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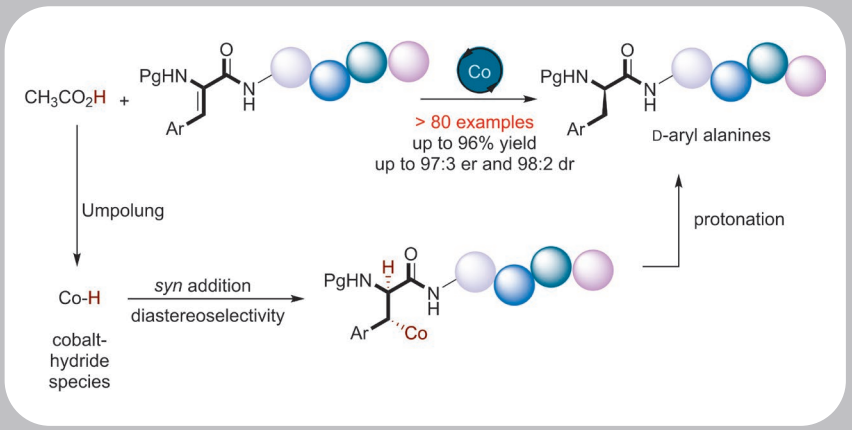
People, Trends and Views in Chemical Synthesis

2024/05

Expedient and Divergent Synthesis of Unnatural Peptides through Cobalt-Catalyzed Diastereoselective Umpolung Hydrogenation

Highlighted article by X. Song, S. Bai, Y. Li, T. Yi, X. Long, Q. Pu, T. Dang, M. Ma, Q. Ren, X. Qin



Thieme

Dear Readers,

This year marks the 25th anniversary of the prestigious Thieme Chemistry Journals Award, which is presented every year to up-and-coming researchers worldwide selected directly by the editorial board members of SYNTHESIS, SYNLETT, and SYNFACTS. Since 1999 – when the award (a one-year complementary subscription to SYNTHESIS, SYNLETT, and SYNFACTS and a certificate) was given for the first time – its aim has been to send a sign of recognition and career encouragement to the new generations of organic chemists. If you have any doubt about the value of this award, please have a look at that first pool of 1999 Awardees, and you will recognise the names of some of the most important and innovative organic chemists of the 21st century. A couple of examples? What about David W. C. MacMillan, Nobel Prize 2021, and Peter H. Seeberger, a giant of carbohydrate chemistry? But the other 13 Awardees are all very important names in the realm of organic chemistry, including two colleagues who left us way too soon and I would like to remember here: David Y. Gin and Carsten Schmuck.

A few years ago, we also started publishing interviews with some of the Thieme Chemistry Journals Awardees – Young Career Focus articles as we dubbed them – which adds further to the prestige and visibility of this recognition. In this issue we publish the first of the interviews with a 2024 Awardee (for the full list see: https://www.thieme.de/en/thieme-chemistry/thieme-chemistry-journals-awardees-107362.htm): John J. Molloy (Germany). This issue also features three Literature Coverage articles. The first one covers a new synthesis of unnatural peptides through cobalt-catalyzed diastereoselective umpolung hydrogenation, that was recently reported in Sci. Adv. by the group of X. Qin and Q. Ren (P. R. of China). The second comes from the group of N. Cramer (Switzerland) and deals with their catalytic enantioselective reductive Eschenmoser–Claisen rearrangements recently reported in Science. The issue is completed by another groundbreaking work recently published in *Science* by the group of R. Koenigs (Germany), who developed photosensitization-enabled Pauson–Khand-type reactions of non-conjugated dienes with nitrenes, leading to fused heterocycles which are the product of a (2+2+1) cycloaddition reaction.

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Expedient and Divergent Synthesis of Unnatural Peptides through Cobalt-Catalyzed Diastereoselective Umpolung Hydrogenation

Sci. Adv. **2023**, *9*, eadk4950

In recent years, there has been a growing interest in harnessing peptides as therapeutic agents for treating various diseases. Currently, the global market boasts more than 80 commercially available peptide drugs, with approximately 170 in diverse stages of clinical trials and an additional 500 undergoing preclinical studies. Unnatural peptides with amino acid residues beyond the 20 canonical amino acids have demonstrated superior proteolytic stability, bioactivity and pharmacokinetics compared with their natural counterparts. Among them, noncanonical aryl alanines are notably prevalent in pharmaceuticals due to their exceptional versatilities (Figure 1). Consequently, the ongoing exploration of methods to synthesize unnatural peptides containing noncanonical aryl alanine residues and their potential therapeutic applications remains highly desirable.

In a recent publication in *Science Advances*, the group of Professors Xurong Qin and Qiao Ren at Southwest University (P. R. of China) developed a diastereo- and regioselective cobalt-catalyzed umpolung hydrogenation for the divergent and expedient synthesis of unnatural aryl alanine peptides (Scheme 1E). In this research article, they disclosed that commercially available acetic acid and methanol can serve as safe

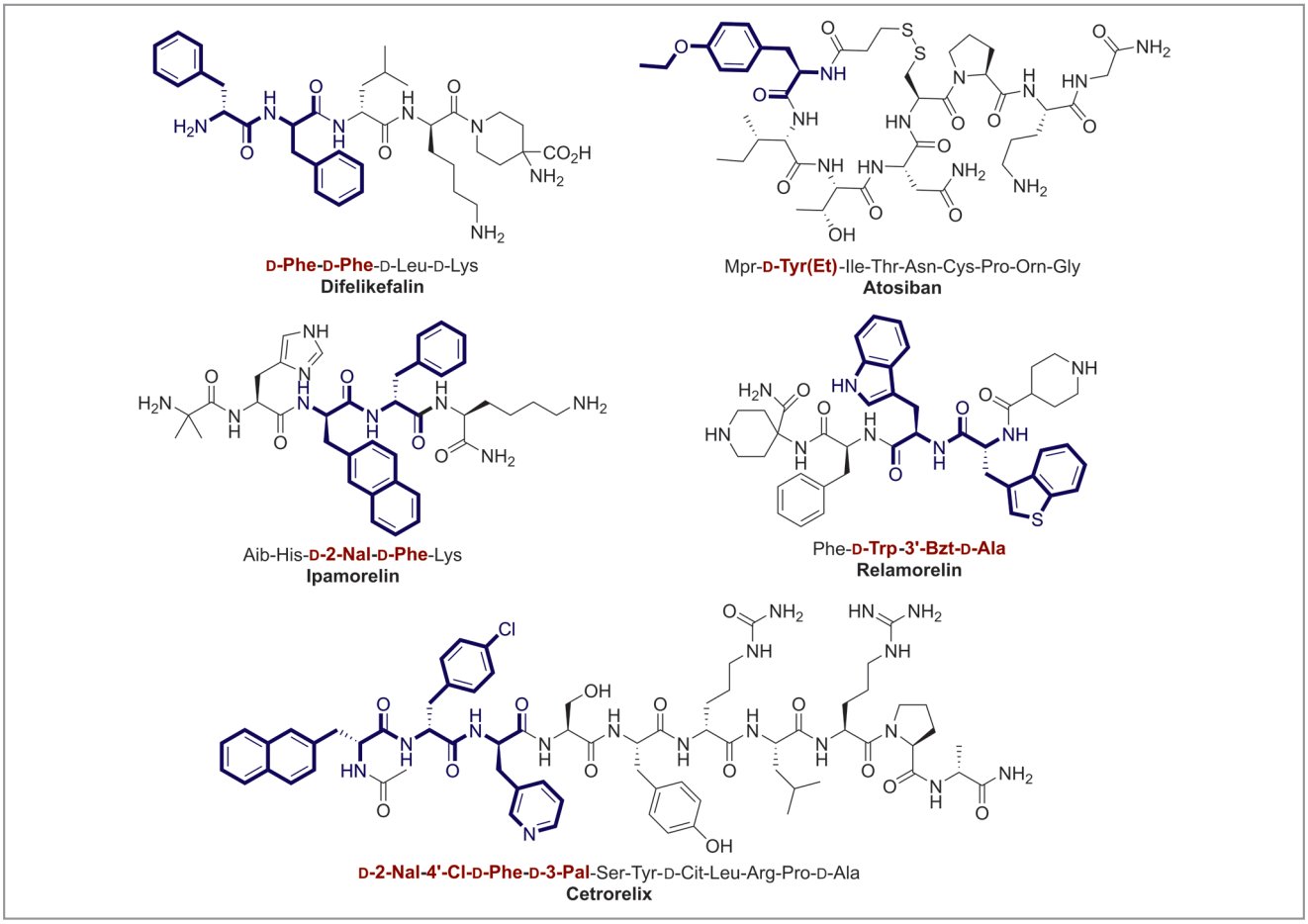

Figure 1 Selected peptide drugs containing unnatural aryl alanine residues

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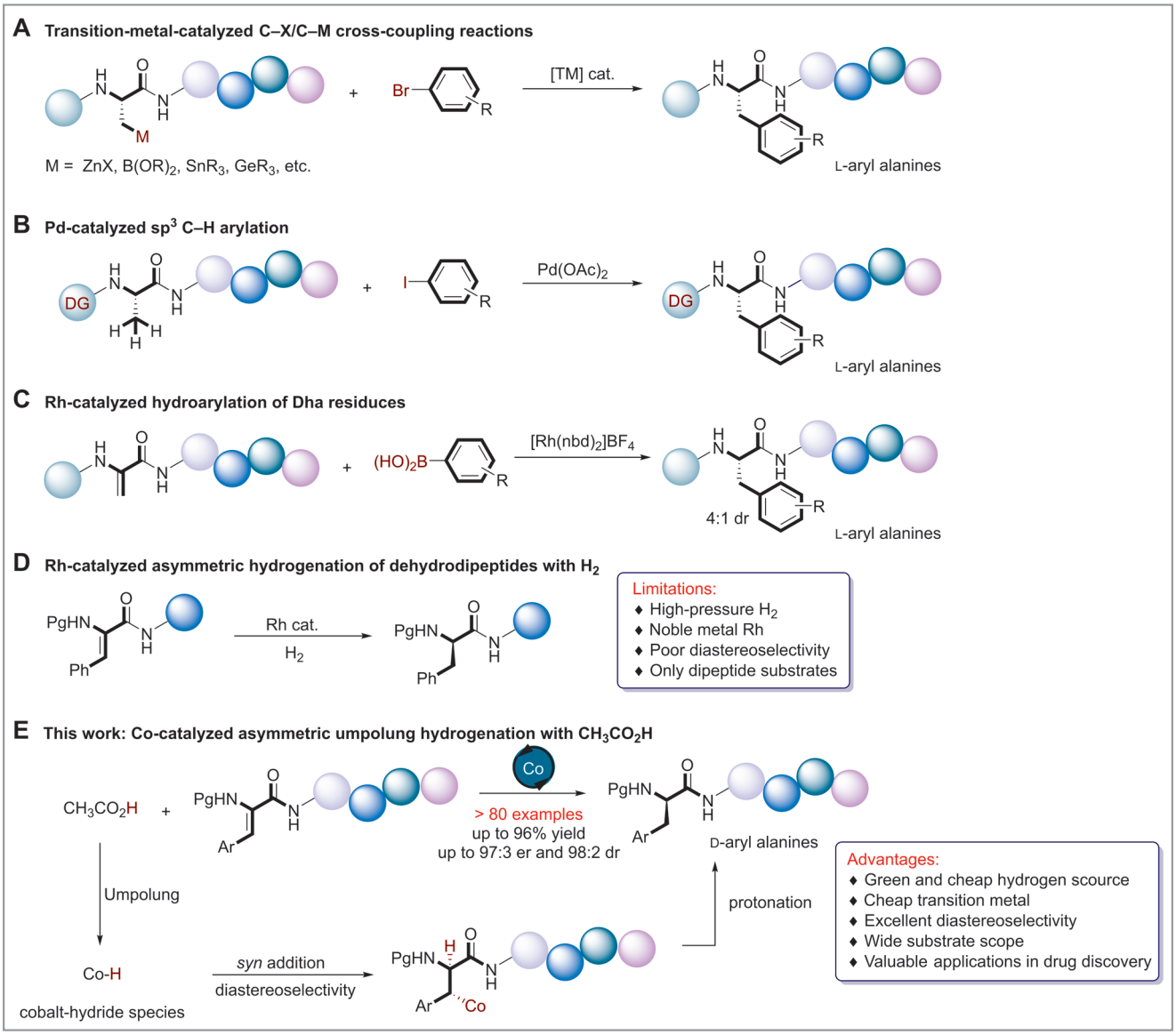
and cheap hydrogen sources, avoiding the safety hazards associated with the storage and usage of high-pressure hydrogen gas.

Professor Qin explained to SYNFORM the background of their work and the research questions they aimed to answer at the onset of the project. "The coupling reagent mediated condensation of unnatural aryl alanines through dehydration is a widely used and reliable approach for peptide formation. However, this approach has several limitations, including the tedious preparation of unnatural aryl alanines, poor atom economy, inevitable side reactions, and the potential risk for racemization/epimerization of the α-stereocenter caused by the over-activation of carboxyl groups by coupling reagents," he said, continuing: "An alternative strategy involves the transition-metal-catalyzed cross-coupling reactions between aryl halides and Ala^{M} reagents (Scheme 1A). While this reaction provides reliable access to L-aryl alanine moieties, it still grapples with limitations, such as the labile or challenging-to-synthesize nature of some Ala^{M} reagents." Recent groundbreaking work by several groups, including Lavilla/Albericio, Ackermann, Yu, Wang, and Chen, has pioneered Pd-catalyzed C–H arylation of L-alanine derivatives to produce unnatural



Scheme 1 Transition-metal-catalyzed methods of unnatural aryl alanine residues incorporation in peptides

aryl alanine peptides (Scheme 1B). However – according to Professor Qin – this protocol typically demands an external directing group for excellent site-selectivity, leading to additional and cumbersome steps for installation and detachment, sometimes even irremovability. "Another approach is Rh-catalyzed hydroarylation of dehydroalanines, which can provide unnatural aryl alanine peptides in 4:1 dr (Scheme 1C). Although there has been some progress in rhodium-catalyzed hydrogenation of dehydrodipeptides using H_2 gas (at 30–70 atm under specific conditions), significant challenges persist (Scheme 1D). These challenges mainly revolve around limited structural diversity, especially concerning peptide length, and the relatively modest level of diastereoselectivity achieved thus far," he said.

Professor Qin explained further: "Transition-metal-catalyzed asymmetric hydrogenation has been certified as a powerful tool for the preparation of a wide range of pharmaceuticals, agrochemicals, bioactive compounds, and natural products. However, most asymmetric hydrogenation catalysts are based on scarce and costly heavy noble metals including Rh, Ru, Ir, and Pd, occurring at very low abundances in the earth's crust ($5x10^{-5}$–10^{-4} ppm). In addition, these heavy noble metals not only incur high costs in the production process but also require recovery and recycling due to environmental concerns." Recently, according to Professor Qin, there has been a renewed interest in using low-cost, earth-abundant, and biologically compatible 3d transition metal catalysts such as Mn, Fe, Co, Ni, and Cu for asymmetric hydrogenation. However, these strategies might employ high-pressure hydrogen gas, a severe safety hazard during transport, storage and use.

"In our recent work, described in the title article, a wide range of dehydropeptides with varying lengths, sequences, and steric/electronic properties, were successfully hydrogenated into the corresponding unnatural aryl alanine-based peptides in moderate to excellent yields and with high enantioselectivities or diastereoselectivities," said Professor Qin, who continued: "This protocol can also be successfully extended to biologically relevant molecules and pharmaceutically derived dehydropeptides." Notably, the formal synthesis of several representative natural products and drugs further exemplified the versatility of this catalytic hydrogenation system. "Besides," emphasized Professor Qin, "this strategy eliminates the need for synthesizing chiral noncanonical aryl alanines before peptide formation, and this hydrogenation reaction does not result in racemization or epimerization. Importantly, the underlying mechanism was extensively explored through deuterium labeling, control experiments, HRMS identification, and UV-Vis spectroscopy, which supported a reasonable Co^{I}/Co^{III} catalytic cycle."

Professor Qin concluded: "We believe that this cobalt-catalyzed umpolung hydrogenation offers a novel approach for the divergent and efficient synthesis of unnatural aryl alanine peptides using readily available sources. This research holds appeal for both the chemical and medicinal communities."

About the authors

X. Song

Xinjian Song was born and raised in Wenzhou, P. R. of China and attended Southwest University (P. R. of China), where he earned his bachelor's degree in pharmaceutical engineering (2020), and master's degree in pharmaceutical chemistry (2023).

Prof. Q. Ren

Qiao Ren grew up in Sichuan, P. R. of China and attended Sichuan University (P. R. of China), where she completed her B.Sc. She earned her Ph.D. from the National University of Singapore (Singapore) under the guidance of Professor Jian Wang. In 2014, she began her independent career at Southwest University working on the development of photocatalysis, asymmetric catalysis and natural product synthesis.

Prof. X. Qin

Xurong Qin grew up in Chongqing (P. R. of China). He earned his B.Sc. degree from Shaanxi Normal University (P. R. of China) and later completed his Ph.D. at Sichuan University (P. R. of China). In 2014, he worked as a postdoctoral fellow/research scientist at University of Washington (USA) and Nanyang Technological University (Singapore). Since 2019, he has worked as a professor in the College of Pharmaceutical Sciences at Southwest University (P. R. of China). His research interests include transition-metal-catalyzed hydrogenation/deuteration and pharmaceutical process chemistry.

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Young Career Focus: Dr. John Molloy (Max Planck Institute of Colloids and Interfaces, Germany)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. John Molloy (Max Planck Institute of Colloids and Interfaces, Germany).

Biographical Sketch

Dr. J. Molloy

Born in Glasgow (Scotland), **John J. Molloy** carried out his undergraduate studies at the University of Strathclyde (UK). During this time, he completed a one-year industrial placement in drug discovery working at the Beatson Institute for Cancer Research (Garscube Estate, Glasgow, UK). John completed his Master's thesis (2014) in the group of Prof. Allan Watson and remained in the same research group at the University of Strathclyde to carry out his doctoral studies where his work focused on chemoselective reactions of organoboron compounds. During his doctoral studies, John was supported with PEER/PECRE funding from the Scottish Funding Council that allowed him to visit the group of Prof. Ryan Gilmour (Münster, Germany) on a three-month secondment working on the geometrical isomerization of alkenes via energy transfer. Following his Ph.D. studies (2018), and a short secondment at the University of St Andrews (UK), John returned to the group of Prof. Gilmour funded by the Alexander von Humboldt foundation. There, John continued his work on the geometric isomerization of alkenes, while also focusing on enantioselective difluorination of alkenes via hypervalent iodine catalysis. After completing his postdoctoral studies (2020), John began his independent research at the Max Planck Institute of Colloids and Interfaces (Germany) working as a group leader in the department of director Prof. Seeberger (2021). During this time, his research has been supported by Der Fonds der Chemischen Industrie (FCI) with a Liebig stipend and also from the Daimler and Benz foundation with the award of a stipend for young researchers. John is also a lecturer at Freie Universität Berlin (Germany).

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Dr. J. Molloy Our research group is inspired by the unique properties of boron, both as a synthetic handle to explore chemical space, and as a design feature in medicinal chemistry to interact with biomolecules. Central to boron's utility as an organic substituent is its ability to readily fluctuate between two discrete hybridized forms that can completely change the intrinsic properties of the functionality. This is the key factor that interests our research group. We currently focus on the particular effect boron hybridization can elicit on photochemical and photocatalytic processes.[1] We look to use these properties, not only to enable activation of organoboron precursors to access high-energy intermediates, but also to regulate their subsequent reactivity in chemical transformations (Scheme 1). We recently disclosed a study highlighting the role of the boron p-orbital in enabling the catalyst-free activation of C–I bonds to generate α-boryl radicals using only light and a simple Lewis base additive.[2] We believe this operationally simple protocol can be strategically merged with other catalysis platforms to construct complex 3D organoboron scaffolds in a streamlined manner. Aside from the construction of boron molecules, we also have a keen interest in their interaction with biomolecules and hope to share some of our developments in the future.

SYNFORM *When did you get interested in synthesis?*

Dr. J. Molloy I guess I would separate this into two sections: theoretical and practical. I was very fortunate at the University of Strathclyde as they have many outstanding and engaging organic chemistry lecturers. I believe it was there that I became deeply interested in organic synthesis from a theoretical standpoint. I've always been really interested

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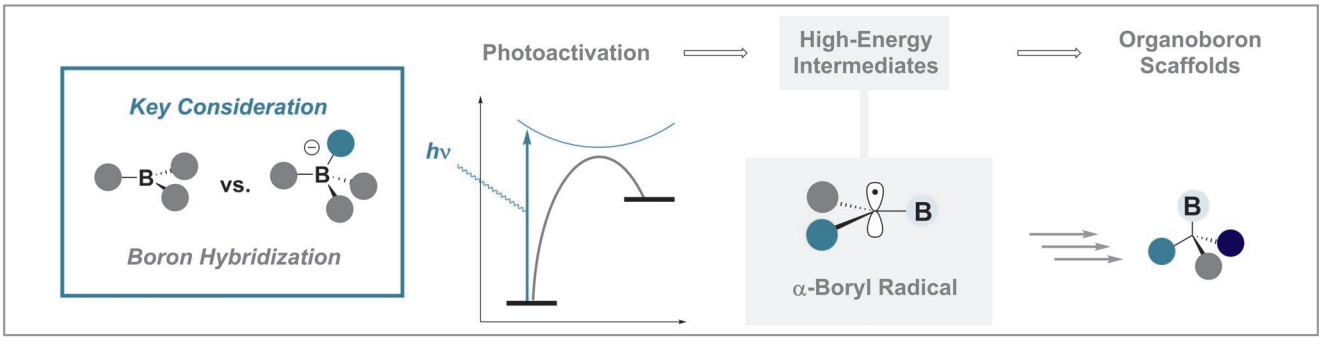

Scheme 1 An overview of the Molloy group's research harnessing boron hybridization to access high-energy intermediates for the synthesis of complex organoboron molecules.

in problem solving and puzzles, and synthesis struck me as exactly this. Ultimately, all the synthetic tools are often there, it is up to you to work out how to build up the molecule or develop novel reactions to get where you want to be. I believe this is ultimately what sparked my interest. Now that I have started giving lectures myself at Freie Universität Berlin, I've tried to replicate the enthusiasm and engagement my lecturers showed me, in the hope of inspiring the next generation to take up organic synthesis.

From a practical aspect this was most certainly during my industrial placement at the Beatson institute for Cancer Research where I really got the bug for making molecules. This was a really small drug discovery unit (10–20 people) which meant I got to see all aspects of a hit-to-lead project. I had two amazing supervisors (Catherine Barber and Duncan MacCarthur) who really invested a lot of time in training me in the lab practically. I think having a list of targets and not only designing my own routes to make them, but also seeing how they performed in the biological assays once they were made, was particularly exciting and really spurred me on to make more.

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

Dr. J. Molloy I think it is almost impossible to select one, so I'll select a few that stand out on a personal level. The first would be my first ever publication with Prof. Allan Watson.[3] Allan was an outstanding mentor and really had a hand in developing me into the inquisitive scientist I am today. I think on the projects I worked on we were never happy with just developing a new reaction; we were always keen to answer the question "why?". This paper was the first of a very enjoyable time growing as a researcher in his lab.

The second would be my first paper as co-corresponding author during my time as a postdoctoral researcher with Prof. Ryan Gilmour.[4] Here we answered a long-standing challenge with geometric isomerization of alkenes by energy transfer, extending this away from conjugated styrenyl systems by using boron to regulate reactivity. Ryan was (and still is) an incredible mentor who really believed in me as a scientist and gave me a lot of creative freedom but was always there to give unwavering support and guidance. I think this period was wonderful training for me in moving to an independent career, for which I am incredibly grateful.

The third would be securing an independent position at the Max-Planck Institute of Colloids and Interfaces. I think I can probably speak for all new PIs that there is nothing more daunting/exciting than the first day running your own research group. This was an incredible time for me and I'm extremely grateful to our director Prof. Seeberger for his continued support and guidance in this role.

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

Dr. J. Molloy I still play football as much as I can as it's a great way to take your mind off work and reset while keeping active/fit. The good thing is that in Germany you can usually find a club to play in no matter what level you are at (important for someone from Scotland with very little natural talent). Aside from this I quite like travelling and visiting new cities to explore. My brother lives in Spain and parents live in Cyprus so it is always great to get away and visit sunnier climates. I'm a big advocate for making time outside of the lab. It's always important to have time away, because usually when you return, with a fresh head, problems are a lot easier to solve.

SYNFORM *If you had not become a chemist, what other profession do you think you would have entered?*

Dr. J. Molloy This may come as a surprise, but I was very close to becoming an actor. When I was younger, I was involved in a lot of drama plays/productions and I ended up playing the leading role in a short independent film. The film went to a few film festivals and to everyone's surprise I was nominated for a new talent Scottish BAFTA in 2008. Things really snowballed from there and I had a casting agent and went for auditions for some pretty big roles. Unfortunately, nothing came off before university and my casting agent suggested I continue into university with acting. However, this came with the caveat that it is usually paired with singing, dancing or music. Fortunately for everyone, I have the movement of a refrigerator and a voice only a mother could love and decided a career in chemistry was perhaps better for me (and everyone else).

SYNFORM *What is the most exciting aspect of your job, the one you like the most?*

Dr. J. Molloy This is an easy answer! The most exciting aspect of my job is the students. It is really satisfying to see how much they develop over time, becoming engaged in their projects and excited to share results and talk about science. It is amazing to see them working together, coming up with their own ideas, and solving problems all on their own. I am always so proud of all of them. To see this excitement and know that you play a role in shaping their future is the most rewarding part, even though it is always inevitably sad to see them leave the group and move on to bigger and greater things.

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Catalytic Enantioselective Reductive Eschenmoser–Claisen Rearrangements

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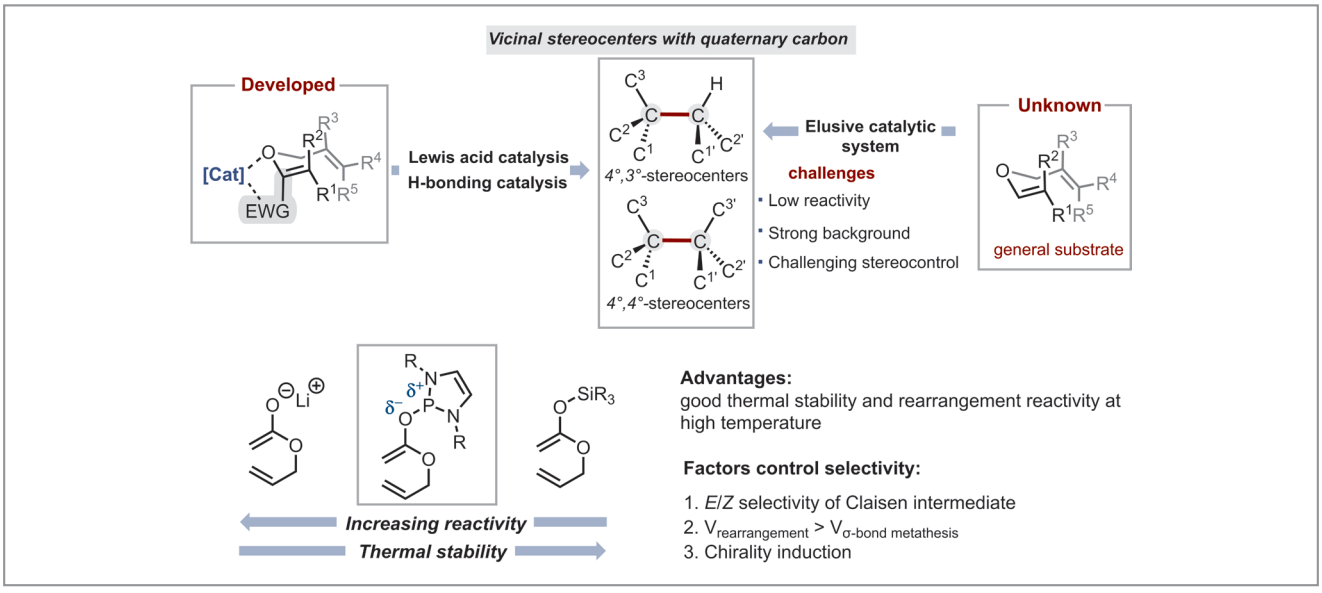
SYNFORM met with Professor Nicolai Cramer, from the École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland, to talk about his group's recent article in *Science*. "The Claisen rearrangement has a history of more than 100 years of synthetic usage since its discovery. Being a stereoselective sigmatropic rearrangement, it has been utilized extensively in constructing carbon stereocenters, especially to control the relative stereochemistry of contiguous stereocenters containing all-carbon quaternary carbons," he told SYNFORM about the reasons for pursuing this study (Scheme 1), adding: "However, achieving catalytic enantioselective Claisen rearrangements poses a formidable challenge for catalysis. Reported tactics involve Lewis acids or hydrogen-bonding catalysis and rely heavily on the presence of an additional chelating functionality on the substrate, thereby limiting the scope of the methods. Catalytic enantioselective systems applicable towards unbiased and general Claisen substrates remain an unsolved problem. The primary hurdle lies in the low reactivity exhibited by non-activated Claisen substrates in forming highly hindered carbon–carbon bonds. Consequently, these processes generally require elevated reaction temperatures, leading to the occurrence of strong background reactions and rendering stereoinduction processes exceedingly challenging."

Professor Cramer explained that, unlike the reported catalytic modes involving weak interactions, the designed covalent substrate–catalyst bond encountered during the 1,3,2-diazaphospholene (DAP) catalysis provides an attractive pathway to overcome these challenges. "The phosphorus–nitrogen bond of the DAP-bonded Claisen intermediate has good thermal stability and its uniquely polarized nature improves rearrangement propensity," he added.

The Cramer laboratory previously discovered reductive Claisen rearrangements with allyl α,β-unsaturated ester substrates (*Angew. Chem. Int. Ed.* **2019**, *58*, 8893–8897). "The DAP-catalyzed conjugate reduction directly triggers the [3,3]-Claisen rearrangement, yielding the corresponding allyl carboxylic acids in high yields," Professor Cramer explained further. He continued: "However, no substantial enantioselectivity could be observed with this substrate class. Critical factors in controlling stereoselectivity include: a) high *E/Z* ratio for the generated ketene acetal intermediate, b) faster rearrangement rate of DAP-ketene acetal intermediate than



Scheme 1 Challenges in catalytic enantioselective Claisen rearrangements

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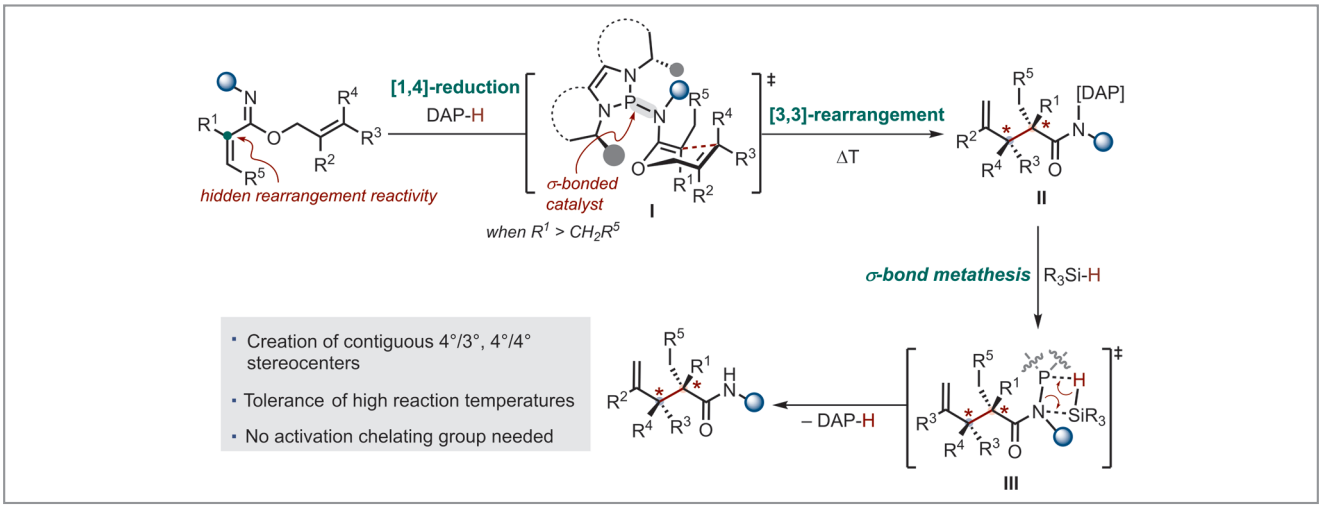
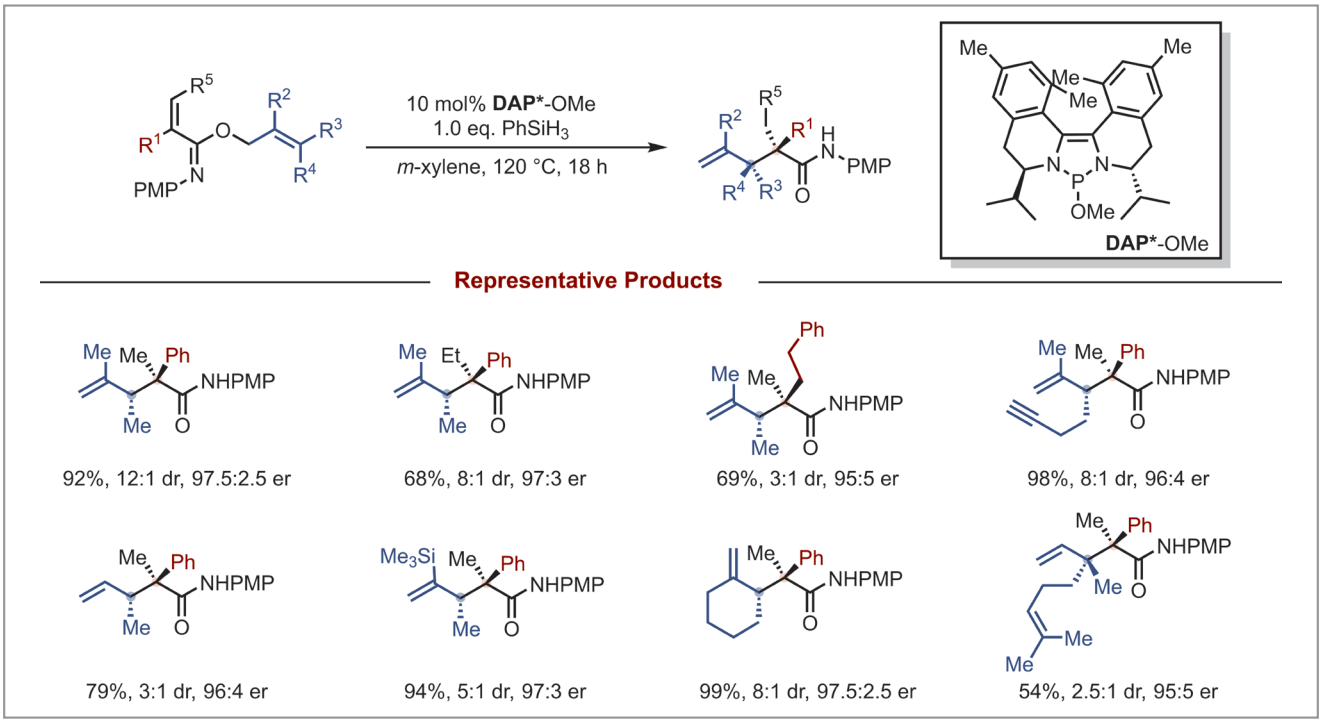


Scheme 2 DAP-catalyzed enantioselective reductive Eschenmoser–Claisen rearrangement

catalyst dissociation, c) provision of an appropriate chirality induction environment through the DAP catalyst."

Inspired by their recent work on DAP-catalyzed reductive aza-Mislow–Evans rearrangement reactions (*Angew. Chem. Int. Ed.* **2023**, *62*, e202301076), the group found that the aza-ketene acetal intermediate provides an adequate geometry control during the conjugate reduction (Scheme 2). Professor Cramer said: "We identified allyl imidates as suitable substrates for the reductive Claisen rearrangement. The relatively slower reacting P–N bond of the intermediate prevents premature catalyst cleavage in the presence of the terminal reductant, allowing the reaction to be compatible with high temperatures, and as well eliminating the need for an activated chelating group."

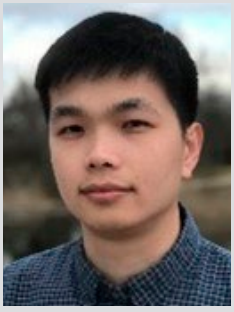


Scheme 3 Representative obtained products

During the reaction optimization, Dr. Guoting Zhang observed an unusual temperature effect. “Best stereoselectivities were achieved at high reaction temperatures (120 °C), while lower temperatures caused a weaker diastereomeric ratio,” remarked Professor Cramer, who continued: “This phenomenon likely stems from a faster equilibration *E*/*Z* ratio of the DAP-ketene acetal intermediate at elevated temperatures. Various amides containing contiguous quaternary/tertiary or quaternary/quaternary carbon stereocenters were synthesized with good to excellent yield and selectivities.”

“Our method facilitates the convenient stereodivergent synthesis of all four possible stereoisomers of the rearrangement product with high stereoselectivity by swapping to the enantiomer of the DAP*-catalyst,” said Professor Cramer, adding: “In addition, the method provides a synthetically exploitable pathway to construct the quaternary carbon stereocenters in natural products such as (+)-aphanorphine and clerodane diterpenoids (see Scheme 3).” Professor Cramer concluded: “We believe that our report will significantly advance the development of enantioselective Claisen rearrangement reactions, and act as a boost for the further development of the field of DAP catalysis.”

About the authors



Dr. G. Zhang

Guoting Zhang obtained his PhD from Wuhan University (P. R. China) under the guidance of Prof. Aiwen Lei. His thesis described the development of photoredox/cobalt-catalyzed oxidative coupling reactions. In 2018, he joined Stanford University (USA) as a postdoctoral researcher in Prof. Trost’s group, where he contributed to the development of ruthenium-catalyzed alkene/alkyne coupling reactions and total synthesis of natural products. Transitioning to Prof. Cramer’s group in 2021, his current postdoctoral research revolves around diazaphospholene (DAP)-catalyzed reductive transformations.

Dr. M. D. Wodrich

Matthew D. Wodrich earned BS and PhD degrees from the University of Arizona (USA) and University of Georgia (USA), respectively. Following several postdoctoral positions in Switzerland, he was appointed to a permanent scientist position at the École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland in 2015 and promoted to senior scientist in 2019. His current research interests lie in developing and applying computational tools to better understand and identify new homogeneous catalysts.

Prof. N. Cramer

Nicolai Cramer earned his PhD in 2005 at the University of Stuttgart (Germany) under the guidance of Prof. S. Laschat. After a postdoctoral stint with Prof. B. M. Trost at Stanford University (USA), he completed his habilitation at ETH Zurich (Switzerland) from 2007 to 2010 with Prof. E. M. Carreira. Subsequently, he moved to the École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland as assistant professor, was tenured in 2013, and promoted to full professor in 2015. His research encompasses sustainable catalytic enantioselective transformations and their implementation in synthesis. A focus is placed on asymmetric C–H functionalizations enabled by novel ligand designs.

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Photosensitization Enables Pauson–Khand-type Reactions with Nitrenes

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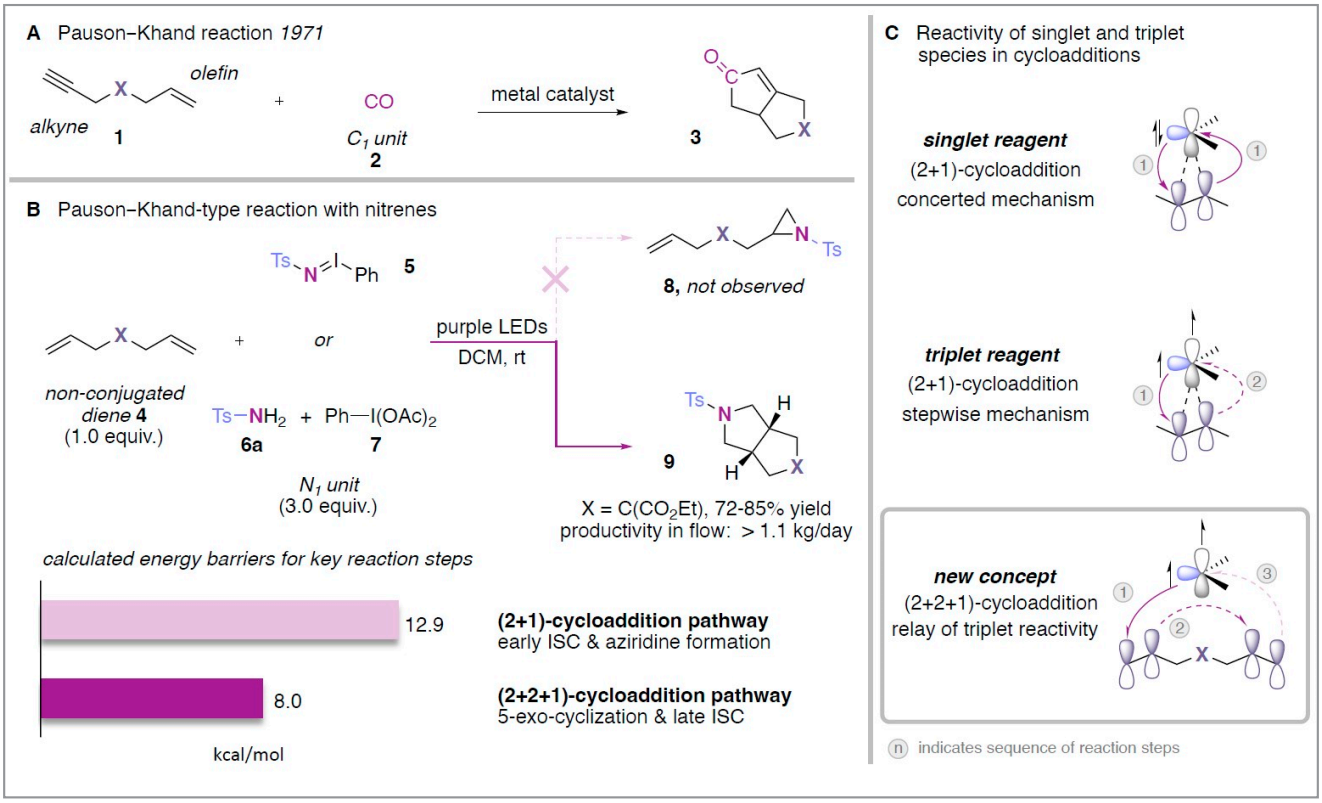
Even 50 years after the landmark discovery of cobalt-catalyzed (2+2+1) cycloaddition reactions, the Pauson–Khand reaction remains one of the most synthetically intriguing among this type of processes. It features the reaction of an alkyne and an olefin with carbon monoxide to furnish cyclopentenones (Scheme 1A), and significant developments with regards to both unsaturated reaction partners and the catalyst were made. Nowadays, the Pauson–Khand reaction finds widespread applications, ranging from total synthesis towards applications in drug synthesis and bulk chemical synthesis. The most significant limitation of Pauson–Khand reactions, however, lies within the necessity to use carbon monoxide as a C_1 building block.

For the last few years, Professor Rene Koenigs' group at RWTH Aachen University (Germany) has been particularly interested in the development of metal-free carbene and nitrene chemistry, where photochemical or photocatalytic applications and spin-state-dependent reactivity are in the spotlight. Professor Koenigs said: "The spin state of carbene or nitrene reagents plays a key role in the reaction outcome of cycloaddition reactions; for example, singlet reagents react in a concerted, stereospecific cycloaddition, whereas triplet reagents react in a stepwise mechanism, which for example allows the development of stereoconvergent cyclopropanation reactions as recently described by our group."

Professor Koenigs went on to explain that when considering nitrene intermediates, the triplet spin state is often the preferred spin state and as such, nitrenes – in the absence of a stabilizing metal complex – commonly react on the triplet spin surface via initial formation of an initial triplet addi-



Scheme 1 Pauson–Khand reaction and Pauson–Khand-type reactions with nitrenes

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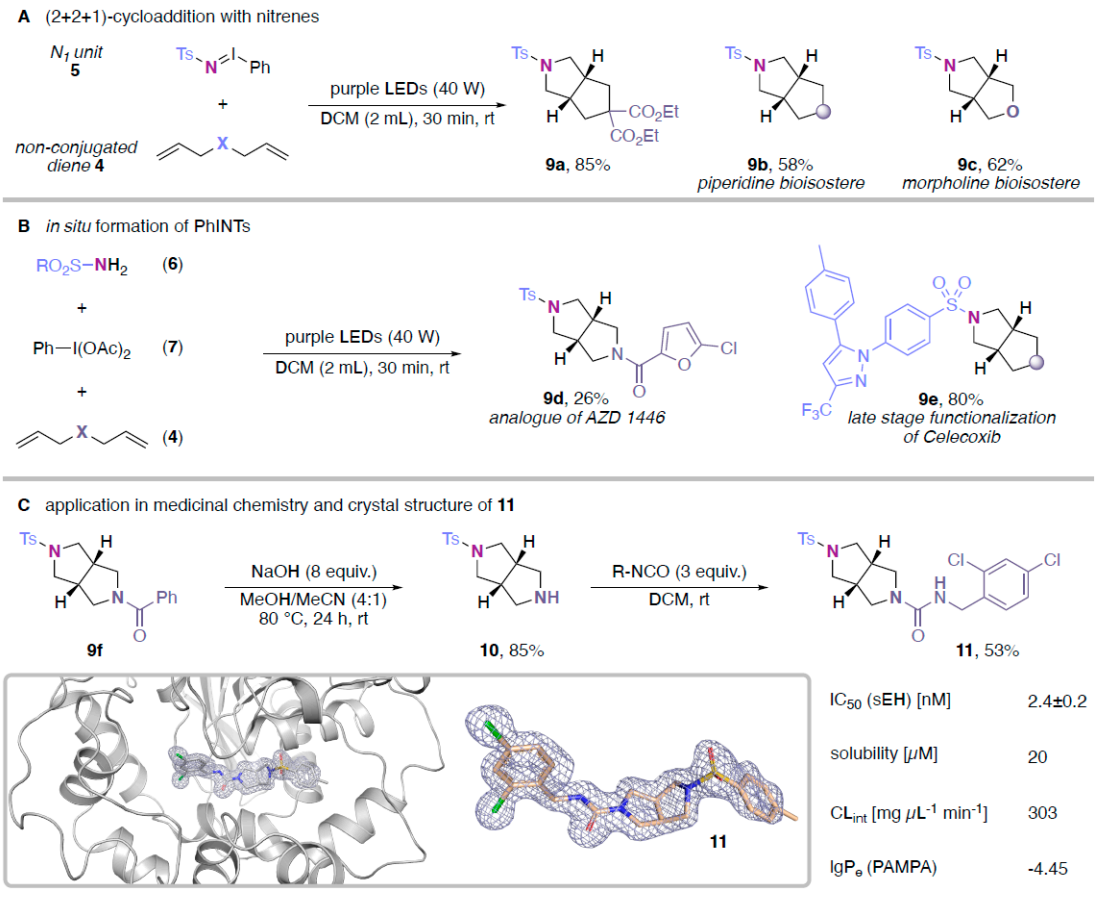
tion product. To achieve cycloaddition reactivity, intersystem crossing from triplet to singlet spin surface is mandatory and must occur before the final bond/ring forming event. Professor Koenigs hypothesized that: "The triplet reactivity of the initial addition product can be used to forge a new C–C bond instead of intersystem crossing." Such a strategy thus relays the triplet reactivity, as he continued to explain: "A late intersystem crossing then sets the stage to forge a third bond-forming event and results in the product of a (2+2+1) cycloaddition reaction – or a Pauson–Khand-type reaction with a nitrene (Scheme 1B, 1C)."

When examining the reaction of a non-conjugated diene and an iminoiodinane, the Koenigs group indeed observed a high selectivity leading to a (2+2+1) cycloaddition product (Scheme 2A). Further simplification was achieved by the observation that iminoiodinane can be intermittently accessed under purple light irradiation (Scheme 2B). Professor Koenigs stated: "The reaction products are bicyclic bioisosteres of common saturated heterocycles such as piperidine, morpholine, and piperazine. The starting materials are really simple reagents: a non-conjugated diene, a sulfonamide and diacetoxy-iodobenzene." Following a collaborative research strategy, a research team with scientists from Enamine Ltd. (Ukraine), Kyiv Taras Shevchenko University (Ukraine), and Goethe University in Frankfurt/M. (Germany) was formed to translate this groundbreaking discovery to industrial scale and medicinal chemistry applications. "This is a really exciting discovery and it shortens synthesis routes from more than 5 steps to a single step," said co-author Dr. Sci. Pavel Mykhailiuk (Enamine Ltd.). Together with a team of researchers at Enamine Ltd., a flow synthesis was then achieved, which allows the synthesis of more than 1 kg of such bicycles per day. Ewgenji Proschak, from Goethe University, commented: "These are ideal bioisosteres for many applications in medicinal chemistry." Together with a team of researchers, a set of novel and highly potent inhibitors of soluble epoxide hydrolase were synthesized



Scheme 2 (2+2+1)-Cycloaddition reactions with nitrenes towards application in medicinal chemistry

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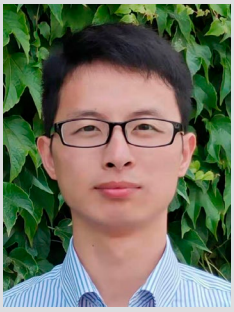
and tested in a typical medicinal chemistry screening setting (Scheme 2C).

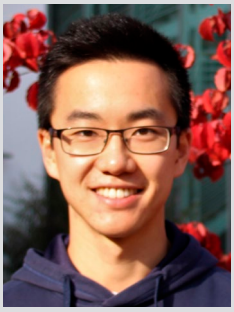
A combination of experimental and computational mechanistic analysis revealed that the initial hypothesis of an early intersystem crossing vs. late intersystem crossing is key to driving either conventional (2+1) or (2+2+1) cycloaddition chemistry. "Specifically, the barrier for an early intersystem crossing is simply unfavored and instead a 5-*exo*-cyclization reaction occurs and leads to the (2+2+1) reactivity. This concept opens up a plethora of new applications of advanced cycloaddition reactions and we are really excited about new developments in this area," concluded Professor Koenigs.

About the authors



Dr. F. Li

Fang Li obtained his B.A. in chemical engineering and technology from West Anhui University (P. R. of China) in 2012. He completed master's research on design, synthesis and characterization of cyclic conjugated molecules for optoelectronic nanomaterials with Prof. Shengxiong Xiao and earned an M.S. in 2016 from Shanghai Normal University (P. R. of China). He obtained his Ph.D. in organic chemistry in 2022 from RWTH University (Germany), working with Prof. Rene M. Koenigs. After a one-year postdoctoral stay at the RWTH University in 2023, he started his independent career at Shanghai Normal University. Recently, he has focused on molecular electronics and single-molecule electronics.

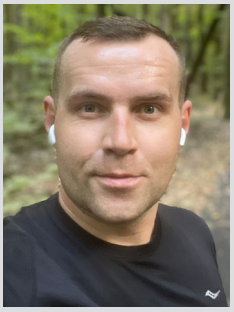


Dr. W. F. Zhu

Wenxin Felix Zhu received his B.Sc. and M.Sc. in chemistry from Goethe University of Frankfurt, Germany. He then joined the group of Prof. Eugen Proschak as a doctoral candidate, where his studies focused on the synthesis of bioactive heterocycles for pharmacological applications. He worked on target validation of ion channels as well as new chemical reactivities to assemble polycyclic heterocycles. In regard of the latter, he also completed a visiting stay in the laboratory of Prof. Rene Koenigs at RWTH Aachen (Germany) to study nitrene chemistry experimentally and computationally.

Dr. C. Empel

Claire Empel studied chemistry at the RWTH Aachen University (Germany) and the University of New South Wales (Sydney, Australia), and obtained her M.Sc. in 2020. In March 2020 she started her PhD in the group of Prof. Rene M. Koenigs, focusing on experimental and theoretical studies of carbene transfer reactions. She was initially funded by an RWTH Scholarship for Doctoral Students and since late 2020 by a Kekulé Scholarship from the Fonds der Chemischen Industrie and obtained her PhD in January 2023. She is now working as a PostDoc in the group of Prof. Rene M. Koenigs in collaboration with Prof. Debabrata Maiti (IIT Bombay, India), focusing on theoretical studies of metal-catalyzed C–H functionalization and light-mediated carbene and nitrene transfer reactions.



Dr. O. Datsenko

Oleksandr Datsenko was born in Ukraine. In 2006, he graduated from Taras Shevchenko National University of Kyiv (Ukraine) with a speciality in inorganic chemistry. Until 2012, he worked as a head of laboratory in the Ukrainian Organic Synthesis (UOS). During 2012–2015, he worked on a PhD project with Prof. Igor Komarov. In 2015, Oleksandr joined Enamine as a head of the photochemical laboratory. His research interests include photochemistry, 3D-shaped scaffolds and radical chemistry.

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Dr. A. Kumar

Adarsh Kumar was born and raised in India. He obtained his Ph.D. in 2018 at the CSIR-Institute of Microbial Technology, Chandigarh, India, under the mentorship of Dr. Karthikeyan Subramanian. His doctoral research focused on characterizing hypothetical essential proteins from *Mycobacterium tuberculosis* using structural biology and biophysical methods. Continuing his interest in mechanistic studies, he moved to The Florida State University, Tallahassee, Florida, USA, as a postdoctoral researcher, where his research focused on elucidating the mechanisms of enzymes involved in human DNA base excision repair pathways through time-resolved crystallography. In 2021, he joined The Structural Genomics Consortium, Frankfurt am Main, Germany, under the guidance of Prof. Dr. Stefan Knapp, where he is currently involved in structure-based drug discovery, with a particular emphasis on determining the structures of target–ligand complexes and conducting structure-based fragment screening to identify novel binding sites on the target proteins.

J.H.M. Ehrler

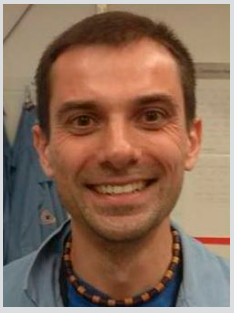
Johanna H. M. Ehrler received her B.Sc. and M.Sc. in chemistry from the Goethe University Frankfurt (Germany), where she studied photolabile protecting groups as well as proteins from antibiotic-resistant bacteria. She then joined the laboratory of Prof. Ewgenij Proschak as a Ph.D. student. Her doctoral research focuses on lipid signal transduction cascades along with G-protein-coupled receptors as therapeutic targets.

Dr. I. Atodiresei

Iuliana Atodiresei studied chemistry at the Al. I. Cuza University of Iasi, Romania and TU Braunschweig, Germany where she spent 9 months as a Socrates exchange student, performing research in the field of cross-conjugated compounds in the group of Professor H. Hopf. After obtaining her M.Sc. degree in 2001, she joined the group of Professor C. Bolm at the RWTH Aachen University, Germany where she carried out her doctoral studies in the field of asymmetric synthesis. In 2005 she joined the group of Professor G. Raabe, focusing on the determination of the absolute configuration of organic molecules by means of CD spectroscopy and theoretical investigations. In 2010 she joined the group of Prof. M. Rueping, widening her research interests and expanding her expertise towards X-ray crystal structure analysis. Currently, she is a senior scientist at the RWTH Aachen involved in the structure elucidation of organic molecules by spectroscopic, crystallographic, and theoretical means.

Prof. Dr. S. Knapp

Stefan Knapp studied chemistry at the University of Marburg (Germany) and the University of Illinois (USA). He received his Ph.D. in protein crystallography from the Karolinska Institute in Stockholm. He joined Pharmacia (Nerviano, Italy) in 1999 and left the company in 2004 to establish a research group at the Structural Genomics Consortium at the University of Oxford. From 2008 to 2015 he was Professor of Structural Biology at Oxford University (UK) and from 2012 to 2015 Director of Chemical Biology at the Target Discovery Institute at Oxford University. In 2015, he joined the University of Frankfurt as Professor of Pharmaceutical Chemistry. Since 2017, he is also the CSO of the SGC (Structure Genomics Consortium) node at Goethe University Frankfurt. His research interests are the elucidation of molecular/structural mechanisms of kinase regulation using high-resolution structures, the design of selective kinase inhibitors, and the inhibition of protein interaction domains such as bromodomains, which are the main readers of the epigenetic acetylation code, and E3 ubiquitylating ligases.



Dr. P.K. Mykhailiuk

Pavel K. Mykhailiuk was born in Kerch, Ukraine. In 2008 he received a Ph.D. in biochemistry from the Technical University of Karlsruhe (KIT, Germany) with Prof. Anne Ulrich, and a Ph.D. in organic chemistry from Taras Shevchenko National University of Kyiv (Ukraine) with Prof. Igor Komarov. In 2009 he returned to Ukraine and joined Enamine company, where he is currently involved in the discovery of novel building blocks for medicinal chemistry and agrochemistry. During his stay at Enamine, he

visited the groups of Prof. Thorsten Bach (TUM, Germany), Prof. Janine Cossy (ESPCI, France), and Prof. Phil Baran (Scripps, U.S.) as a research scientist to deepen his knowledge of organic chemistry. His research interests include fluoroorganic chemistry, diazo compounds, photochemistry, and bioisosteric replacements.

Prof. E. Proschak

Ewgenij Proschak is a Professor of Drug Design at the Institute of Pharmaceutical Chemistry at the Goethe University (GU) of Frankfurt (Germany). After his doctoral and postdoctoral studies at Goethe University, he became an Independent Group Leader at the Lipid Signaling Research Center (LIFF) in Frankfurt. The German Research Council (DFG) awarded him a Heisenberg Professorship, which was tenured by the GU. He has worked on hit identification and hit-to-lead optimization for fatty acid mimetics targeting enzymes, nuclear receptors and G-protein coupled receptors. His current research interests are the design and synthesis of multitarget drugs for the treatment of inflammatory conditions and metabolic syndrome.

Prof. R.M. Koenigs

Rene M. Koenigs obtained his PhD in 2011 from RWTH Aachen University (Germany) under the guidance of Prof. Magnus Rueping. He subsequently moved to Grünenthal GmbH (Germany), working as a medicinal chemist on GPCR and ion channel targets in pain and inflammation research under the supervision of Dr. Paul Ratcliffe and Dr. Henning Steinhagen. In 2015, he was appointed as junior professor at RWTH Aachen University and was promoted to full professor in 2022. His research interests focus on carbene and nitrene chemistry, photochemistry and photocatalysis, continuous-flow chemistry and fluorine chemistry.

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