallation followed by outer-sphere C-C bond formation (Figure 2), which effectively suppressed C_β-hydride elimination of the alkyliron species and is the key to our reaction's success." Professor Holland stated: "⁵⁷Fe-Mössbauer spectroscopy studies suggest that the major iron species in solution are iron(II) complexes that serve as reservoirs for the catalyst, and the organoiron intermediates that are catalytically active exist at very low concentrations."

Dr. Zhang employed DFT calculations to evaluate the energetics of viable catalytic mechanisms based on the mechanistic experiments. "This stepwise carbometallation pathway, which proceeds via **TS1** through an outer-sphere mechanism, is calculated to have a much lower barrier than the concerted addition pathway (via **TS1a**)," Dr. Zhang elaborated further,

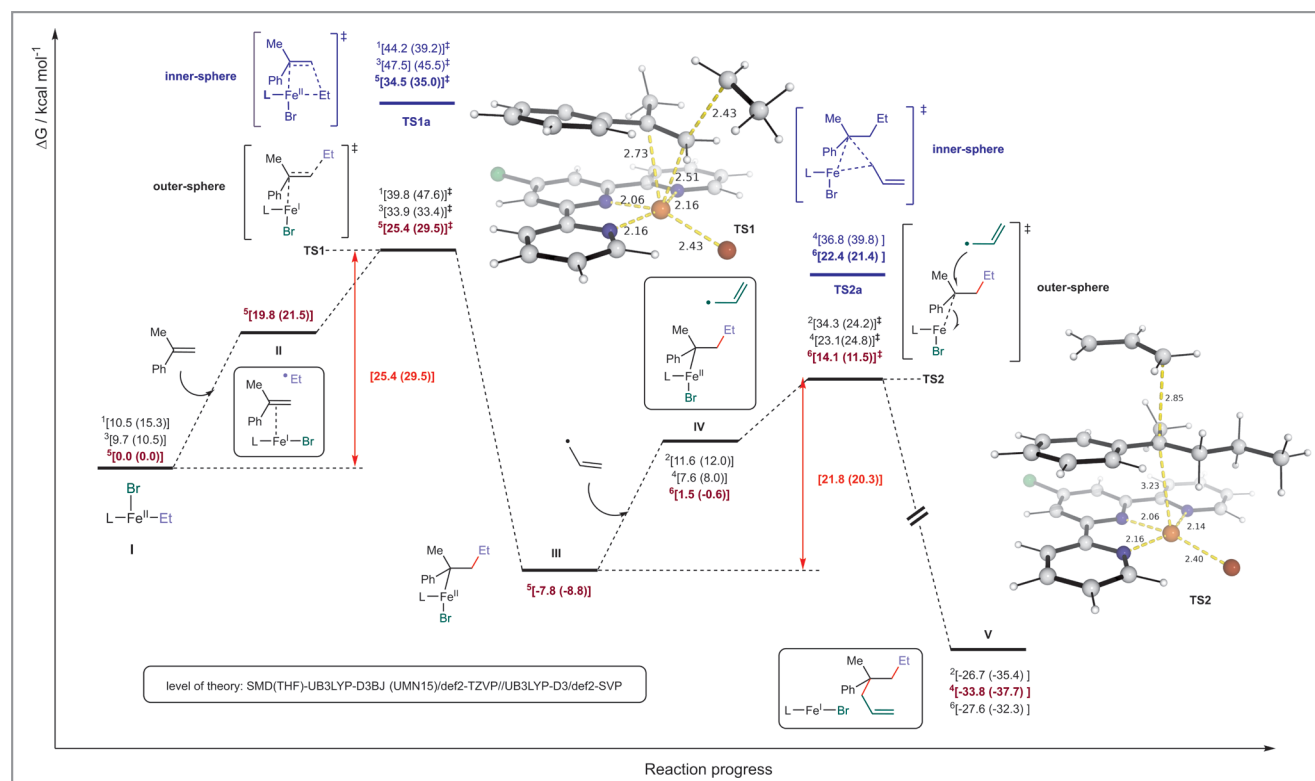


Figure 2 Computed Gibbs energy profile showing the two key C(sp³)-C(sp³) bond-forming steps in iron(II)-catalyzed conjunctive alkylation.

adding: “Calculations also show that formation of the second C(sp³)-C(sp³) bond occurs via an outer-sphere transition state **TS2**, as opposed to the more commonly known inner-sphere reductive elimination mechanism (via **TS2a**.” Professor Koh remarked: “Our newly proposed dialkylation mechanism eliminates previous limitations and allows us to significantly broaden the scope of conjunctive dialkylation.”

Professor Koh concluded by examining future perspectives of this work: “By harnessing the power of Fe-catalyzed conjunctive alkylation, we have provided a new platform for as-

sembling congested sp³-hybridized carbon frameworks, which could potentially expedite the synthesis of numerous natural products and pharmaceuticals containing densely functionalized alkyl-alkyl linkages. The unique reaction mechanism also opens the door to a wider range of transformations and new chemical space. Extending the use of this alkylation strategy to target various unsaturated hydrocarbon compounds for rapid generation of synthetically elusive C(sp³)-rich building blocks holds greater promise than ever before.”

Mattias Fankle

About the authors



Dr. T.-D. Tan

Tong-De Tan obtained his Ph.D. from Xiamen University (P. R. of China) in 2021 (with Professor Long-Wu Ye). After that, he joined Professor Ming Joo Koh's group at the National University of Singapore for his postdoctoral research. His research interests are mainly focused on base-metal-catalyzed dicarbofunctionalization of unsaturated bonds.



J. M. I. Serviano

Juan M. I. Serviano obtained his B.S. degree in chemistry from Temple University (USA) where he performed undergraduate research under the supervision of Associate Professor Graham E. Dobereiner. He then joined the lab of Professor Patrick L. Holland at Yale University (USA) where his current research is on elucidating the mechanisms of radical alkene functionalization reactions catalyzed by first-row transition-metal complexes.



Professor P. L. Holland

Patrick L. Holland is a Professor in the Department of Chemistry at Yale University (USA). He obtained his PhD at the University of California, Berkeley (USA), under the supervision of Professor Robert Bergman and Professor Richard Andersen. Afterwards, he performed postdoctoral research in the lab of Professor William Tolman at the University of Minnesota (USA). Research in the Holland lab primarily

focuses on studying compounds containing first-row transition metals to understand their reactivity and develop new catalysts. The compounds studied span different fields, which include small-molecule activation (particularly N₂), bioinorganic chemistry, and organometallic catalysis.



Dr. X. Zhang

Xinglong Zhang received his BA (2014) from the University of Cambridge and MSc (2016) and DPhil (2019) from the University of Oxford, UK. After a brief postdoctoral stint at the California Institute of Technology (Caltech), USA, he joined the Institute of High Performance Computing (IHPC), A*STAR, Singapore, as a research scientist in 2020. His research interests include computational catalysis in transition-metal-catalyzed C-H functionalization and asymmetric organocatalysis (<https://xinglong-zhang.github.io>).



Professor M. J. Koh

Ming Joo Koh is an Associate Professor in the Department of Chemistry at the National University of Singapore. He obtained his Ph.D. with Professor Amir H. Hoveyda at Boston College (USA) and carried out postdoctoral studies in the same group. Research in the Koh group focuses on developing sustainable and practical transformations that address critical challenges in chemical synthesis through base-metal catalysis, radical chemistry and cross-coupling.

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