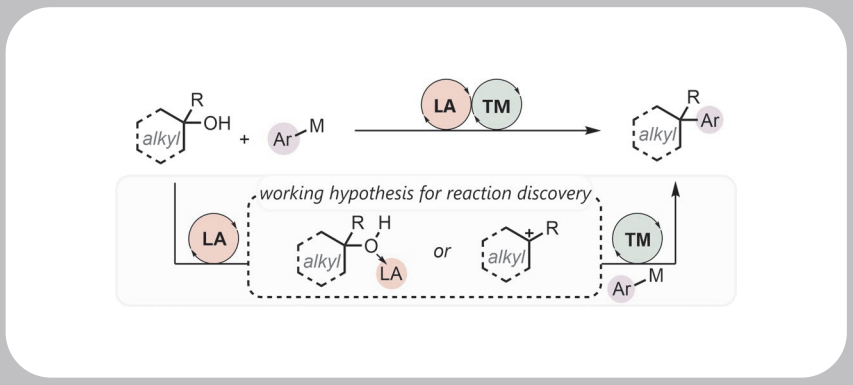
Synform

People, Trends and Views in Chemical Synthesis

2024/01

Deoxygenative Suzuki–Miyaura Arylation of Tertiary Alcohols through Silyl Ethers

Highlighted article by A. Cook, P. St. Onge, S. G. Newman



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Thieme

Dear Readers,

Welcome to a new year of SYNFORM!! And what a pyrotechnic start we have: an interview with Prof. Debabrata Maiti (Indian Institute of Technology Bombay, India) who will join the Editorial Board of SYNLETT as its new Editor-in-Chief with effect of January 2024. Welcome to the Thieme Chemistry family, Debabrata! And best wishes to Benjamin List, who will stay on the SYNFACTS board, despite the massive increase of commitments resulting from his recent Nobel Award!

The first Literature Coverage article of 2024 comes from the group of S. G. Newman (Canada), who developed a novel deoxygenative Suzuki–Miyaura arylation of tertiary alcohols using silyl ethers and an unusual bis-imidazolium *N*-heterocyclic carbene (NHC) ligand. A second Literature Coverage article stems from the work of R. Giri's group (USA) on a new approach to the intermolecular alkene cyclopropanation by using active methylene compounds – such as malonates – and photosensitized molecular oxygen. The issue is closed by a third Literature Coverage article, this one covering a fascinating subject, namely the synthesis and properties of cyclic sandwich compounds, recently published in Nature by the group of P. W. Roesky (Germany).

Enjoy your reading!

In this issue

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Editorial Board Focus: Prof. Debabrata Maiti (Indian Institute of Technology Bombay, India)

Background and Purpose. From time to time, SYNFORM portraits Thieme Chemistry Editorial Board or Editorial Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. This Editorial Board Focus presents Prof. Debabrata Maiti (Indian Institute of Technology Bombay, India) who will join the Editorial Board of SYNLETT as its new Editor-in-Chief with effect of January 2024.

Biographical Sketch

Professor D. Maiti

Debabrata Maiti is a synthetic scientist specializing in organometallic chemistry and catalysis and serving as professor of chemistry at the Indian Institute of Technology Bombay, Mumbai (India). He was born (1980) in West Bengal, India. He received his B.Sc. from RKMVM, Belur, University of Calcutta (India) in 2001 and M.Sc. from IIT Bombay in 2003. He received his PhD from Johns Hopkins University (USA) in 2008 under the supervision of Prof. Kenneth D. Karlin. He spent two years as a Post-Doctoral Fellow at Massachusetts Institute of Technology (USA) with Prof. Stephen L. Buchwald before joining the Department of Chemistry at IIT Bombay as an Assistant Professor in 2011. He was promoted to Associate Professor (2015) and to Professor (2021) and was named the Institute Chair Professor in 2022. In 2022, he was elected as a fellow of Academy of Sciences (FASc). He is the coauthor of 266 papers and 17 issued patents. He served as an associate editor for *The Journal of Organic Chemistry* during the period of 2017–2023. He was awarded the Shanti Swarup Bhatnagar Prize, the prestigious Indian national award for excellence in scientific research, for Chemical Sciences for the year 2022 for his significant contributions to developing transition-metal catalysis for transforming organic molecules to prepare value-added materials by site-selective functionalization, leading impact on agrochemicals and pharmaceuticals industry. In 2024, he joins SYNLETT as Editor-in-Chief.

INTERVIEW

SYNFORM *What fascinates you most about organic chemistry and synthesis?*

Professor D. Maiti I am fascinated by the creative problem-solving and the ability to design and synthesize complex molecules with specific properties.

SYNFORM *Tell us more about your current research activities.*

Professor D. Maiti Our group is mainly focusing on developing highly efficient catalytic reactions using the tools of organic/organometallic synthesis and physical organic chemistry. In this context, one of our primary activities is focused on the selective activation of C–H bonds and their functionalization with appropriate coupling partners. Although C–H bonds are prevalent in organic compounds, breaking them and replacing another molecule for the hydrogen atom is challenging. Selectivity is also an issue when there are multiple comparable C–H bonds in the molecule and only one needs to be activated. To achieve selective activation of C–H bonds, our group is actively involved in the discovery of novel organometallic catalysts and the design of ligands. This site-specific C–H functionalization technique would allow for the introduction of new chemical groups toward the end of a synthetic sequence, which means new molecules can be rapidly accessed without laborious de novo chemical synthesis.

Besides C–H bond activation, we also aim to harness the power of cutting-edge electrocatalytic and photocatalytic strategies to overcome energy barriers for chemical bond manipulation that are unattainable by current synthetic methods. Transition-metal-catalysed cross-coupling is a transformative method for carbon–carbon bond formation that accounts for 12% of reactions conducted in the pharmaceutical industry.

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We realized that next-generation cross-coupling reactions are needed to support the greater three-dimensionality of pharmaceuticals and to reduce reliance on precious metals and unstable aryl/alkyl nucleophile reagents in the discovery and manufacture of medicines. In this endeavour, our group is developing catalysts for $C(sp^2)$–$C(sp^3)$ and $C(sp^2)$–$C(sp^2)$ cross-electrophile coupling that rely on abundant aryl and alkyl halide/pseudohalide electrophiles.

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

Professor D. Maiti In the modern scientific landscape, synthetic chemistry plays a pivotal role by serving as the cornerstone of innovation in various disciplines. Its prospects are fuelled by the ability to design and create novel molecules with precise functionalities, offering solutions to complex challenges in medicine, materials science, and technology. With advancements in green chemistry, synthetic methods are becoming more sustainable, aligning with global efforts for environmentally conscious practices. The integration of artificial intelligence and automation enhances the efficiency of synthetic processes, accelerated drug discovery and materials development. As a dynamic and evolving field, synthetic chemistry continues to drive scientific progress, offering exciting prospects for groundbreaking discoveries in the coming years.

SYNFORM *What should be the role of publishers over the next 10 years?*

Professor D. Maiti Over the next decade, publishers will play a pivotal role in navigating the evolving landscape of scholarly communication. Embracing technological advancements, publishers must lead in the development of innovative platforms and tools that enhance accessibility, collaboration, and data integration. The promotion of open access initiatives will gain prominence, fostering wider dissemination of knowledge. Publishers will also be instrumental in addressing ethical considerations, ensuring transparency and reproducibility in research. Collaborative efforts between publishers, institutions, and researchers will be essential for shaping a dynamic and inclusive future for academic publishing.

SYNFORM *Please comment on joining the editorial board of* SYNLETT *as new Editor-in-Chief and share your vision for the journal.*

Professor D. Maiti I am honoured to be appointed as the new Editor-in-Chief of SYNLETT, a prestigious journal renowned for its commitment to excellence in organic chemistry research. With a strong background in the field, I am eager to contribute to the journal's legacy and further elevate its standing within the scientific community.

My vision for SYNLETT is rooted in fostering innovation and collaboration. I aim to enhance the journal's global reach by actively engaging with researchers and authors across diverse sub-disciplines of organic chemistry. By implementing rigorous yet transparent peer-review processes, we will ensure the publication of high-impact research that pushes the boundaries of synthetic organic chemistry.

Furthermore, I am committed to nurturing the next generation of researchers. Initiatives supporting early-career scientists and providing them with a platform to showcase their work will be a priority, reinforcing SYNLETT's role in shaping the future of organic chemistry.

I am excited about the collaborative journey ahead with the esteemed editorial board. Together, we will fortify SYNLETT's legacy as a beacon of excellence in organic synthesis, fostering a vibrant scholarly community and pushing the boundaries of scientific discovery.

SYNFORM *As Editor-in-Chief, what are your recommendations to researchers who want to publish their results in* SYNLETT*?*

Professor D. Maiti As Editor-in-Chief of SYNLETT, I advise researchers to meticulously align their submissions with the journal's scope, emphasizing the significance of their work in synthetic organic chemistry. Craft manuscripts with clarity, conciseness, and a focus on key findings, ensuring a compelling narrative. Rigorously detail experimental procedures and provide comprehensive supporting information to enhance reproducibility. Demonstrate ethical research conduct, engage thoughtfully with reviewers' feedback, and adhere to SYNLETT's citation style. Timely submission and responsiveness to editorial queries are essential for expediting the publication process and maintaining the journal's commitment to excellence.

SYNFORM *Finally, on a personal note, what do you do in your free time?*

Professor D. Maiti In addition to my academic interests, I have a passion for the fine arts, particularly classical music and painting. I also enjoy partaking in stimulating philosophical debates with colleagues and students, discussing

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profound ideas and their implications on our society. When time permits, I also cherish the opportunity to be in the great outdoors. These activities allow me to recharge my mind and spirit, ensuring that I return to my academic pursuits with renewed vigour and creativity.

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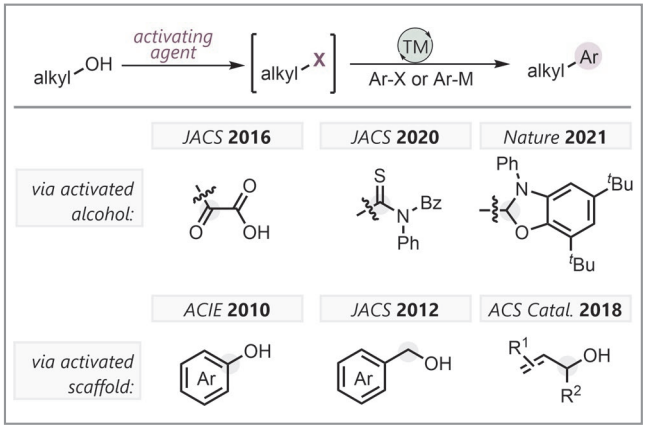
Deoxygenative Suzuki–Miyaura Arylation of Tertiary Alcohols through Silyl Ethers

Nat. Synth. **2023**, *2*, 663–669

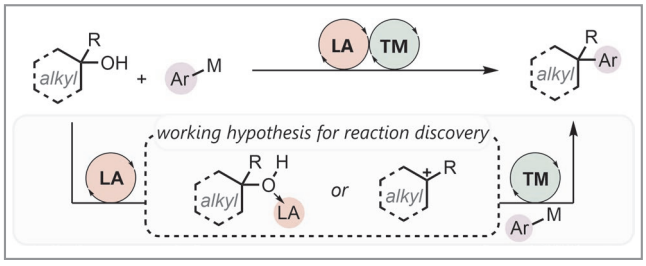
Suzuki–Miyaura cross-couplings are among the most utilized chemical reactions in the contemporary chemical industry, providing a rapid method for chemists to build molecular complexity. "While this method of forming carbon–carbon bonds is practical, two notable limitations exist: (1) The majority of Suzuki–Miyaura reactions feature the generation of biaryl linkages. The products are thus often flat molecules that lack the three-dimensional architecture that is common within bioactive molecules and natural products. (2) Most Suzuki–Miyaura reactions use organo(pseudo)halides as electrophilic reaction partners. Such species are scarcely available in nature, often toxic/carcinogenic, and generate heavy metal–halide salts as waste products," explained Professor Stephen Newman at the University of Ottawa (Canada), whose research group has a strong interest in this area of organic chemistry. "As chemists, we are problem-solvers. And as chemists, we should continuously push towards the development of methods that use naturally accessible substrates while generating the least amount of hazardous waste as possible," he added.

Alcohols have been identified as an ideal alternative to (pseudo)halide electrophiles in cross-coupling reactions. However, their successful employment in these transformations poses challenges due to their strong carbon–oxygen bonds and the potential for catalyst inhibition by alkoxides generated under the basic conditions typically employed. "Chemists have developed two key approaches towards employing alcohols in Suzuki–Miyaura arylations – the use of stoichiometric activating agents that render the carbon–oxygen bond weak enough to cleave (*J. Am. Chem. Soc.* **2016**, *138*, 13862–13865; *J. Am. Chem. Soc.* **2020**, *142*, 13246–13254; *Nature* **2021**, *598*, 451–456), or the use of carefully chosen activated alcohol scaffolds that afford stabilized reactive intermediates upon C–O bond activation (*Angew. Chem. Int. Ed.* **2010**, *49*, 4566–4570; *J. Am. Chem. Soc.* **2012**, *134*, 14638–14641; *ACS Catal.* **2018**, *8*, 86–89) (Scheme 1)," said Professor Newman.

Professor Newman's group has developed a method that obviates the aforementioned limitations in Suzuki–Miyaura arylations, offering a surprisingly simple method to achieve the arylation of a broad range of accessible aliphatic alcohols. "By using alcohols as reaction partners instead of (pseudo)halides, this method generates water as a waste product rather than metal–halide salts," explained Professor Newman. He continued: "Classical Lewis acid catalysis is used to facilitate activation of the C–O bond, rendering it reactive for Ni-catalyzed Suzuki–Miyaura coupling (Scheme 2). Mechanistic support provides evidence for an S_N1-like activation pathway, which to our knowledge has scarcely been reported as a strategy to mediate cross-coupling reactions. Thus, this reaction not only provides an effective method for generating complex, medicinally relevant structures from accessible materials, but it also contributes to the fundamental development of how we think about reaction mechanisms in cross-coupling chemistry."



Scheme 1 Selected examples of aliphatic alcohol arylation methods



Scheme 2 Dual catalysis approach to direct alcohol arylation *(this work)*

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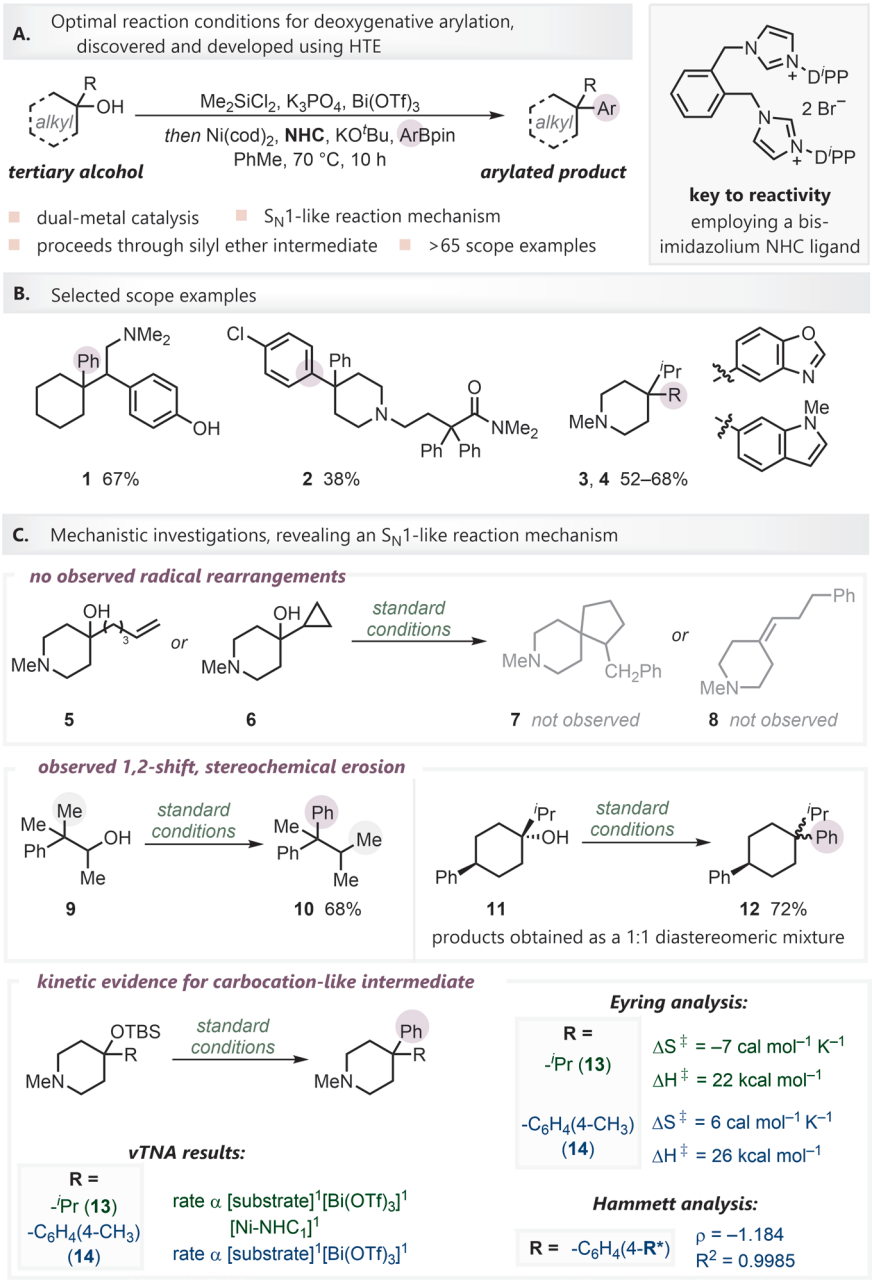
Professor Newman told SYNFORM that, as most chemistry research projects do, this work commenced with a mechanistic hypothesis. He said: "It is known that alcohols can be activated through Lewis acid catalysis to generate carbocation or carbocation-like intermediates (*Eur. J. Org. Chem.* **2011**, *2011*, 647–666). We imagined that we could exploit this reactivity by using a transition-metal catalyst to sequester these intermediates, thereby generating a formal oxidative addition complex that could undergo transmetalation and C–C bond-forming reductive elimination."

Immediately, the group was faced with a problem – with thousands of potential catalysts and chemical compounds available to be tested, how could they arrive at a single set of reaction conditions that would lead to success? "We turned towards the high-throughput experimentation labs housed within the Centre for Catalysis Research and Innovation (CCRI) at the University of Ottawa for an answer," said Professor Newman. He continued: "The screening of approximately 800 different reaction conditions led to many tears shed from the eyes of the lead author on this work, alongside the discovery of a chemical reaction that employs $Bi(OTf)_3$ as a Lewis acid catalyst and a specialized nickel catalyst to facilitate the arylation of tertiary alcohols. We found that the key to reactivity was the employment of an unusual bis-imidazolium N-heterocyclic carbene (NHC) ligand, which had not yet been broadly identified as a privileged scaffold. Future prospects within our research group will seek to explore further applications of these bis-imidazolium NHCs in catalysis, while also developing insight into what makes them effective for this transformation."

Further optimization of this arylation reaction saw the authors realize a substantially higher reaction yield upon including a chlorosilane as a drop-in additive, which rapidly converts the unprotected alcohol into a silyl ether intermediate (Scheme 3A). "With the optimized set of reaction conditions in hand, we were able to successfully arylate a range of tertiary, cyclic alcohols with variably functionalized aryl pinacol boronic esters (Scheme 3B)," remarked Professor Newman. He revealed that yields up to 84% were obtained in the presence of phenol, ester, chloro, fluoro, amine and alkyne functionalities as well as variously functionalized *N*- and *O*-containing heterocycles. Chemoselective activation of tertiary cyclic alcohols was further demonstrated in the presence of primary, secondary and tertiary acyclic alcohols.

"While we were satisfied with the successful development of a method to arylate non-π-activated tertiary alcohols, we recalled that this project began with a mechanism in mind," said Professor Newman. He went on: "Seeking evidence to either support or refute the originally hypothesized mechanism, we prepared a series of substrates designed to probe the existence of various reactive intermediates. Collectively, we observed stereochemical erosion of a diastereomerically pure alcohol, 1,2-carbocation shifts, and no evidence of radical rearrangements. Further, a kinetic analysis of this transformation, conducted through variable time normalization analysis (vTNA), Hammett and Eyring analyses, revealed evidence supporting the generation of an electrophilic intermediate, though the first order dependence on Ni in the reaction of non-π-activated alcohols suggests a true carbocation is not likely formed (Scheme 3C)."

"In summary, we have disclosed a nickel/bismuth dual-catalyzed method for the Suzuki–Miyaura arylation of non-π-activated tertiary alcohols," said Professor Newman, continuing: "This reaction allows the transformation of easily accessible substrates at a $C(sp^3)$-hybridized position without the requirement to proceed through activated halide or pseudohalide intermediates. To the best of our knowledge, this method exists among scarce reports of the interception of carbocation-like intermediates by transition metals, potentially opening an avenue for further disclosures pertaining towards the employment of $C(sp^3)$-hybridized electrophilic partners in cross-coupling chemistry." Professor Newman concluded: "Current research within the group is focused on expanding the scope of this transformation beyond tertiary alcohols and beyond aryl pinacol boronic acid coupling partners."



Scheme 3 (A) Optimal reaction conditions for deoxygenative arylation, discovered and developed using THE. (B) Selected scope examples. (C) Mechanistic investigations, revealing an S_N1-like reaction mechanism.

About the authors

A. Cook

Adam Cook is a PhD candidate at the University of Ottawa (Canada). He completed his undergraduate education at the University of Ontario Institute of Technology (presently known as OntarioTech U, Canada), conducting research on Brønsted-acid catalysis under the supervision of Dr. Yuri Bolshan. Along the way, he was awarded a research scholarship that saw him investigate the Lewis acidity of boron catalysts under the supervision of Dr. Rebecca Melen at Cardiff University. Presently, he works in the lab of Dr. Stephen Newman utilizing high-throughput chemical techniques to prod the ever-expanding world of nickel-catalyzed carbon-oxygen bond activation.

P. St-Onge

Piers St-Onge completed his B.Sc. at the University of Toronto (Canada) where he conducted research on FLP catalysis under the supervision of Professor Douglas Stephan and soon-after pursued the development of novel synthetic pathways to access cyclobutanols in the laboratory of Professor Sophie Rousseaux. Piers is currently a 4th year Ph.D. candidate at the University of Ottawa (Canada) where he investigates the unique reductive properties of siloxanes and alkoxide bases for both synthesis and de-functionalization reactions.

Prof. S. Newman

Stephen G. Newman grew up in Newfoundland, Canada and attended Dalhousie University (Canada), where he completed his B.Sc. He received a PhD University of Toronto (Canada) studying palladium catalysis in the laboratory of Mark Lautens and carried out postdoctoral studies in the lab of Prof. Klavs F. Jensen at the Massachusetts Institute of Technology (USA) where he investigated new continuous processes for chemical manufacturing. Stephen is currently an Associate Professor at the University of Ottawa (Canada) where he holds the Tier 2 Canada Research Chair in Sustainable Catalysis.

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Photosensitized O_2 Enables Intermolecular Alkene Cyclopropanation by Active Methylene Compounds

Science **2023**, *381*, 545–553

Cyclopropanes are important structural motifs in pharmaceuticals. Their significance stems from the ability to modulate a drug's therapeutic properties by enhancing potency and brain permeability and decreasing off-target effects. For these reasons, several FDA-approved drugs, including Nirmatrelvir (Paxlovid™) for Covid-19, Telaprevir for Hepatitis C and Abacavir for HIV/AIDS (Figure 1) among many more, feature cyclopropane rings in their structural architecture. Cyclopropanes are most conveniently derived from alkenes, and several powerful methods, such as the Simmons–Smith, the Johnson–Corey–Chaykovsky, the Kulinkovich and rhodium-catalyzed reactions, convert a swathe of alkenes into cyclopropanes. Yet, these methods require the use of synthetically challenging and highly energetic materials (diazoalkanes and dihaloalkanes) and operationally less amenable bases (LDA, KHMDS, $NaNH_2$ or BuLi). Cyclopropanation of alkenes with operationally simple, bench-stable and non-explosive reagents has always been a difficult challenge in organic synthesis. In a recent publication in *Science*, the group of Professor Ramesh Giri at The Pennsylvania State University (USA) disclosed a novel stepwise radical cyclopropanation of unactivated alkenes achieved directly with active methylene compounds under catalytic photoredox conditions with visible-light blue LED, by harnessing an O_2/I_2 couple as an electron shuttle system for

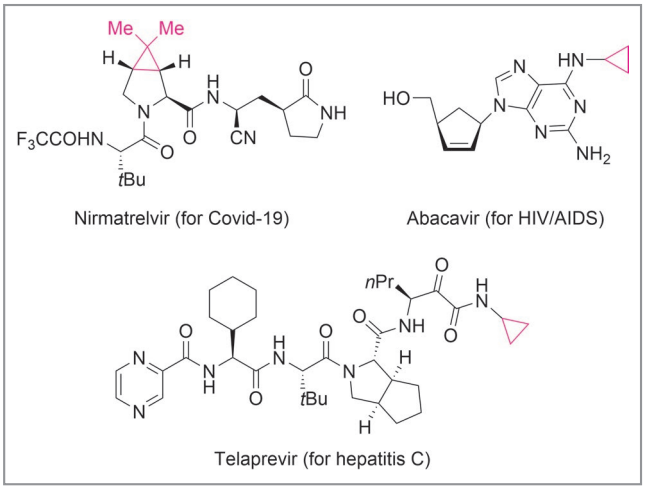

Figure 1 Selected market drugs with a cyclopropyl ring

both generating an α-carbon radical and turning over a photocatalyst (PC). Professor Giri explained: "This new method is operationally simple and conducted in air with bench-stable chemicals and without requiring stringent safety and sensitivity measures. Since an unlimited number of functionally diverse active methylene compounds are either commercially available or can be readily synthesized, the current method provides a very straightforward and practical approach for the conversion of unactivated alkenes into cyclopropanes."

Among different methods available, the metal-catalyzed addition of donor/acceptor-stabilized diazoalkanes to alkenes remains the most preferred route for cyclopropanation. "The premise in this method is the generation of reactive but donor/acceptor-stabilized carbenoid intermediates through the loss of N_2 for direct insertion into alkenes to create two requisite carbon–carbon (C–C) bonds," explained Professor Giri. He continued: "Since carbenes can be viewed as a 'double radical' species with two electrons on the divalent carbon, we envisioned that cyclopropanation could be effected by stepwise generation of carbon radicals under catalytic photoredox conditions from active methylene compounds with the eventual loss of two hydrogen atoms (Scheme 1A). We opted for the use of oxidants as intermediary electron shuttles since the direct electron transfer from a PC to an active methylene compound would require a thermodynamically untenable loss of a hydride from the acidic α-carbon of an active methylene compound. While this working principle was theoretically sound, there was no literature support for stepwise radical addition of an active methylene group to an alkene to create a cyclopropyl ring. Consequently, our initial studies largely focused on examining a large toolkit of oxidants and extracting an acceptable oxidant as an electron shuttle." Initially, the authors were extremely surprised that an unusual combination of oxygen and alkyl iodides furnished cyclopropanated products in quantitative yields (Scheme 1B). "However, our detailed mechanistic studies later revealed that oxygen was acting as the sole electron transporter as anticipated to shuttle electrons from the PC to the active methylene compounds (Scheme 1C)," commented Professor Giri. "Alkyl iodides were simply dissociating to generate traces of iodine under the photoredox conditions and enabling the PC to turnover during the catalytic process, and also potentially pair with the

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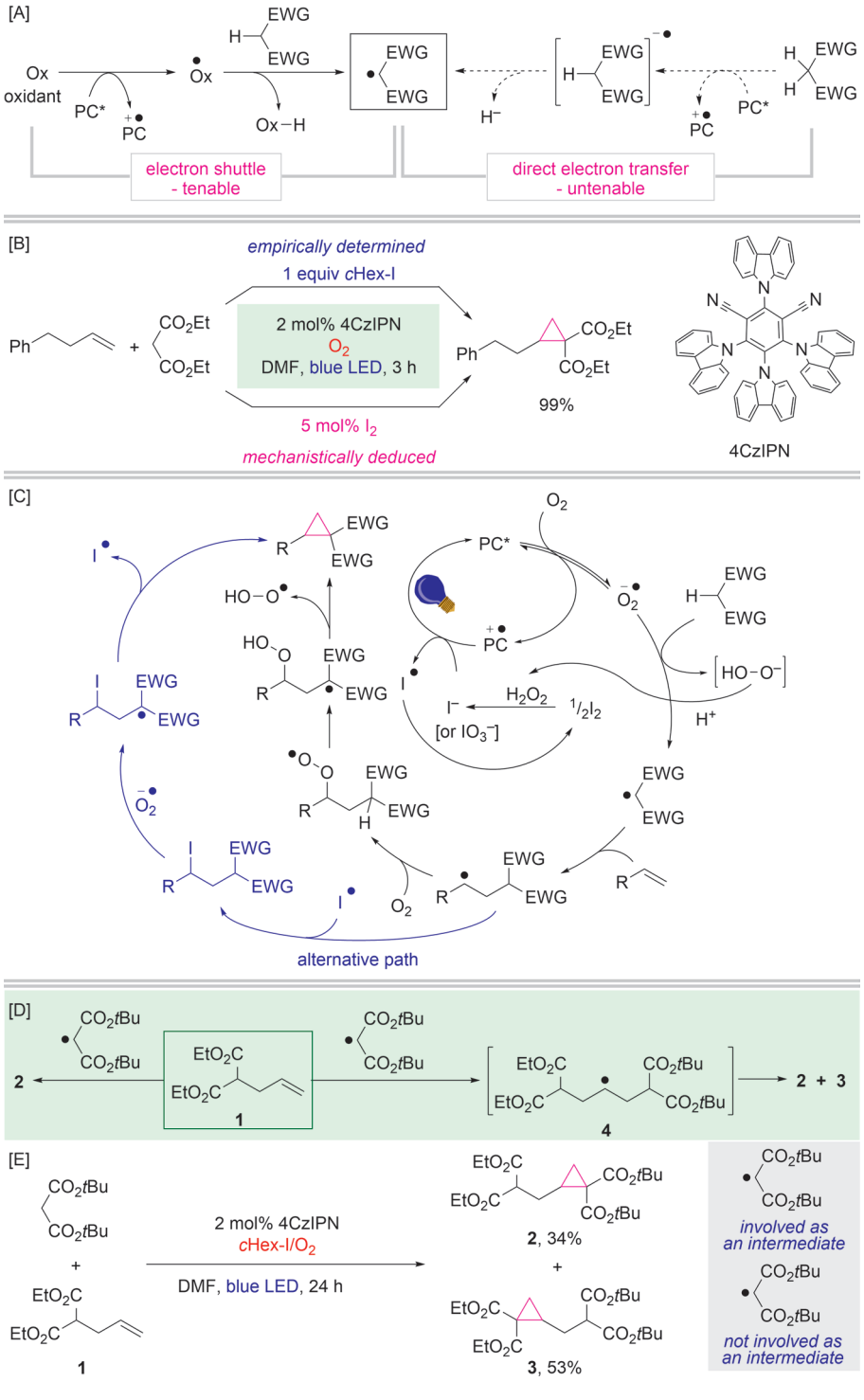


Scheme 1 [A] Hypothesis for electron shuttle to generate carbon radicals. [B] Reaction conditions for alkene cyclopropanation. [C] Proposed catalytic cycle. [D] Design of allylmalonate **1** as a probe to discern carbenes from radicals. [E] Mechanistic experiment with allylmalonate probe **1**.

alkyl radical for a radical S_N2 ring closure. We unambiguously established the role of iodine by simply replacing alkyl iodides with 5 mol% iodine under the standard conditions, which also generated the cyclopropanated product in quantitative yield."

Professor Giri revealed that during the reaction development, a key question about whether the current cyclopropanation still proceeded via a carbene intermediate clouded the excitement of their success in directly cyclopropanating unactivated alkenes intermolecularly with active methylene compounds. "Since there was no direct way to discern radicals from carbenes under the catalytic conditions, we designed an experiment with allylmalonate **1** as a mechanistic probe (Scheme 1D)," said Professor Giri. He explained: "The probe **1** features an innate diethyl malonate motif that would function as an innocuous bystander, should the reaction proceed by a carbene intermediate, enabling the formation of cyclopropane **2** as the sole product. However, it would function as a non-innocent internal competitor to intercept a pre-ring-closure intermediate **4** should the reaction proceed by stepwise radical intermediates, leading to the production of a mixture of cyclopropanes **2** and **3** as the end products. Indeed, our experiment with the probe **1** furnished a 2:3 mixture of cyclopropanes **2** and **3** (Scheme 1E), thereby unambiguously confirming that the cyclopropanation of the alkene occurs through a stepwise radical addition – instead of carbene insertion."

"Our reaction has a remarkably broad substrate scope both with alkenes and active methylene compounds (Figure 2)," remarked Professor Giri. He continued: "In this publication, we demonstrated cyclopropanation of a range of terminal and 1,2-disubstituted internal alkenes with 18 different active methylene groups bearing a combination of ester, amide, ketone, nitrile, sulfonyl and isocyanate. Active methylene compounds containing furanyl, thiophenyl and pyridyl heterocycles were also compatible. These reactions proceeded with good diastereoselectivity when there was a large size disparity between two substituents on the active methylene compounds. The reaction also shows remarkable compatibility with diverse functionalities on alkenes, tolerating sensitive groups like carbonate, carbamate, epoxide, alkyne, halides, phosphates and free hydroxyls. Furthermore, it can be applied to alkenes present in complex natural products, drugs, and bioactive molecules including steroids, alkaloids, flavonoids, terpenoids, fatty acids, vitamin E and nonsteroidal anti-inflammatory drugs (NSAIDs) such as loxoprofen, indomethacin and ketorolac, and antibiotic penicillin. Most importantly, our method tolerated isocyanate and amide moieties – that are relevant in pharmaceutical and medicinal chemistry – for introducing cyclopropyl amides and ureas, which are currently accessed in a three-step process commencing with the cyclopropanation of acrylic esters by diazomethane. The 1,1-dicarbonyl- and 1-carbonyl-1-sulfonylcyclopropyl products generated by our methods are also highly significant in drug discovery since they display a range of inhibitory activities against biological targets including Alzheimer's disease."

Professor Giri concluded: "This novel cyclopropanation reaction is enabled by a photoredox catalyst excited under blue LED in ambient conditions, avoiding stringent safety and precautionary requirements for this class of reactions. The process is enabled by the ability of photosensitized dioxygen to function as an electron transporter to transit electrons from PC* to active methylene sets for the generation of α-carbon radicals. The reaction demonstrates a remarkably broad scope concerning both the active methylene compounds and alkenes bearing a diverse set of functionalities. It can be successfully applied to cyclopropanate alkenes in complex molecules, including pharmaceuticals and natural products. We anticipate that the development of this method will create a new dimension in the field of cyclopropanation, and will inspire further global research in this area."

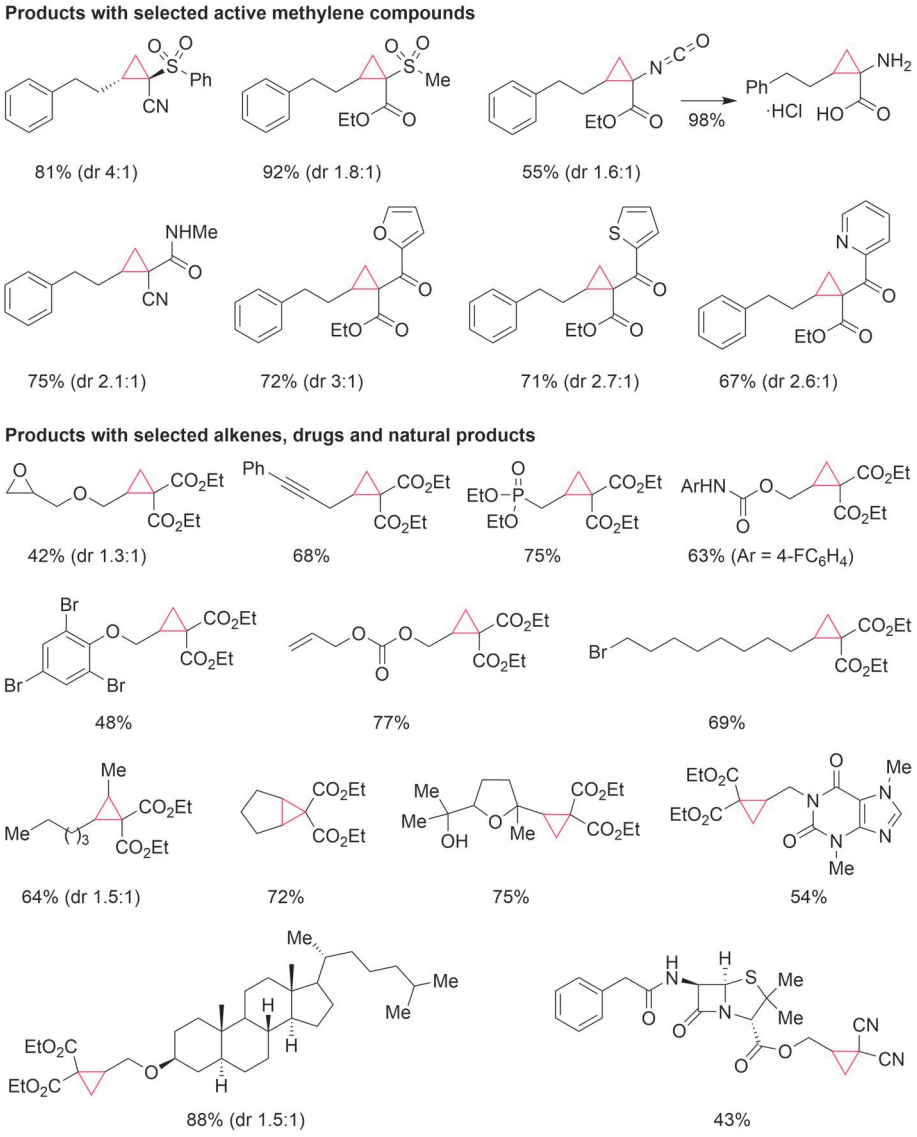
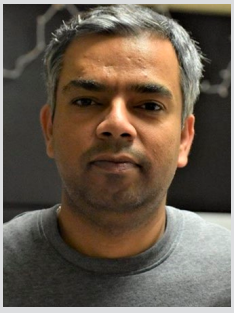


Figure 2 Selected scope of the cyclopropanation reaction. Reaction conditions: 1.0 mmol scale (in 6 dram vials), 5.0 mL DMF, 440 nm blue LED (36 Watt Kessil lamp, 100% intensity), ambient temperature (~35–40 °C), O_2, 3– 24 h. Yields are for isolated products; dr was determined by ^{1}H NMR.

About the authors

Dr. D. Poudel

Dhruba Poudel was born in Nepal. He earned his bachelor's degree in chemistry in 2010 from Tri-Chandra College, Kathmandu, Nepal, and his master's degree in organic chemistry in 2013 from Central Department of Chemistry, Kirtipur, Nepal. In 2016, he moved to the USA to pursue higher studies. He was awarded a PhD in chemistry in 2021 from Miami University of Ohio, USA, working under the supervision of Dr. Richard Taylor with the primary focus of his research being synthesis and/or study of dendritic macromolecules, bioconjugates, molecular antennae, and fluorescence transfer. In 2021, he started his career as a postdoctoral scholar at Penn State University (USA) under the supervision of Prof. Ramesh Giri. His current research work focuses on functionalization of alkenes using photoredox catalysis. As a postdoc, he has recently developed an innovative method for intermolecular cyclopropanation of alkenes under visible light in the presence of a sensitizer using methylene compounds containing electron-withdrawing groups on either side of them.



Dr. A. Pokhrel

Amrit Pokhrel was born and raised in Nepal and received his MSc in chemistry at Tribhuvan University (Nepal) in 2004. Following his master's studies, he worked as instructor of chemistry at the undergraduate level. In 2021, he received his doctoral degree from the University of New Mexico (USA) under the supervision of Professor Martin Kirk where he investigated molybdoenzyme models using spectroscopic and computational techniques. After a stint of postdoctoral research at Penn State (USA) with Prof. Ramesh Giri, he started work as a research scientist in a biopharma company based in Maryland (USA).

R. K. Tak

Raj Kumar Tak was born in Rajasthan, India. He completed his master's degree from Rajasthan University Jaipur (India). He received his PhD in chemistry from Central Salt and Marine Chemicals Research Institute, India in 2018 under the supervision of the late Prof. Dr. R. I. Kureshy working on stereoselective reactions. In April 2019 he received a JSPS Post-Doctoral Fellowship and worked under Prof. Dr. Masakatsu Shibasaki at the Microbial Chemistry Research Foundation (BIKAKEN), Tokyo, Japan. Raj started his second postdoc at Penn State (USA) in September 2021 under the supervision of Prof. Ramesh Giri, where his research focused on asymmetric dicarbofunctionalization and photocatalysis.

Dr. M. Shankar

Majji Shankar was born in Ichapuram, India. In 2012, he received an MSc degree from Acharya Nagarjuna University (India), then he joined Prof. Akhila K. Sahoo's group at the School of Chemistry, University of Hyderabad (India) to pursue his doctoral studies and worked in the area of transition-metal-catalyzed C–H annulation. In December 2020, he moved to Japan and worked on the synthesis of hetero-nanographenes as a postdoctoral researcher under the supervision of Prof. Kenichiro Itami at ITbM, Nagoya University. Currently, he is a postdoctoral researcher in the lab of Prof. Ramesh Giri at the Penn State (USA). His research interests lie in the development of new methodologies and dicarbofunctionalization reactions of alkenes.

Prof. R. Giri

Ramesh Giri was born in Chitwan, Nepal and graduated with distinction from Tribhuvan University (Nepal) with an MSc in organic chemistry in 2000 under the supervision of Prof. S. M. Tuladhar. As a Shell Centenary Scholar, he received his MPhil in bioorganic chemistry in 2003 from the University of Cambridge (UK) with the late Prof. J. B. Spencer. He earned his PhD in chemistry from The Scripps Re-

search Institute (USA) in 2009 with Prof. Jin-Quan Yu, where he studied Pd-catalyzed C–H functionalization. As a postdoctoral fellow with Prof. John F. Hartwig at UC Berkeley/UIUC (USA), he conducted mechanistic studies on Ullmann amination and biaryl ether forming processes. In 2012, he joined the faculty at the University of New Mexico (USA) as an Assistant Professor where he was promoted to Associate Professor in 2018. In 2019, he moved to Pennsylvania State University (USA) as a Weinreb Early Career Professor and was promoted to Full Professor in 2022. He has received an NSF CAREER Award, an NIH MIRA Award and a Thieme Chemistry Journals Award. His research group focuses on developing transition-metal and visible-light photoredox catalyzed reactions, largely focusing on the development of alkene difunctionalization reactions and investigating their mechanisms.

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Synthesis and Properties of Cyclic Sandwich Compounds

Nature **2023**, *620*, 92–96

The ground-breaking discovery of the first sandwich complex, ferrocene, marked the birth of modern organometallic chemistry. The structure of sandwich compounds, consisting of a central metal ion complexed by two planar aromatic ligands, is reminiscent of a classical sandwich, with the flat ligands representing two slices of bread covering the filling, the central metal. The appreciation for this unprecedented structural motif culminated in the award of the 1973 Nobel Prize in Chemistry to Fischer and Wilkinson for their work on elucidating the molecular structure of ferrocene.

Ever since, the sandwich motif has inspired organometallic chemists on their journey towards exciting novel compounds for a plethora of applications and sparked the hunt for larger and larger sandwiches. Going beyond the prototypical sandwich structure, $[M(C_nH_n)_2]$, multidecker sandwich complexes with alternating aromatic ligands and metals have been assembled (*Synth. React. Inorg. Met.-Org. Chem.* **1972**, *2*, 239–248; *J. Phys. Chem. A* **2005**, *109*, 9–12; *New J. Chem.* **2011**, *35*, 517–528; *J. Phys. Chem. C* 2014, *118*, 5896–5907; *J. Am. Chem. Soc.* **2017**, *139*, 9895–9900). However, no structural motif apart from longer and longer one-dimensional chains has been reported until the publication of the title article, and the existing rare examples of circular oligomeric metallopolymers were held together by bridging units between individual sandwich subunits, instead of direct metal–ligand interactions alone (*Chem. Lett.* **1994**, *23*, 67–68; *Angew. Chem. Int. Ed.* **1997**, *36*, 387–389; *Angew. Chem. Int. Ed.* **2007**, *46*, 9069–9072; *Nat. Chem.* **2016**, *8*, 825–830).

Professor Peter Roesky at the Karlsruhe Institute of Technology (Germany) told SYNFORM: "In recent work by our group, we realized a bending in the sandwich structure of lanthanide quadruple-decker complexes featuring a triisopropylsilyl-substituted cyclooctatetraenediide ligand as the slice of bread (*Angew. Chem. Int. Ed.* **2021**, *60*, 24493–24499). Now, what happens when growing a bent sandwich chain further and further? Right – at one point the chain ends will meet, resulting in a circular sandwich complex."

Intrigued by this realization, the group dived into the synthesis of half-sandwich complexes. Professor Roesky explained: "These consisted of only one metal ion and one aromatic ligand, based on the cyclooctatetraene derivative described above, which would formally constitute an ideal monomeric starting point for constructing longer and longer bent chains. And indeed, starting from solvent-stabilized half-sandwich complexes of the type $[M(Cot^{TIPS})(thf)_3]$ (M = Sm, Eu, Yb, Sr; Cot^{TIPS} = 1,4-$(^iPr_3Si)_2C_8H_6^{2-}$; thf = tetrahydrofuran) enabled us to let bent chains grow until the ends met (see Figure 1), giving birth to an entirely new compound class, cyclic metallocenes, or *cyclocenes*, for short."

Their initial synthetic attempts focused on Eu(II). Professor Roesky said: "Already, by shining UV-light on the reaction mixture, a visual change in the luminescence from blue (starting material) to orange was observed (see Figure 2), evidencing the formation of a new species even without elaborate analytics."

However, succeeding in the synthesis of these compounds only marked the first of many, many milestones. "The fact that the center of the cyclocenes is empty generates a substantial amount of unfilled space within the solid-state structure, rendering the crystallographic characterization inherently difficult," remarked Professor Roesky. He continued: "Thus, a careful optimization of the crystallization conditions needed to be carried out to obtain single crystals sufficiently large to result in X-ray diffraction data of publishable quality. Apart from the synthetic challenge, refinement of the obtained structures proved to be a formidable and time-consuming task."

To explore the reasons for the formation of the cyclic structures, the authors expanded the general synthetic strategy from Eu(II) to metal ions of similar ionic radii, Sm(II) and Sr(II). Professor Roesky recalled: "Isostructural 18-membered cyclocenes were obtained in all these experiments, giving an indication that the size of the metal ion plays a crucial role, and that the lanthanide f-orbitals are not structure-determining. In line with this, subsequent experiments carried out with the smaller ion Yb(II) resulted in a differently sized cyclocene, a four-membered ring."

"Elaborate quantum chemical calculations with TURBOMOLE (https://turbomole.org) corroborated and rationalized these experimental findings," said Professor Roesky. He continued: "The bending of the individual sandwich subunits within the cyclocenes proved to be determined by the steric demand of the ligand's substituents. While unsubstituted cyclooctatetraene yielded the well-known linear sandwich structure, the introduction of bulky groups induced a deviation from linearity, the extent of which was shown to be dependent on the size of the ring substituents."

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Professor Roesky explained that the energy gained upon closure of the ring is decisive, making cyclocenes the preferred structure over any other conceivable arrangement.

"The fact that employing Yb led to a smaller ring than Sm, Eu and Sr was traced back to the higher Lewis acidity of Yb, rendering the removal of all THF molecules from the half-sandwich starting material unfeasible," said Professor Roesky. He went on: "Instead, one solvent molecule remained attached to the Yb ion, resulting in a more pronounced bending and consequently a smaller cyclocene."

Professor Roesky explained that carrying out quantum chemical calculations on molecular systems of this size (up to 1386 atoms and about 25000 cartesian basis functions for the 18-membered-ring structure) with moderate computational resources and energy consumption was solely enabled by the high efficiency of modern quantum chemical software packages.

"In summary, we pioneered the synthesis of cyclic multidecker sandwich complexes, overcoming the previous limitation of metallocene chemistry to linear structural motifs," said Professor Roesky. He added: "Our approach is based on the structurally induced self-assembly of monomeric half-sandwich complexes to discrete molecular nanorings."

Professor Roesky acknowledged that while it is still too early to estimate the future impact of this work to the full extent, the synthesis and structural characterization of the archetypical cyclocenes undoubtedly add to the synthetic chemistry toolbox, opening a new chapter in the intriguing world of organometallic chemistry.

The work has laid the foundation for future explorations of cyclocenes all over the periodic table. "Constructing rings of different sizes and making use of the large empty space in the ring center for host–guest chemistry are the initial focus of our research," said Professor Roesky, continuing: "Stabilizing the structures in solution would allow for exciting further experiments to be carried out. Apart from that, establishing ways of communication between the metal ions in the ring may lead to unprecedented electronic properties. Future applications may, for instance, lie in the use of cyclocenes as switchable molecular gateways or channels."

Professor Roesky concluded: "We have made the first step in a new direction, now being excited and looking forward to the surprises the future holds in store for us."

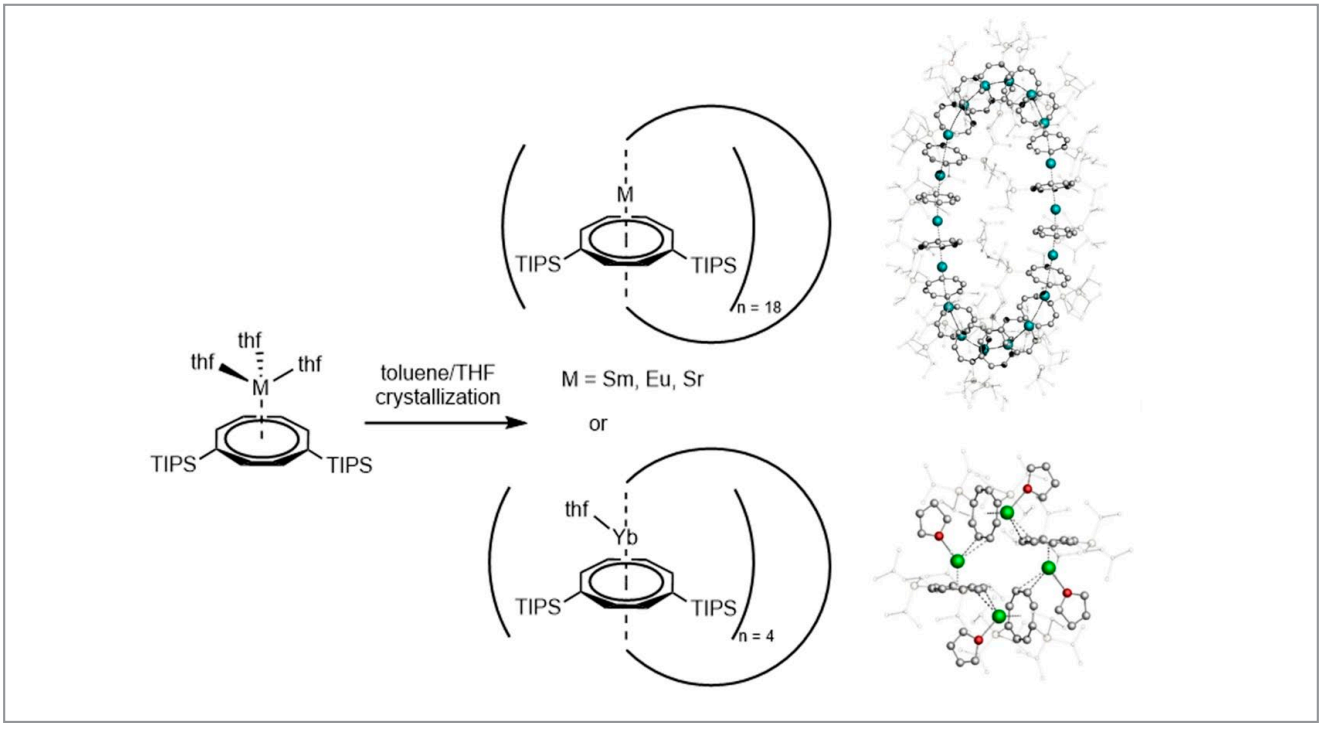

Figure 1 Synthesis and representative solid-state molecular structures of the 18-membered (Sm, Eu, Sr) and 4-membered (Yb) cyclocenes (reproduced with permission from *Nature* **2023**, *620*, 92–96).

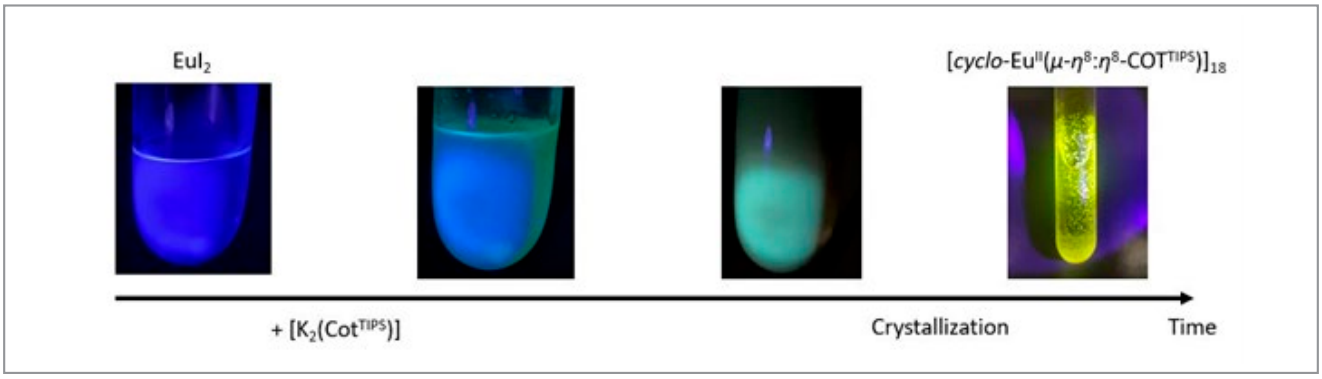

Figure 2 Formation and luminescence of the 18-membered Eu cyclocene under UV light.

About the authors

Dr. L. Münzfeld

Luca Münzfeld obtained his master's degree in chemistry at Karlsruhe Institute of Technology (KIT, Germany) in 2018. Subsequently, he pursued a PhD at the same university in the group of Professor Peter W. Roesky. Becoming bored with academia, he switched to the dark side in 2021 and started making vitamins in industry. He received his PhD in 2022 with distinction for his work on lanthanide sandwich compounds featuring unique structural motifs and properties.

Dr. A. Hauser

Adrian Hauser studied chemistry at the Karlsruhe Institute of Technology (KIT, Germany) and received his master's degree in 2019 under the supervision of Prof. Dr. Peter W. Roesky. He subsequently completed his PhD in the same research group, working on the synthesis of carbon-based lanthanoid sandwich compounds and the activation of group 15 elements. In September 2023, he decided to turn his back on academic research and earn the big bucks in vitamin synthesis.

S. Gillhuber

Sebastian Gillhuber finished his master's degree in chemistry under supervision of Prof. Florian Weigend at the Karlsruhe Institute of Technology (KIT, Germany) in 2021. He subsequently joined the groups of Prof. Peter W. Roesky (KIT) and Prof. Christopher Barner-Kowollik (Queensland University of Technology, QUT, Australia) for joint PhD studies, working on metal-functionalized polymers.

Dr. S. Lebedkin

Sergei Lebedkin received a PhD in chemical physics at the Institute of Chemical Physics of the Russian Academy of Sciences (Russian Federation) in 1993. After postdoctoral research at the Max Planck Institute for Nuclear Physics in Heidelberg (Germany), he worked at the Research Centre Karlsruhe (Germany) as a research fellow. He joined the group of Prof. Manfred Kappes at the Institute of Nanotechnology (now part of KIT, Germany) in 1999. His research interests include Raman and luminescence spectroscopy and microscopy applied to metal-organic complexes and nanosized metal-cluster compounds.

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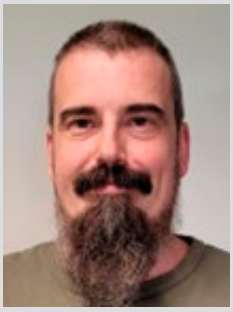
Nicolai D. Knöfel received his master's degree in chemistry from the Karlsruhe Institute of Technology (KIT, Germany) in 2015, followed by a PhD study in the group of Professor Peter W. Roesky (Department of Inorganic Chemistry, KIT). He received his PhD with distinction in 2019, with a research focus on metallopolymers and multiply bonded transition metals. He is currently working as a laboratory manager in the chemical industry.

Dr. C. Zovko

Christina Zovko undertook her chemistry studies at the Karlsruhe Institute of Technology (KIT, Germany). She began her doctorate in the group of Professor Peter W. Roesky in the field of inorganic chemistry. Following her PhD, she successfully completed her Master of Business Administration at the Collège des Ingénieurs. Since 2023 she has been working as a Division Controller in the chemical industry.



Dr. M. Gamer

Michael Gamer graduated in chemistry from the University of Karlsruhe (TH, Germany) in 1999. He started his PhD thesis under the supervision of Prof. P. W. Roesky in Karlsruhe and finished it at the Free University of Berlin (Germany) in 2003. Since 1996 he has been associated with the Roesky group in various positions, since 2008 in a permanent position as 'Akademischer Rat' at the Karlsruhe Institute of Technology (Germany).

Prof. F. Weigend

Florian Weigend obtained his doctoral degree in chemistry from the University of Karlsruhe (TH, Germany) in 1999 and completed his habilitation in theoretical chemistry in 2007. After positions as researcher and group leader at the Institute of Nanotechnology at the Karlsruhe Institute of Technology (KIT, Germany), he joined the University of Marburg (Germany) in 2020 as the head of the applied quantum chemistry unit. Since 2007, he has been a member and CEO of TURBOMOLE GmbH. His research interests include the development and implementation of basis sets and relativistic methods for the calculation of molecular properties as well as the application of the developed methods to gather an in-depth understanding of the properties of molecular systems of chemical interest.

Prof. M. M. Kappes

Manfred Kappes received a PhD in physical chemistry at MIT (USA) in 1981. After postdoctoral research at the University of Bern (Switzerland), he joined Northwestern University (USA) as an assistant professor in 1987 and became an associate professor in 1991. In 1992 he moved to Karlsruhe (Germany) where he is a professor in the institute of physical chemistry of KIT with a joint appointment at the institute of nanotechnology. His research interests include optical spectroscopy of nanosystems at low temperatures (ranging from CNTs to trapped molecular ions), hybrid mass spectrometry including method development as well as structure and reactivity of transition-metal clusters (both bare and ligand-stabilized).

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Prof. P. W. Roesky

Peter Roesky obtained his diploma in chemistry in 1992 from the University of Würzburg (Germany) and his doctoral degree from the Technical University of Munich (Germany) in 1994. After postdoctoral work at Northwestern University, USA (1995–1996), he completed his habilitation at the University of Karlsruhe (Germany) in 1999. He was appointed a full professor at the Freie Universität Berlin (Germany) in 2001, during which he joined the faculty of chemistry and biochemistry. In 2008, he became a full professor of inorganic functional materials at the Karlsruhe Institute of Technology (KIT, Germany). From 2013 to 2015, he served as Dean of the Faculty of Chemistry and Biosciences at KIT. His current research interest revolves around the synthetic inorganic and organometallic chemistry of s-block metals, silicon, phosphorus, gold, and lanthanides.

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