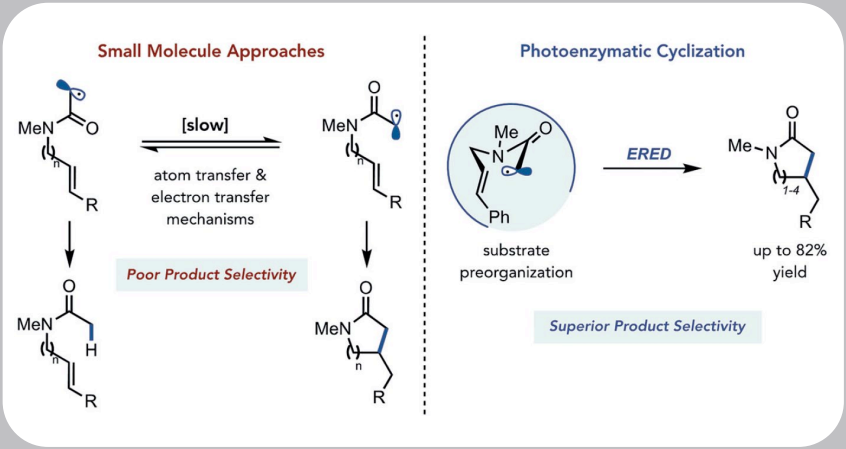
Synform

People, Trends and Views in Chemical Synthesis

2023/05

SYNLETT Best Paper Award 2022: A Photoenzyme for Challenging Lactam Radical Cyclizations

Highlighted article by B. T. Nicholls, T. Qiao, T. K. Hyster



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Thieme

Dear Readers,

In this May issue of SYNFORM we honour the other 2022 Best Paper Award winners. In the April issue we interviewed Professor Christoph Schneider and co-authors from the University of Leipzig (Germany), who were the recipients of the SYNTHESIS Best Paper Award 2022. In this issue we have the great pleasure to feature the interview with Professor Todd K. Hyster, and co-authors Bryce T. Nicholls and Tianzhang Qiao, from Cornell University (USA), who are the recipients of the SYNLETT Best Paper Award 2022 for their article "A Photoenzyme for Challenging Lactam Radical Cyclizations" (*Synlett* **2022**, *33*, 1204–1208). The interview – in our typical SYNFORM style – provides background information on their prize-winning research, as well as about current research activities ongoing in the group. The other articles in this very rich May issue include two more interviews, the first with Professor Thierry Ollevier (Université Laval, Canada), who joined the Editorial Board of *SynOpen* as the new Editor-in-Chief; the second with Professor Jung Min Joo (Kyung Hee University, South Korea) who joined the Editorial Board of SYNTHESIS; both with effect of January 2023. Welcome to the Thieme Chemistry family!! The issue is completed by two Literature Coverage articles: the first covers the Rh and Zn cocatalyzed [4+2]-cycloaddition of yne-vinylcyclobutanones – developed by Z.-X. Yu (P. R. of China) – to afford 5/6, 6/6 bicycles and other multicycles with a vinyl group at the bridgehead position. The second covers the synthesis of *meta*-substituted arene bioisosteres from [3.1.1]propellane, as reported by E. A. Anderson (UK) in a recent Nature paper.

Enjoy your reading!

In this issue

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 Synform **2023/05**, A80 • Published online: April 14, 2023 • DOI: 10.1055/s-0040-1720594

Editorial Board Focus: Professor Thierry Ollevier (Université Laval, Canada)

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 Professor Thierry Ollevier (Université Laval, Canada) who joined the Editorial Board of *SynOpen* with effect of January 2023.

Biographical Sketch

Prof. T. Ollevier

Thierry Ollevier was born in Brussels (Belgium) and obtained his B.Sc. (1991) and Ph.D. (1997) at the Université of Namur (Belgium). He was a post-doctorate fellow at the Université Catholique de Louvain (Belgium) under I. E. Markó (1997), a NATO post-doctorate fellow at Stanford University (USA) under B. M. Trost (1998–2000), then post-doctorate fellow at the Université de Montréal (Canada) under A. B. Charette (2000–2001). After an Assistant Professor appointment (2001) at Université Laval (Québec, Canada), he became first an Associate Professor (2006) and is now a Full Professor. Current research in his group aims at designing novel catalysts, developing catalytic reactions and applying these methods to chemical synthesis. He is active in the areas of iron catalysis, ligand design, asymmetric catalysis, fluorine chemistry, diazo and diazirine chemistry, flow chemistry, and bismuth chemistry. He has published more than 80 papers and 35 encyclopedia articles and book chapters. He served as an Associate Editor of *RSC Advances* from 2015 to 2022 and was admitted as a Fellow of the Royal Society of Chemistry (2016). After five years serving as an Advisory Board member of *SynOpen*, he was appointed as Editor-in-Chief of *SynOpen* in January 2023.

INTERVIEW

SYNFORM *Please comment on your role as Editor-in-Chief of SynOpen.*

Prof. T. Ollevier As the Editor-in-Chief, I am very ably supported by a great Executive Board. In addition to the Executive Board, we are establishing an Associate Board that brings a wide range of expertise and diversity to the team. Finally, we have a very dynamic group of Advisory Board Members who provide valuable help and efficiently promote *SynOpen* worldwide. Both the Associate and the Advisory Board members are actively committed to supporting *SynOpen* and Thieme.

SYNFORM *How do you describe the value of a product such as SynOpen to the chemistry community?*

Prof. T. Ollevier *SynOpen* is a sister journal to SYNTHESIS and SYNLETT. It is an open access, international journal reporting current research results in the chemical sciences since 2017. As many of you might know already, the scope of the journal covers mainly, but not exclusively, the areas of synthesis, catalysis, organometallic chemistry, medicinal chemistry, photochemistry, sustainable chemistry, polymers and materials synthesis. *SynOpen* employs the unique crowdsourced peer-review system called "Select Crowd Review", providing a very rapid peer-review service to its authors with first decisions as fast as 72 hours. The journal offers the opportunity to publish both experimental and theoretical studies, and is geared towards publishing high-quality work that deserves to be considered for publication in an open access format. Numerous studies have shown that publishing open access offers huge benefits, from increased citation, faster impact, and compliance with open access mandates. Science should be as accessible and useful as possible worldwide, and

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the more scientists you reach the stronger science can be. Open access provides chemists with increased international exposure and citations. Authors within the chemistry community working on interdisciplinary areas, when publishing in *SynOpen*, can choose between a variety of publications formats based on their needs. The journal welcomes articles such as: Graphical Reviews, Reviews and Short Reviews, Spotlights, Papers, Letters, Practical Synthetic Procedure (PSP). Graphical Reviews and Spotlights are unique formats proposed in *SynOpen*. We are all excited and await *SynOpen's* very first impact factor this summer.

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

Prof. T. Ollevier Organic chemistry is a very active and key research field and will continue to be. It brings new synthetic methods and access to complex molecules, and thus offering new tools to pharmaceutical, agrochemical and materials industries. However, despite major achievements over the years, significant synthetic challenges remain to be tackled. Synthetic organic chemists continue to set new standards in terms of practicality, efficiency, and elegance. The present role of organic chemistry is of paramount importance as it is directly beneficial to other disciplines and society.

SYNFORM *You are a leading researcher with regard to organic catalysis and green chemistry. Could you tell us more about the importance of that field and your current research activities?*

Prof. T. Ollevier The objective of our research is the development of new synthetic methods, with emphasis on catalytic and enantioselective procedures for the simple preparation of biologically and commercially important molecules. Indeed, all our programs target advancements in green chemistry, which is an area of major strategic and industrial importance, i.e. green metals or metal-free reactions to replace noble metal catalysis. In this regard, our current research activities deal with the development of green synthetic methods. Our research group is active in the areas of iron catalysis, ligand design, fluorine chemistry, and asymmetric catalysis. More recently, the chemistry of diazoalkanes and diazirines, either using green metals or metal-free photochemical processes in continuous flow, has emerged as an important part of our research program. Special attention was also paid to bismuth chemistry and other green synthetic transformations.

SYNFORM *What would you consider your most important scientific achievement to date and why?*

Prof. T. Ollevier My most important achievement to date was the development of new methodologies in iron catalysis. As part of our ongoing interest in asymmetric Fe-catalyzed reactions, we developed the use of efficient chiral C_2-symmetric 2,2′-bipyridine diol ligands possessing, for example, an adamantyl or a CF_3 group in their core structure. These studies include broader structural diversity of chiral ligands to gain a better understanding of the mechanisms of a selection of Fe-catalyzed asymmetric reactions. Catalytic asymmetric processes using chiral iron complexes are indispensable for producing enantiomerically enriched compounds in organic synthesis, providing more economical and efficient processes.

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SYNLETT Best Paper Award 2022: A Photoenzyme for Challenging Lactam Radical Cyclizations

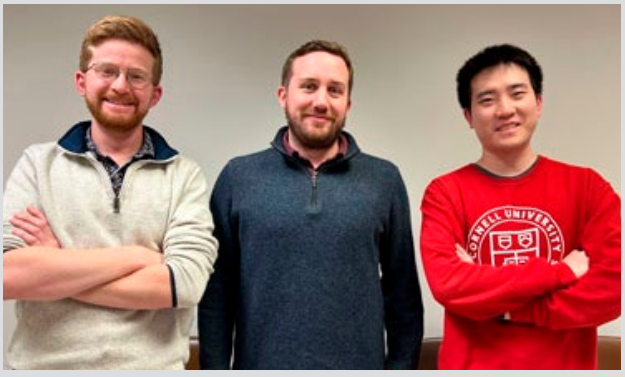
Synlett **2022**, *33*, 1204–1208

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 Todd K. Hyster, with Bryce T. Nicholls and Tianzhang Qiao, from Cornell University, USA, are the recipients of the SYNLETT Best Paper Award 2022. In disclosing the selection, Benjamin List, Editor-in-Chief of SYNLETT, stated: "Controlling the selectivity of radical reactions is a grand challenge in chemical synthesis and catalysis. By using engineered enzymes that preorganize radical substrates in a confined active site to selectively engage in chemical reactions, Todd Hyster and his team provide a beautiful and general solution to this long-standing problem. In the recognized SYNLETT paper, they courageously underline the power of their photoenzymatic approach by comparing it with traditional tin hydride and more modern methods such as iron hydride and photoredox catalysis, clearly establishing the superiority of radical biocatalysis in reductive radical cyclizations."

SYNFORM spoke with Professor Todd K. Hyster, 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



Left to right: Bryce T. Nicholls, Prof. Todd K. Hyster, Tianzhang Qiao

Todd K. Hyster is an Associate Professor of Chemistry and Chemical Biology at Cornell University (USA). He received his B.S. in chemistry from the University of Minnesota (USA) and did his Ph.D. studies with Tomislav Rovis at Colorado State University (USA). As part of his Ph.D., he was a Marie Curie Fellow with Thomas Ward at the University of Basel (Switzerland), then became an NIH Postdoctoral Fellow with Prof. Frances Arnold at Caltech (USA). He started his independent career at Princeton University (USA) in 2015. His group has developed new methods in photoenzymatic catalysis.

Bryce T. Nicholls was born in Alberton, South Africa. He emigrated to the USA in 2014, and in 2018 he graduated with an A.B. in biochemistry from Kenyon College in Gambier, OH (USA). That same year, he began his Ph.D. studies at Princeton University, NJ (USA) in the research group of Todd Hyster – now at Cornell University in Ithaca, NY (USA). His research focuses on developing new photoenzymatic reactions.

Tianzhang Qiao was born in Qinhuangdao, Hebei Province (P. R. of China). He obtained his B.S. degree in chemistry from Nankai University (NKU, P. R. of China) in 2020. While at NKU, he worked as an undergraduate research assistant in Prof. Shou-Fei Zhu's lab. In 2021, he joined Prof. Todd Hyster's lab at Cornell University (USA) to pursue his Ph.D. in organic chemistry. Tianzhang is interested in biocatalysis, and his current research focuses on ene-reductase-catalyzed non-natural photoenzymatic reactions.

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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. T. K. Hyster Our group has been focused on developing methods for synthesizing nitrogen-containing heterocycles because of their prevalence in pharmaceutical and agricultural molecules. One possible strategy is to cyclize acyclic amides. The problem is that rotation around the amide C–N bond is slower than the rate of radical termination. Consequently, most traditional methods for radical cyclization give a mixture of cyclized and acyclic products. In contrast, our photoenzymatic method gives nearly exclusive formation of the cyclized product. This is possible because the enzyme reorganizes the substrate for cyclization prior to radical formation. We think this can be useful to chemists who need to conduct a radical cyclization and want to avoid undesired side product formation.

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

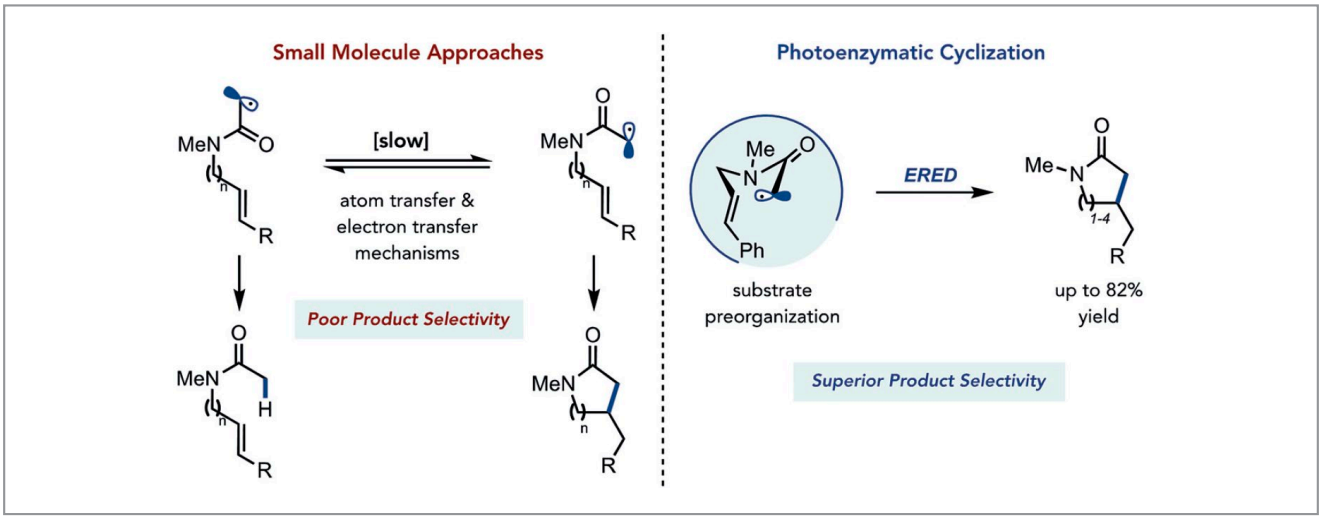
Prof. T. K. Hyster Our group has been focused on developing asymmetric radical cyclizations. When making racemic samples for these reactions, we found that many traditional radical cyclization methods afforded a mixture of cyclized and hydrodehalogenated products. We recognized that our enzymes were better at carrying out these reactions than traditional methods. This work attempted to illustrate the power of biocatalysis not just for asymmetric synthesis but for synthetically challenging bond formations.

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

Prof. T. K. Hyster Our group generally focuses on developing new biocatalytic reactions to solve selectivity challenges in chemical synthesis. We found that when existing enzymes are irradiated with visible light, they gain the ability to carry out electron transfer reactions enabling the formation of organic radicals within their active sites. We are generally interested in how to use this mechanism to facilitate new types of transformations across a broad array of proteins. We recently developed regioselective arene alkylation methods and non-traditional asymmetric cross-electrophile couplings.

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

Prof. T. K. Hyster Small molecule drugs remain an important component of pharmaceutical and agrochemical portfolios. An ongoing challenge is to develop more selective, efficient, and sustainable syntheses. We believe that biocatalysts are an important tool in solving these challenges. It is an incredible time to work in this area because of organic chemists' renewed interest in biocatalysis. Major challenges in this area are to evolve proteins more quickly and to develop enzymes that catalyze reactions that are difficult using traditional



Scheme 1

synthetic approaches. We believe that applying mechanistic insights to unlock new functions can enable the discovery of new bond-forming events currently unknown in the synthetic repertoire. These new disconnections have the potential to significantly accelerate chemical synthesis.

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

Prof. T. K. Hyster This award is a huge stamp of validation for our group. Working at the interface of many different areas, it can be difficult to know if our work is reaching the desired community. Having synthetic organic chemists at SYNLETT identify our work indicates that we are reaching our desired audience.

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Editorial Board Focus: Professor Jung Min Joo (Department of Chemistry, Kyung Hee University, South Korea)

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 Professor Jung Min Joo (Department of Chemistry, Kyung Hee University, South Korea) who joined the Editorial Board of SYNTHESIS with effect of January 2023.

Biographical Sketch

Prof. J. M. Joo

Jung Min Joo earned a bachelor's and master's degree from Seoul National University, South Korea (2001 and 2003, respectively, under Prof. Eun Lee) and a Ph.D. from Princeton University, USA (2008, Prof. Chulbom Lee). She then did postdoctoral work at Columbia University, USA (Prof. Dalibor Sames) and worked as a process chemist at Eli Lilly and Company in Indiana, USA. In 2013, she began as a faculty member at Pusan National University (South Korea), where she became a full professor in 2022. In March 2023, she moved to the Department of Chemistry at Kyung Hee University (South Korea). Her research includes transition-metal-catalyzed C–H functionalization reactions by developing new ligands and development of redox-active organic materials, with a focus on heterocycles.

INTERVIEW

SYNFORM *How do you describe the value of a product such as SYNTHESIS to the chemistry community?*

Prof. J. M. Joo SYNTHESIS is a highly respected journal in the field of synthetic organic chemistry, with a rich history of publishing full papers and reviews since 1969. Its aim is to advance the science of chemical synthesis by providing new reactions and applications with detailed experimental procedures and full characterization of organic compounds. Together with its sister journals SYNLETT, *SynOpen*, and SYNFACTS, SYNTHESIS plays a key role in disseminating knowledge and data related to organic chemistry to address the evolving needs of the chemistry community.

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

Prof. J. M. Joo When I was a graduate student in early 2000, I heard a story from one of the senior organic professors visiting the department. When he was a graduate student in the 1980s, many people thought that organic chemistry had already been so thoroughly developed that no new breakthroughs were possible. However, significant progress had been made in the field since then, and he remained convinced of the potential of organic chemistry. I also believe that organic chemistry has been, and will continue to be, crucial in developing new drugs and materials that can solve various problems in health, energy, and the environment. Although the number of possible small drug-like organic molecules is estimated to be more than 10^{60}, we have only explored a small fraction of this chemical space. Therefore, new methods for synthesizing and designing new organic molecules are needed more than ever.

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SYNFORM *You are a leading researcher with regard to transition-metal catalysis and heterocyclic chemistry. Could you tell us more about how important you perceive this particular topic to be?*

Prof. J. M. Joo Transition-metal catalysts and heterocycles are indispensable tools in the development of drugs, agrochemicals, and functional materials. The selectivity and efficiency of transition-metal catalysts in forming new chemical bonds are critical in the synthesis of target compounds. Furthermore, these catalysts enable new reactivities, allowing the creation of complex molecules in unprecedented ways. In recent years, transition-metal-catalyzed C–H functionalization has been significantly advanced, simplifying synthetic sequences by selectively replacing ubiquitous C–H bonds with functional groups. Similarly, numerous methods have been developed for the preparation of heterocycles, facilitating systematic investigation of the effects of heterocyclic cores and substituents. Collectively, these advancements have expanded the toolbox of organic chemists, thereby enabling greater exploration of the chemical space and the development of novel molecules with improved properties.

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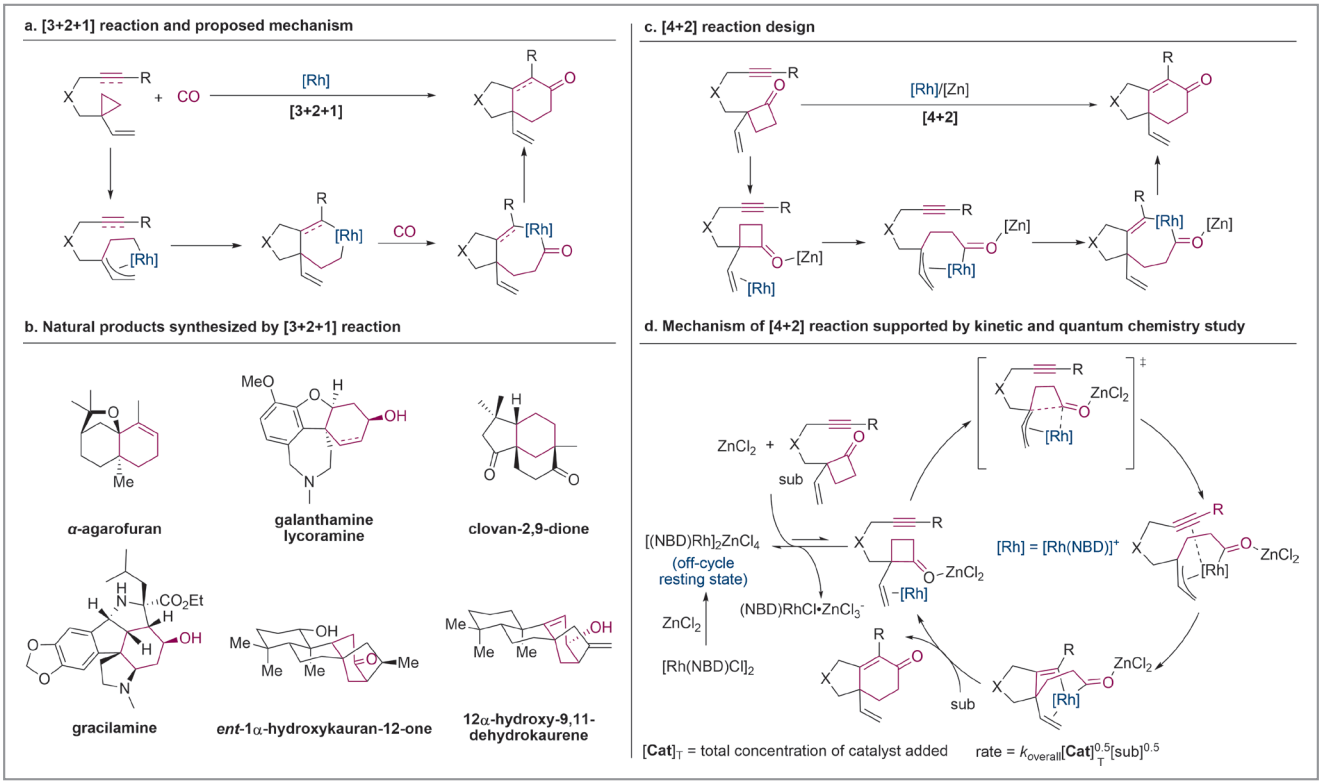
Dual Activation Strategy to Achieve C–C Cleavage of Cyclobutanes: Development and Mechanism of Rh and Zn Co-catalyzed [4+2] Cycloaddition of Yne-Vinylcyclobutanones

J. Am. Chem. Soc. **2022**, *144*, 21457–21469

Prof. Zhi-Xiang Yu and his students from the College of Chemistry, Peking University (P. R. of China) are interested in inventing ring formation reactions, also taking advantage of quantum chemistry calculations and experiments to study the mechanisms of these novel reactions. In addition, the Yu group has been endeavoring to apply these reactions in the synthesis of natural products and pharmaceuticals. "So far, a dozen ring formation reactions, such as four types of [3+2], [3+2+1], [5+1], [4+2], [5+2], three types of [4+2+1], [5+2+1], [7+1], benzo-[7+1] cycloaddition reactions, ene-diene cycloisomerization, and diene-diyne cycloisomerization reactions, have been developed in the group," said Professor Yu. "Among these, the [5+2+1], [3+2+1], and [5+1] cycloaddition reactions, and ene-diene cycloisomerization, have been used in the synthesis of natural products both by us, and by other groups as well." As an example, the Rh-catalyzed [3+2+1] reaction of ene/yne-vinylcyclopropanes and carbon monoxide (Scheme 1), can build 5/6, 6/6 bicycles and other multicycles with a vinyl group at the bridgehead position. Professor Yu said: "We have applied this reaction to synthesize natural products of α-agarofuran, galanthamine, lycoramine, clovan-2,9-dione and gracilamine (Scheme 1b). Prof. Xiaoguang Lei, also from Peking University, elegantly applied this reaction to synthesize *ent*-kaurane diterpenoids in a highly step-economic approach (Scheme 1b)."



Scheme 1 The [3+2+1] reaction and its application in total synthesis of natural products (a, b), [4+2] reaction design (c) and mechanism (d)

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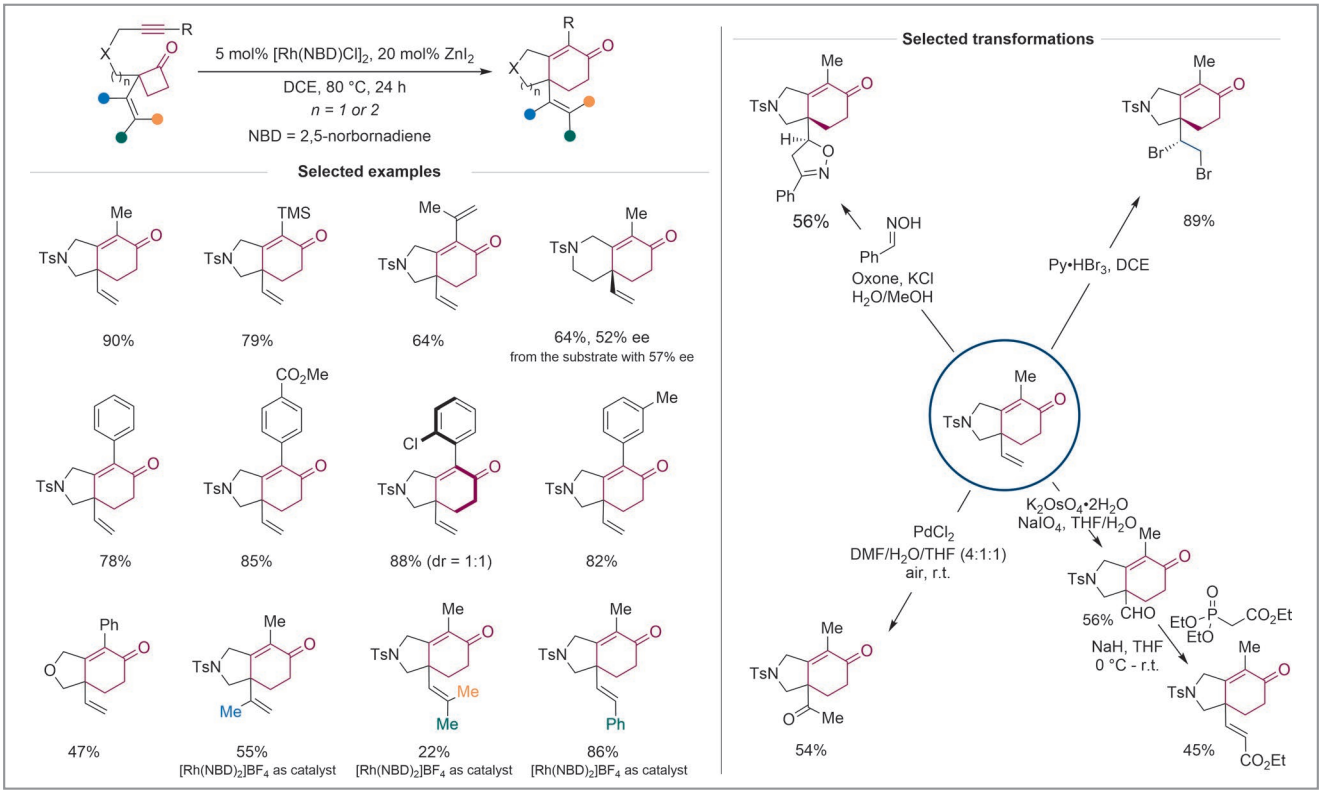
Professor Yu explained that the vinylcyclopropyl group in the substrates of the [3+2+1] reaction acts as a three-carbon synthon. "We also discovered this in two other [3+2] reactions using vinylcyclopropane derivatives as substrates," he added, continuing: "The vinyl group is critical in helping the ring opening of cyclopropane, as that shown in the proposed mechanism of the [3+2+1] reaction in Scheme 1a. Based on these discoveries, we then hypothesized this C–C bond activation mode could also be used to activate four-membered rings." He explained further: "Cyclobutanones have been widely used in cycloaddition chemistry. For example, Prof. Dong Guangbin at the University of Chicago (USA) developed an intramolecular [4+2] reaction of ene/yne-cyclobutanones, which provides a powerful method for synthesizing 5/6 and 6/6 rings. But they did not try to see whether they could apply this to the synthesis of bicyclic molecules with a bridgehead quaternary all-carbon center, which is a challenge in syntheses. We then envisioned a new strategy, introducing a vinyl group to cyclobutanone to help the C–C cleavage, as indicated by the proposed mechanism shown in Scheme 1c, and then this could realize a new [4+2] reaction. We can also introduce a Lewis acid to activate the carbonyl group in the cyclobutanone, so that a metal and Lewis acid co-catalyzed [4+2] reaction can be achieved." To their excitement, the researchers in Professor Yu's group found that the newly designed yne-vinylcyclobutanones underwent [4+2] cycloaddition smoothly using both Rh and Zn as catalysts, and 5/6 or 6/6 bicyclic products with an all-carbon quaternary bridgehead center could be generated (Scheme 2). "The reaction has a broad scope and many examples have been shown in this study," said Professor Yu, adding: "The vinyl group in the [4+2] cycloadduct can be converted into other useful groups, further demonstrating that six-membered carbocycle-embedded bicycles with an all-quaternary carbon in the bridgehead position can be effectively produced by this new cycloaddition reaction. In addition, we found that a chiral substrate can give an enantioenriched product, suggesting this [4+2] reaction can achieve the asymmetric synthesis of cycloadducts, if enantioenriched substrates are used. This can complement our previous [3+2+1] reaction, because an asymmetric version of this reaction has not been realized." Professor Yu and his students also showed that, upon replacement of the vinyl group in the substrate by an ethyl group, the resulting substrate cannot undergo the [4+2] reaction, further supporting the key role of the vinyl group in facilitating the C–C cleavage of the cyclobutanones.



Scheme 2 The [4+2] reaction of yne-vinylcyclobutanones catalyzed by Rh and Zn and further transformations of a [4+2] cycloadduct

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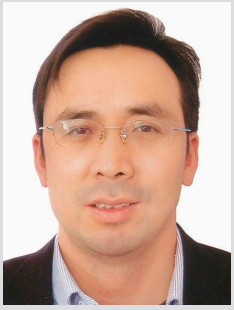
"To gain a deeper understanding of the reaction mechanism, we performed visual kinetic analysis and computational studies. Based on the evidence gathered in these experiments, we proposed that the active catalytic species is cationic Rh, generated via dissociation of dimeric off-cycle species in the resting state, which is possibly formed between the dimeric catalyst and the substrate," added Professor Yu. He continued: "The rate-determining step is the C–C cleavage in the cyclobutanone, assisted by both Rh and Zn. We also measured the rate law of the [4+2] reaction. The other two roles of Zn, in helping the in situ generation of cationic Rh catalyst to occur slowly and preventing catalyst deactivation, were also evidenced by our mechanistic investigation. This information is shown in Scheme 1d and related insights will be helpful for the future design of new reactions and catalysts."

"The present [4+2] reaction can be regarded as an equivalent of our previous [3+2+1] reaction, which has proven its broad utility in the synthesis of several natural products with a bridgehead quaternary carbon center," said Professor Yu, who concluded: "Therefore, we can envision that this new [4+2] reaction of yne-vinylcyclobutanones will also become a powerful tool for synthetic chemists. We also believe that such a new strategy of using a vinyl group to activate four-membered rings will inspire the development of more reactions via C–C cleavage chemistry."

About the authors

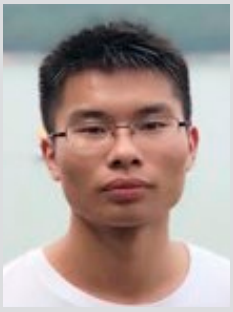


Prof. Z.-X. Yu

Zhi-Xiang Yu was trained as a chemist at Wuhan University, P. R. of China (1987–1991), Peking University, P. R. of China (1994–1997), and the Hong Kong University of Science & Technology, P. R. of China (1997–2001) for his Bachelor's, Master's and Doctoral degrees, respectively. He completed his postdoctoral studies from 2001–2004 at UCLA (USA). In 2004, he started his independent career at Peking University, rising from associate professor to full professor and is now a Changjiang Professor. He is interested in studying reaction mechanisms, developing ring-formation reactions, and applying these reactions in natural product synthesis and drug discovery.

Dr. G-Y. Zhang

Guan-Yu Zhang obtained his B.Sc. degree from Peking University (P. R. of China) in 2014. Under the guidance of Prof. Zhi-Xiang Yu, he obtained his Ph.D. in January 2023. He is interested in developing new reactions and studying reaction mechanisms. He is now an industrial chemist.



P. Zhang

Pan Zhang obtained his B.Sc. degree from Wuhan University (P. R. of China) in 2018 under the supervision of Profs. Zhen Li and Qianqian Li. He is currently a fifth-year graduate student in Prof. Zhi-Xiang Yu's group at Peking University. He is interested in reaction development and computational and experimental study of reaction mechanisms.

B-W Li

Bing-Wen Li received his B.S. degree in chemistry from Jilin University (P. R. of China) in 2020 under the supervision of Prof. Won-Jin Chung. He is currently pursuing his Ph.D. at Peking University (P. R. of China) under the supervision of Prof. Zhi-Xiang Yu. He works in the fields of computational chemistry and organic synthesis.

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Dr. K. Liu

Kang Liu carried out postdoctoral studies on reaction development and total synthesis in Peking University, P. R. of China (2018–2020), supervised by Professor Zhi-Xiang Yu. He received his Ph.D. from Wuhan University, P. R. of China (2013–2016), studying asymmetric synthesis under the guidance of Professor Chun-Jiang Wang. He is now an industrial chemist.

Dr. J. Li

Jun Li received his B.S. (2012) and Ph.D. (2017) in organic chemistry from Wuhan University (P. R. of China) under the supervision of Prof. Chun-Jiang Wang. He completed his postdoctoral studies from 2018–2020 at Peking University (P. R. of China) in Prof. Zhi-Xiang Yu's group. His research interests include asymmetric catalysis and computer-aided molecular design and synthesis. He is now an industrial chemist.

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Synthesis of *meta*-Substituted Arene Bioisosteres from [3.1.1]Propellane

Nature **2022**, *611*, 721–726

Bicyclo[1.1.1]pentanes (BCPs) have emerged as important structures in drug development as bioisosteres for *para*-substituted benzene rings. The group of Professor Ed Anderson at the University of Oxford (UK) has had a long-standing interest in the molecule [1.1.1]propellane, the usual precursor to a BCP, from both synthetic and mechanistic perspectives. "BCPs display increased solubility and metabolic stability compared to their aromatic parents, while retaining the 180° substitution geometry and, often, bioactivity (Scheme 1A),"[1,2] said Professor Anderson, adding: "BCPs have spearheaded an armada of small-ring cage hydrocarbons that 'escape the aromatic flatland' through their three-dimensionality, which has been linked to higher clinical success rates of drug candidates.[3,4] However, a bioisostere for *meta*-substituted arenes that accurately mimics their 120° substitution geometry has, to date, been absent from this collection (Scheme 1B)."

Prof. Anderson stated that an obvious extension of his group's research into ring-opening reactions of [1.1.1]propellane was to explore its next stable higher congener, namely [3.1.1]propellane, which they recognised could lead to a bicyclo[3.1.1]heptane product, that perfectly mimics the geometry of a *meta*-substituted benzene (Scheme 1C). The group faced two questions: whether [3.1.1]propellane could indeed serve as a versatile precursor to bicyclo[3.1.1]heptanes (BCHeps), and whether BCHeps would bestow equivalent property benefits as BCPs in drug candidates. Before these questions could be addressed, the first challenge was to prepare [3.1.1]propellane on a synthetically useful scale, as previous approaches from the 1980s and 1990s delivered only milligram quantities, hindering synthetic explorations.[5,6]

A scalable synthesis of [3.1.1]propellane was first developed by the group (Scheme 1D). Masters student Nils Frank commented: "We were inspired by the tetrahalide propellane synthesis strategy established by Szeimies, and were able to replace a number of awkward synthetic steps in the known approaches to [3.1.1]propellane by employing a Kulinkovich cyclopropanation/rearrangement sequence. This streamlined the chemistry and offered easy access to the required tetrahalide precursor, with only one column purification required."

By overcoming this synthetic bottleneck, the door was opened to explore the reactivity of [3.1.1]propellane. Nils Frank and postdoc Dr Jeremy Nugent trialled a range of methodologies applicable to [1.1.1]propellane ring-opening on [3.1.1]propellane. "Our group's own methodology was easily translated onto [3.1.1]propellane, such as the photoredox-catalyzed addition of organic halides," Nils explained (Scheme 1E). He continued: "We were fortunate that even a complex three-component metallaphotoredox reaction reported by the MacMillan group for [1.1.1]propellane proved possible to carry out on [3.1.1]propellane without much modification. However, many reactions failed – especially anionic methodologies that are successful on the smaller [1.1.1] system." Prof. Anderson added: "Our long-standing collaboration with computational chemists Alistair Stirling and Prof. Fernanda Duarte revealed the source of this reactivity difference. We believe this derives from the unique abilities of three-membered rings to stabilise electron density; as [3.1.1]propellane features one less cyclopropane than [1.1.1]propellane, this disfavours reactions with anions."[7]

The ring-opening reactions of [3.1.1]propllane delivered a wide variety of BCHep products (Scheme 1E), several of which proved suitable for X-ray crystallography. This enabled DPhil student Helena Pickford to confirm the predicted 120° angle between the bridgehead substituents (Scheme 1F). DPhil student Bethany Shire then found that iodo-BCHeps can be cross-coupled with aryl Grignards in excellent yields using an iron-catalysed Kumada cross-coupling developed previously in the group.[8] "Derivatising the BCHep iodides was significant, as this opened up the rapid synthesis of BCHep pharmaceutical analogues," said Prof. Anderson. The group was thus able to prepare analogues of the anti-cancer drug Sonidegib (Scheme 1G) and the anti-seizure drug URB597. Collaboration with Prof. Paul Brennan enabled evaluation of a range of physicochemical and pharmacokinetic properties, which indeed revealed increased resistance towards metabolic degradation – one of the main hoped-for benefits of the BCHep. Promising data on improved membrane permeability were also observed. Prof. Anderson concluded: "These measurements were crucial to validate the design principle of the BCHep, and we hope will inspire medicinal chemists to test this structure in drug design settings."

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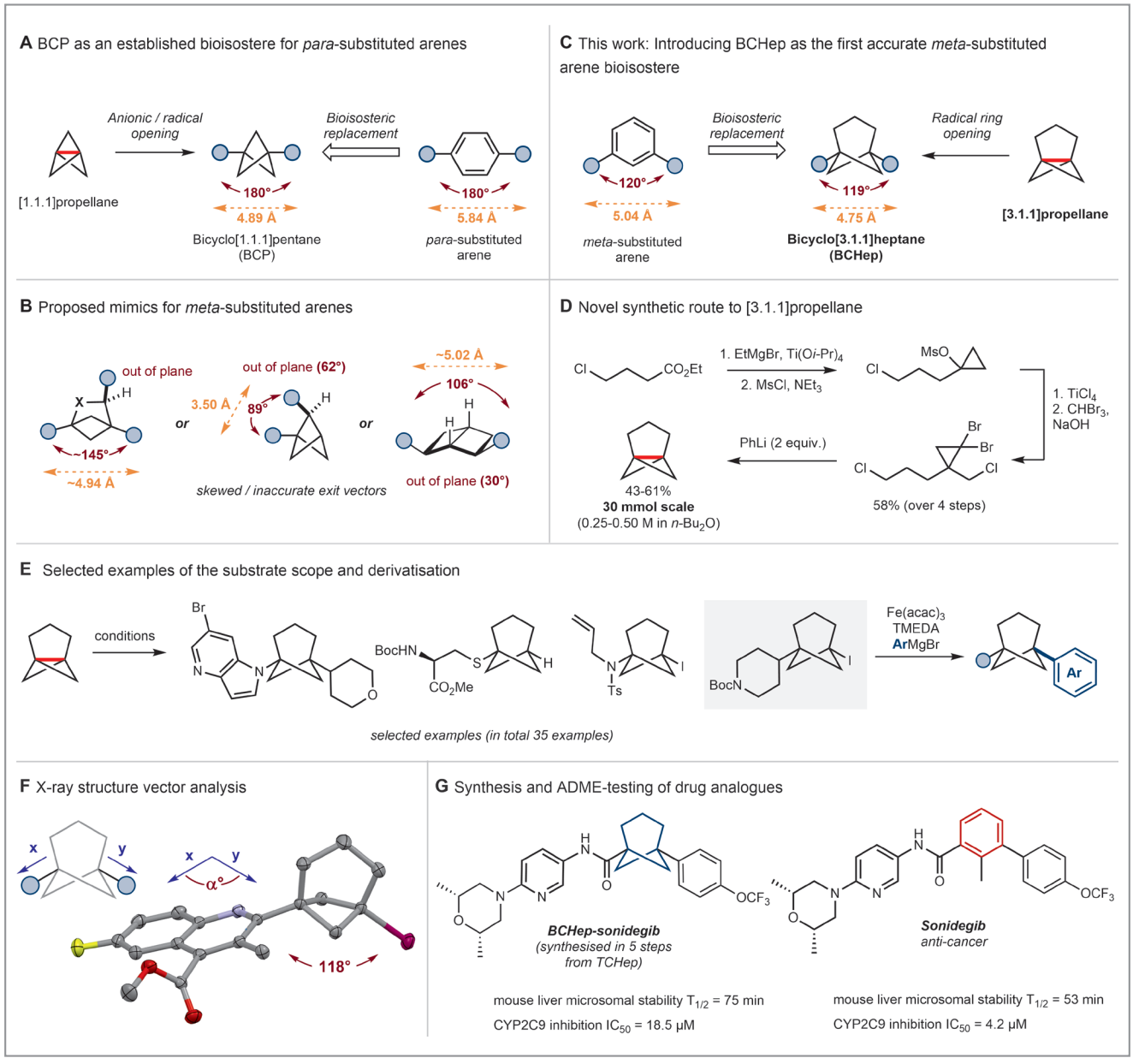

Scheme 1 Synthesis of *meta*-substituted arene bioisosteres from [3.1.1]propellane

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N. Frank

Nils Frank received his BSc degree from the Karlsruhe Institute of Technology (Germany) in 2020, during which time he also undertook an internship in the group of Professor Tobias Ritter at the Max Planck Institute for Coal Research (Germany), working on thianthrenation chemistry. He joined the group of Professor Anderson at the University of Oxford (UK) from 2020 to 2022, where he graduated with an MRes degree. In addition to his work on [3.1.1]propellane synthesis and reactivity, he also researched cycloaddition reactions of thiophene *S*,*S*-dioxides. In 2022, he joined F. Hoffmann-La Roche AG (Basel, Switzerland) for a one-year internship in medicinal chemistry before commencing his doctoral studies.

Dr. J. Nugent

Jeremy Nugent received his PhD from The Australian National University (Australia) in 2016 working with Professor Martin Banwell on the synthesis of various natural products. After a further year working as a postdoctoral fellow with Prof. Banwell, and a short stint with Vertex Pharmaceuticals, he moved to the University of Oxford (UK) to take up a Marie Skłodowska-Curie Fellowship working with Professor Ed Anderson. There, he developed new methods to synthesise bicyclo[1.1.1]pentanes and bicyclo[3.1.1]heptanes, important motifs in drug discovery. In 2022, he joined Samsara Eco (Australia) as Head of Chemistry.

Dr. B. R. Shire

Bethany Shire received her MChem degree from the University of Oxford (UK) in 2017; during this time, she explored enynamide cycloisomerisations with Prof. Edward Anderson. She then joined the EPSRC Synthesis for Biology and Medicine Centre for Doctoral Training (SBM CDT) at Oxford, and completed her DPhil studies in 2022 on catalytic methods for the synthesis of bicyclo[1.1.1]pentanes under the supervision of Prof. Anderson. She was then awarded an EPSRC Doctoral Prize to conduct further research into the applications of bicycloalkyl groups as bioisosteres.

Dr. H. D. Pickford

Helena Pickford received her MChem degree in 2017 from the University of Oxford (UK), where she worked on the synthesis of trigoxyphin natural products with Profs. J. Robertson and L. Wong. In 2022, she completed her DPhil as part of the EPSRC Synthesis for Biology and Medicine Centre for Doctoral Training (SBM CDT) at the University of Oxford. Her work involved the synthesis of heteroatom-substituted bicyclo[1.1.1]pentanes under the supervision of Prof. Anderson. Helena then joined the group of Prof. Matt Fuchter at Imperial College London (UK), where her research currently includes the synthesis of photoswitchable pharmaceuticals.

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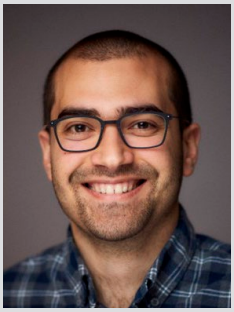
Dr. P. Rabe

Patrick Rabe is a senior postdoctoral researcher in the Chemistry Research Laboratory at the University of Oxford (UK). In 2016, Patrick finished his PhD at the Kekulé Institute of Organic Chemistry and Biochemistry at the University of Bonn (Germany) on "Mechanistic Studies on Bacterial Terpene Synthases" with Prof. Jeroen S. Dickschat. For his doctoral thesis he received the 2017 Dechema doctoral award. Since 2017 he has been working in the group of Prof. Chris Schofield at Oxford (UK) on time-resolved crystallography and spectroscopy studies on oxygenases, with a fellowship funded by the Deutsche Akademie für Naturforscher Leopoldina (2017–2019).

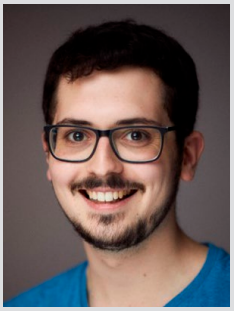
Dr. A. J. Sterling

Alistair Sterling received his DPhil from the University of Oxford (UK) in 2021 under the supervision of Profs. Fernanda Duarte and Ed Anderson. Following postdoctoral studies with Prof. Duarte funded by an EPSRC Doctoral Prize, he joined the group of Prof. Martin Head-Gordon at the Lawrence Berkeley National Lab and the University of California, Berkeley (USA), where his research interests include theoretical physical organic chemistry and reaction development.



Dr. T. Zarganis–Tzitzikas

Tryfon Zarganis–Tzitzikas obtained his B.Sc. in chemistry from Aristotle University of Thessaloniki (Greece) in 2010 and his M.Sc., summa cum laude, in synthetic organic chemistry in 2012 at the same university. In 2017, he obtained his Ph.D., cum laude, in medicinal chemistry under the guidance of Prof. Alexander Dömling in the Group of Drug Design at the University of Groningen (Netherlands). His thesis focused on innovative multicomponent reactions and their use in medicinal chemistry. Tryfon then joined Symeres B.V. as a medicinal chemist working on immuno-oncology projects. Since 2014, he has been a co-founder and CSO of TelesisPharma B.V. (Netherlands), a company focusing on exploring novel synthetic routes to APIs using multicomponent reactions. In 2018, he joined Prof. Paul Brennan's group at the Oxford Drug Discovery Institute (UK) as a senior postdoctoral scientist focusing on dementia targets, funded by Alzheimer's Research UK.



T. Grimes

Thomas Grimes received his MChem degree from Durham University (UK) in 2017. He spent the final year of his degree in the epigenetics department at GSK in Stevenage (UK), working on the synthesis of BD2 selective BET bromodomain inhibitors. Following his degree, he worked for two years as a contract chemist based at the Eli Lilly Erl Wood site where he worked on a variety of Eli Lilly and Elanco projects. He joined the Alzheimer's Research UK Oxford Drug Discovery Institute at the University of Oxford (UK) as a Research Assistant in 2019 to work on the design of NLRP3 inflammasome inhibitors, and in 2022 began his DPhil within the same group under the supervision of Prof. Paul Brennan.

Dr. R. C. Smith

Russell C. Smith received his PhD in organic chemistry from the University of Illinois Urbana Champaign (USA) under the tutelage of Professor Scott Denmark focusing on the mechanistic understanding of the silicon-based cross-coupling reaction. He then traversed out to California to conduct his postdoctoral studies with Professor Brain Stoltz at the California Institute of Technology (USA) on efforts toward the total synthesis of ineleganolide. His professional career began at Janssen PRD in San Diego, CA (USA) as a medicinal chemist working in the area of immunology for over 9 years. Russell then returned to the Midwest in early 2020 to transition to AbbVie, joining the Centralized Organic Synthesis (COS) group where he currently holds the position of Senior Scientist II. He has recently been involved in the development of novel on-DNA method developments and applications while maintaining productive and active collaborations between the pharmaceutical and academic sectors.

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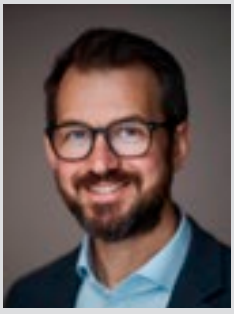
Professor C. J. Schofield

Chris Schofield's research centres on contributing to a chemistry-based understanding of systems of biological importance, including mechanisms of antibiotic resistance and the regulation of genetic machinery. An important aspect of his work has concerned enabling the exploitation of basic science results for societal/medicinal benefit, including for treatment of infectious diseases and hypoxia-related diseases (e.g. anaemia and cancer). Two current major research fields of the group are antibiotics/antibiotic resistance and the biochemistry and biology of oxygenases and hypoxia.



Professor P. E. Brennan

Paul Brennan received his PhD in organic chemistry from UC Berkeley (USA). Following post-doctoral research at the University of Cambridge (UK), Paul spent eight years working in the pharmaceutical industry at Amgen and Pfizer. In 2011, Paul joined the Structural Genomics Consortium at the University of Oxford (UK). Over the course of his career, Paul has worked on most major classes of drug targets: kinases, GPCRs, ion-channels, metabolic enzymes, and epigenetic proteins. Paul is currently Professor of Medicinal Chemistry and Chief Scientific Officer of the Alzheimer's Research UK Oxford Drug Discovery Institute in the Centre for Medicines Discovery at the University of Oxford. His research is focused on finding new treatments for dementia.

Professor F. Duarte

Fernanda Duarte is an Associate Professor in the Department of Chemistry at the University of Oxford (UK), a position she has held since 2018 following appointments at the University of Edinburgh, UK (Chancellor's Fellow), the University of Oxford (Newton Fellow), and Uppsala University, Sweden (PDRA). She leads a diverse team of researchers working at the interface of organic chemistry, supramolecular catalysis, and computational chemistry. Her research interests are centred on the prediction of chemical reactivity in the condensed phase, combining classical, quantum and machine-learning approaches. Her group has also developed a series of computational software to facilitate molecular design and reaction mechanism exploration. She has published over 60 peer-reviewed scientific publications and received several awards, most recently including the 2022 Novartis Early Career Award in Chemistry, and the 2021 RSC Harrison-Meldola Memorial Prize.

Professor E. A. Anderson

Ed Anderson is Professor of Organic Chemistry at the University of Oxford (UK). He began his independent career as an EPSRC Advanced Research Fellow in 2007, during which time he was appointed as Associate Professor at Jesus College, Oxford in 2009, and then as Professor in 2016. His research interests encompass a wide range of synthetic organic chemistry, including natural product total synthesis, transition-metal catalysis and mechanistic study, bicyclo[1.1.1]pentanes and related small rings, antiparasitic natural products, the chemistry of ynamides and yndiamides, and EPR spectroscopy in nucleic acids. He is a recent recipient of the Novartis Chemistry Lectureship (2018), and RSC Bader Award (2020).

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