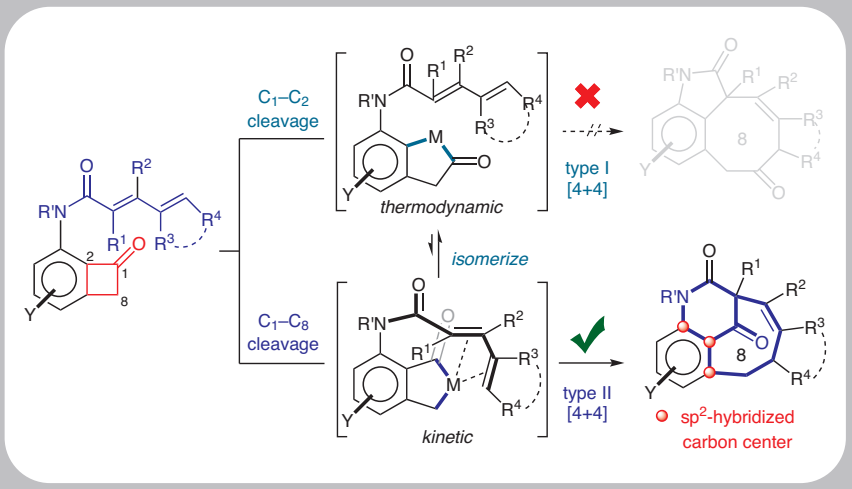
Synform

People, Trends and Views in Chemical Synthesis

2021/09

Regioselective Activation of Benzocyclobutenones and Dienamides Leads To Anti-Bredt Bridged-Ring Systems by a [4+4] Cycloaddition

Highlighted article by J. Zhang, X. Wang, T. Xu



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Thieme

Dear Readers,

This is going to be a brief editorial as I am writing it while I am on annual leave. My family – including our cat Zorro, who travelled for 5 days on the road with a pet courier from Glasgow to Milan – has just re-united for a few weeks, after over one year of separation due to a number of issues, such as the pandemic, Brexit, my move back to Italy, my children attending schools in Scotland, and the list could go on. So, I am sure you will forgive me if I go straight to the key point, which is the content of this new issue of SYNFORM. The first article covers the great work of S. Minakata (Japan) on the iodine-catalyzed intermolecular 1,2-diamination of unactivated alkenes. The following YCF interview features the up-and-coming S. Butler (UK), who speaks with SYNFORM about his exciting work on the design and synthesis of host molecules with applications in molecular imaging and sensing. The next article takes us to "the dark conformational space of macrocycles", fortunately under the expert guidance of A. Yudin (Canada). Finally, we have the chance to travel to the exotic world of strained bridged-ring systems, whose synthesis was recently devised by T. Xu (P. R. of China).

Enjoy your reading... and your holidays too!!

In this issue

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Diastereodivergent Intermolecular 1,2-Diamination of Unactivated Alkenes Enabled by Iodine Catalysis

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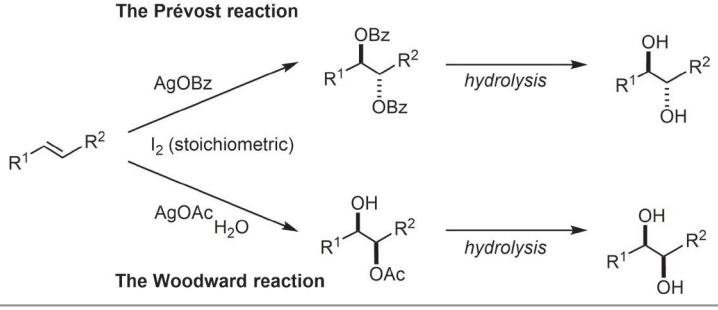
The 1,2-diamine motif is a ubiquitous feature of bioactive compounds, a ligand for organic transformations, and a valuable synthetic intermediate for the construction of complex molecules. Addition reactions to alkenes are upstream transformations in synthetic organic chemistry, because such structures are essential feedstocks in a wide variety of petrochemical processes. Thus, the development of a robust methodology for the 1,2-diamination of alkenes is highly desirable. "Controlling the relative configuration of two nitrogen moieties is crucial for the synthesis of diverse molecules, but there are no versatile and practical methods available for the *anti*- and *syn*-diamination of alkenes with complete control of the stereochemistry of the reaction," said Professor Satoshi Minakata from Osaka University (Suita, Japan). He and his research group are interested in developing fundamental organic transformations: "Even though a nitrogen atom is a ubiquitous atom that is as important as an oxygen atom in a variety of organic molecules, the nitrogen versions of dihydroxylation, i.e., the Prévost and Woodward reactions, remain unexplored," explained Professor Minakata, and this is indeed one of his group's research themes: the development of catalytic aza-Prévost and Woodward reactions (Scheme 1).

Professor Minakata's group has been exploring the molecular-iodine-catalyzed aziridination of alkenes utilizing commercially available and inexpensive *N*-chloro-*N*-sodio-*p*-toluenesulfonamide (chloramine-T) as a potential nitrogen source (*Tetrahedron* **1998**, *54*, 13485–13494; *Angew. Chem. Int. Ed.* **2004**, *43*, 79–81; *Acc. Chem. Res.* **2009**, *42*, 1172–1182). The observation that small amounts of the ring-opened product, a 1,2-diamine, form in the process prompted Professor Minakata to search for a suitable nitrogen source that could be used for both aziridine formation and ring opening. "This simple concept led to the successful *anti*-diamination of alkenes. The strategy also involves the formation of an intermediate, namely, a cyclic iodonium intermediate, which is a strong electrophile for ring opening. We reasoned that if it were possible to prepare a more electron-deficient aziridine – other than the *N*-Ts aziridine – the latter could be regarded as a cyclic halonium derivative that would easily undergo ring-opening," said Professor Minakata. After a series of investigations, an *o*-nitrobenzenesulfonyl (Ns) group was found to be the optimal group for achieving the desired iodine-catalyzed anti-diamination. "Since an Ns group can be readily cleaved by Fukuyama's method, thus leading to the formation of unsubstituted amino groups, the discovery of such Ns group is like *getting two diamonds for the price of one*," explained Professor Minakata (Scheme 2; left).

To achieve the *syn*-diamination of alkenes, Professor Minakata's group designed a bespoke nitrogen source. "If two nitrogen moieties in the same molecule could be added to an alkene in the same manner via iodine-catalyzed aziridination, the reaction would be predicted to proceed in a *syn*-mode," said Professor Minakata. "Since a chloramine salt induces iodine-catalyzed aziridination reactions, the chloramine salt of *N*,*N*′-bis(*tert*-butoxycarbonyl)sulfamide (chloramine-BBS) was designed. Although BBS is a known compound, it is not extensively used in organic synthesis. We were very pleased to find that this nitrogen source was applicable to iodine-catalyzed *syn*-diamination (Scheme 2; right)."



Scheme 1 The Prévost and Woodward reactions

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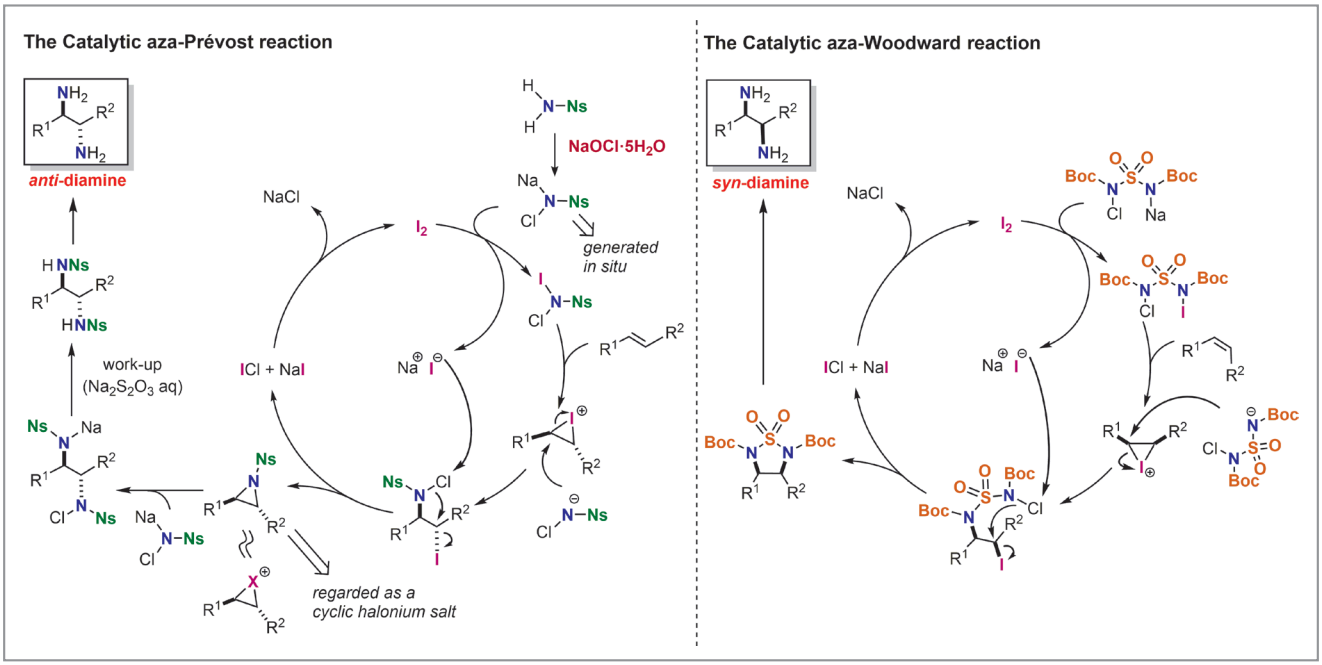
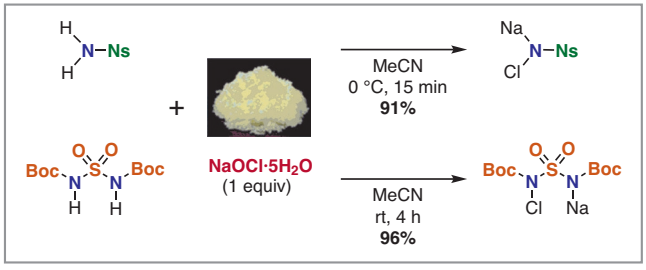


Scheme 2 Diastereodivergent intermolecular 1,2-diamination of unactivated alkenes enabled by molecular iodine catalysis

Professor Minakata emphasized that chloramine salts bearing electron-withdrawing groups on the nitrogen are crucial for such iodine-catalyzed reactions. The group thought that a convenient method for preparing chloramine salts would be needed if the above *anti*- and *syn*-diamination was to be more practical. The finding in 2015 of sodium hypochlorite pentahydrate ($NaOCl·5H_2O$) accelerated the development of the two strategies. "This unique reagent is manufactured and sold by the Nippon Light Metal Company, Ltd.," said Professor Minakata, who was focused on identifying a solid-state reagent that could be used in an organic solvent. As expected, both nitrogen sources, *o*-nitrobenzensulfonamide and *N*,*N*′-bis(*tert*-butoxycarbonyl)sulfamide, were efficiently transformed into the corresponding chloramine salts in acetonitrile (Scheme 3). In particular, chloramine-Ns could be generated in situ for *anti*-diamination reactions, meaning that the reagents needed for such *anti*-diamination reactions, including the catalyst, are all commercially available materials.

Concerning the applications of this approach and future perspectives of this powerful methodology, Professor Minakata noted: "As I wrote in the original paper, immediate applications include the N-modification of products and the aminofunctionalization of alkenes through the formation of reactive aziridine intermediates that can react with various other nucleophiles." He added: "As future prospects, considering that the 1,2-diamine moiety is an important structure



Scheme 3 Preparation of chloramine salts for *anti*- and *syn*-diamination reactions from simple amides with NaOCl pentahydrate

that is found in anti-influenza drugs having neuraminidase inhibition properties (Tamiflu®, Relenza® and Inavir®), the developed methods could facilitate the early discovery of various new drugs, including those against new viruses that promise to pose an increasing threat to mankind in the future."

Professor Minakata concluded: "Our group succeeded in discovering reactions that had been seen before, but were new at the same time! These simple, efficient, convenient, robust, and practical methods have the potential to be used in the synthesis of various organic molecules. I strongly believe that the present diamination reaction could become a *Name Reaction* in the field of organic synthesis."

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About the authors

Prof. S. Minakata

Satoshi Minakata was born in Wakayama in 1964. He received his Ph.D. in 1993 from Osaka University (Japan) under the direction of Professor Yoshiki Ohshiro. After spending two years (1993–1995) at Central Research Laboratories of DIC Corporation (Japan), he was appointed as an assistant professor of Department of Applied Chemistry in Professor Komatsu's group at Osaka University, and promoted to lecturer in 2000. From 1997 to 1998, he worked with Prof. Erick. M. Carreira at the California Institute of Technology (USA) as a visiting associate. In 2002, he was promoted to associate professor and since 2010, he has been a full professor at Osaka University. His research interest centers the development of new methodologies for synthesis of valuable organic molecules from simple molecules.

H. Miwa

Hayato Miwa was born in 1992. He received his Bachelor (2016) and Master (2018) of Engineering degrees from Osaka University (Japan) under the supervision of Professor Satoshi Minakata. Currently, he is working at a chemical company. During his Bachelor's and Master's degree programs, he focused on the development of direct *anti*-diamination of alkenes from nosylamide utilizing sodium hypochlorite pentahydrate enabled by iodine catalysis.

K. Yamamoto

Kenya Yamamoto was born in 1993. He received his Bachelor (2017) and Master (2019) of Engineering degrees from Osaka University (Japan) under the supervision of Professor Satoshi Minakata. Currently, he is working at a chemical company. During his Master's degree program, he focused on the development of iodine-catalyzed *syn*-diamination of alkenes with a chloramine salt derived from *N*,*N*′-bis(*tert*-butoxycarbonyl)sulfamide.

A. Hirayama

Arata Hirayama was born in 1993. He received his Bachelor (2015) and Master (2017) of Engineering degrees from Osaka University (Japan) under the supervision of Professor Satoshi Minakata. Currently, he is working at a chemical company. During his Master's degree program, he focused on the development of iodine-catalyzed *anti*-diamination of alkenes with *N*-chloro-*N*-sodio-*o*-nitrobenzenesulfonamide.

Dr. S. Okumura

Sota Okumura was born in 1987. He received his Bachelor (2010), Master (2012) and PhD (2015) of Engineering degrees from Osaka University (Japan) under the supervision of Professor Satoshi Minakata. The title of his doctoral dissertation is *Development of Novel Synthetic Methods Utilizing Mono- or Trivalent Iodine Reagent*. Currently, he is working at a chemical company. Apart from research for his doctoral degree, he contributed to the early stages of this diamination chemistry.

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Young Career Focus: Dr. Stephen J. Butler (Loughborough University, UK)

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. Stephen J. Butler (Loughborough University, UK).

Biographical Sketch

Dr. S. J. Butler

Stephen J. Butler completed his undergraduate degree at Warwick University, UK, before moving to Australia to study for a PhD at the University of Sydney, under the supervision of Prof. Katrina Jolliffe. His PhD focussed on synthesising cyclic peptide scaffolds as supramolecular receptors for anions. In 2010, he undertook postdoctoral research with Prof. Richard Payne, developing new methodology for the solid-phase synthesis of sulfated peptides, before returning to the UK to work with Prof. David Parker FRS at Durham University, synthesising highly emissive lanthanide complexes as cellular imaging probes. In 2013, Stephen was awarded a Ramsay Memorial Fellowship at Durham University, to develop molecular receptors for ATP. He began a Lectureship at Loughborough University (UK) in 2015, where his current position is Senior Lecturer. He leads an enthusiastic group developing molecular probes based on lanthanide complexes, for the purpose of sensing biological anions, probing enzyme activity and signalling biochemical events in living cells.

INTERVIEW

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

Dr. S. J. Butler We are studying molecular recognition and photophysical techniques. A major research focus in our lab is the design and synthesis of host molecules that bind selectively to biological anions in aqueous media. We are developing these molecules into bioassay tools and cellular imaging probes, which may be applied in a biomedical or clinical setting. Organic synthesis is at the core of our research, combined with photophysical studies of host–guest interactions. Our molecular hosts are based on macrocyclic lanthanide complexes, which offer unique optical properties that are very valuable for biological sensing and imaging. We are studying methods to tune host selectivity and affinity for target anions (e.g. ATP, ADP, AMP) through modifications in the structure and geometry of the macrocyclic ligand.

SYNFORM *When did you get interested in synthesis?*

Dr. S. J. Butler My interest in organic synthesis grew during the third year of my undergraduate degree at Warwick University – the enthusiasm of my lecturers around creating complex organic molecules was very motivating. I developed as a synthetic chemist during my PhD at Sydney University under the guidance of Prof. Kate Jolliffe, where I synthesised large cyclic peptides containing oxazole units that confer rigidity to the peptide macrocycle, and side chains functionalised with binding sites to recognise specific guests. I really enjoyed using organic synthesis to create molecules designed to perform a particular function. This theme continued in my postdoctoral work with Prof. David Parker, involving the construction of highly emissive lanthanide complexes with conjugated aromatic arms for use as optical imaging agents in live-cell imaging experiments. Synthesising a molecule and then testing its ability to achieve a specific task using a

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range of supramolecular experimental techniques was really rewarding.

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

Dr. S. J. Butler From my perspective, organic chemistry allows us to create probes that may be applied at the chemistry/biology interface to advance our understanding of health and disease at a molecular level. In the context of molecular imaging probes, arguably the most important feature is selectivity; the biggest challenge is to create molecules that exhibit higher levels of selectivity, allowing a specific analyte to be distinguished within a complex biological environment. To this end, the modern role of organic synthesis is to develop new methods to integrate multiple recognition motifs within a molecular host structure, which engage their target to generate a distinct host–guest complex structure. The recognition of large biological guests demands new synthetic methodologies to access larger and more intricate host architectures. Synthetic receptors with increased selectivity will open the door to new and improved bioassays and imaging probes required for biomedical and clinical research.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Dr. S. J. Butler I'd like to highlight three active research projects which all started out with a common goal to create new molecular structures designed to perform a specific task:

Supramolecular Anion Recognition (**Figure 1**). We have established key design principles to synthesise molecular hosts which bind a target nucleoside phosphate anion (e.g. ATP, ADP, AMP) with high selectivity in competitive biological media, avoiding interference from biomolecules and anions with similar charge and shape.[1–5] Nucleoside phosphate anions are critical to the maintenance of life and play crucial roles in energy transduction, cellular signalling and membrane transport.[6,7] We have developed a new class of emissive europium complexes bearing arms that bind selectively to ATP and ADP through a combination of electrostatic and hydrogen bonding interactions. Our lead molecule is capable of real-time analysis of kinase enzyme activity by monitoring the production of ADP, thereby providing a convenient luminescence assay for screening of potential kinase inhibitors.[2]

Reactivity-Based Probes (**Figure 2**). The reactivity of molecular probes with biomolecules and endogenous reactive

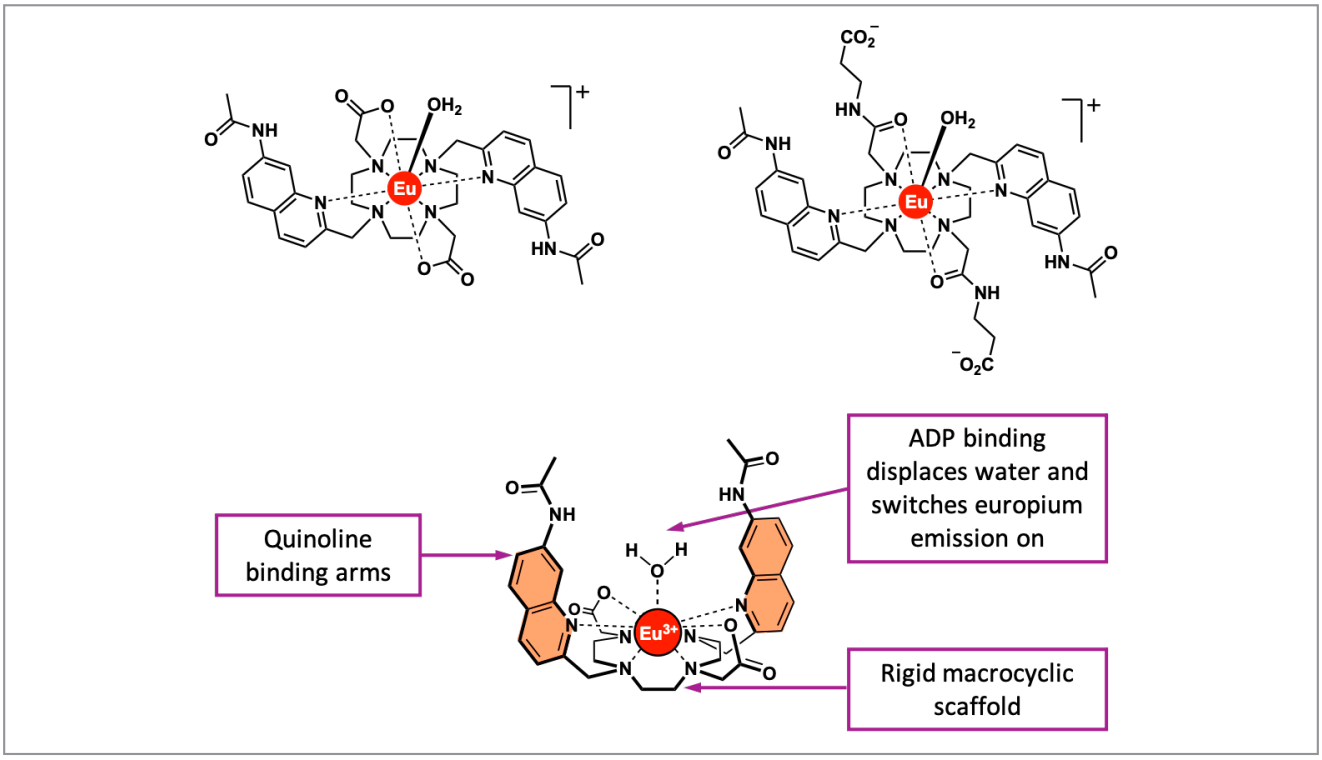

Figure 1 Europium-based host molecules for the recognition of ADP and ATP

species is also being studied in our group. For example, we recently developed a europium-based probe that reacts selectively with peroxynitrite, a short-lived species that causes harmful oxidation of cells. Our probe can be used to visualise peroxynitrite levels in the mitochondria of living cells using fluorescence microscopy.[8] We are also developing new conjugation methods for the site-selective attachment of a paramagnetic probe to cysteine residues of proteins, providing a versatile tool to study the protein by multiple spectroscopic techniques, including NMR, EPR and time-resolved FRET experiments.

Molecular Imaging (Figure 3). We are developing new synthetic approaches to polymeric MRI contrast agents. MRI is invaluable for imaging tumours and diagnosing disease. Contrast agents have been used in the clinic since the 1980s to enhance the image contrast by increasing relaxation of local water molecules. However, these contrast agents are far from optimal and the image contrast is nowhere near the theoretical maximum. We have prepared gadolinium complexes bearing two polymerisable arms, which can be readily polymerised in a single step to form macromolecules with different architectures, such as hyperbranched polymers.[9] By limiting the local motion of the gadolinium complex through crosslinking, we have produced contrast agents with 8-fold higher relaxivities compared to commercial agents (e.g. Gd-DOTA), which could enable lower and safer doses of the contrast agent to be used.

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

Dr. S. J. Butler Perhaps the most significant contribution so far is in the area of supramolecular anion recognition – we have synthesised a new class of receptors that can discriminate between ATP and ADP for the purpose of monitoring kinase enzyme activity in real-time.[2,4] This could underpin new bioassay tools for high-throughput screening of potent kinase inhibitors for the treatment of cancer. I'm proud that some of our molecules are already being used in studies led by biochemists and biologists – I find collaboration with experts in different fields to be very rewarding and certainly the best

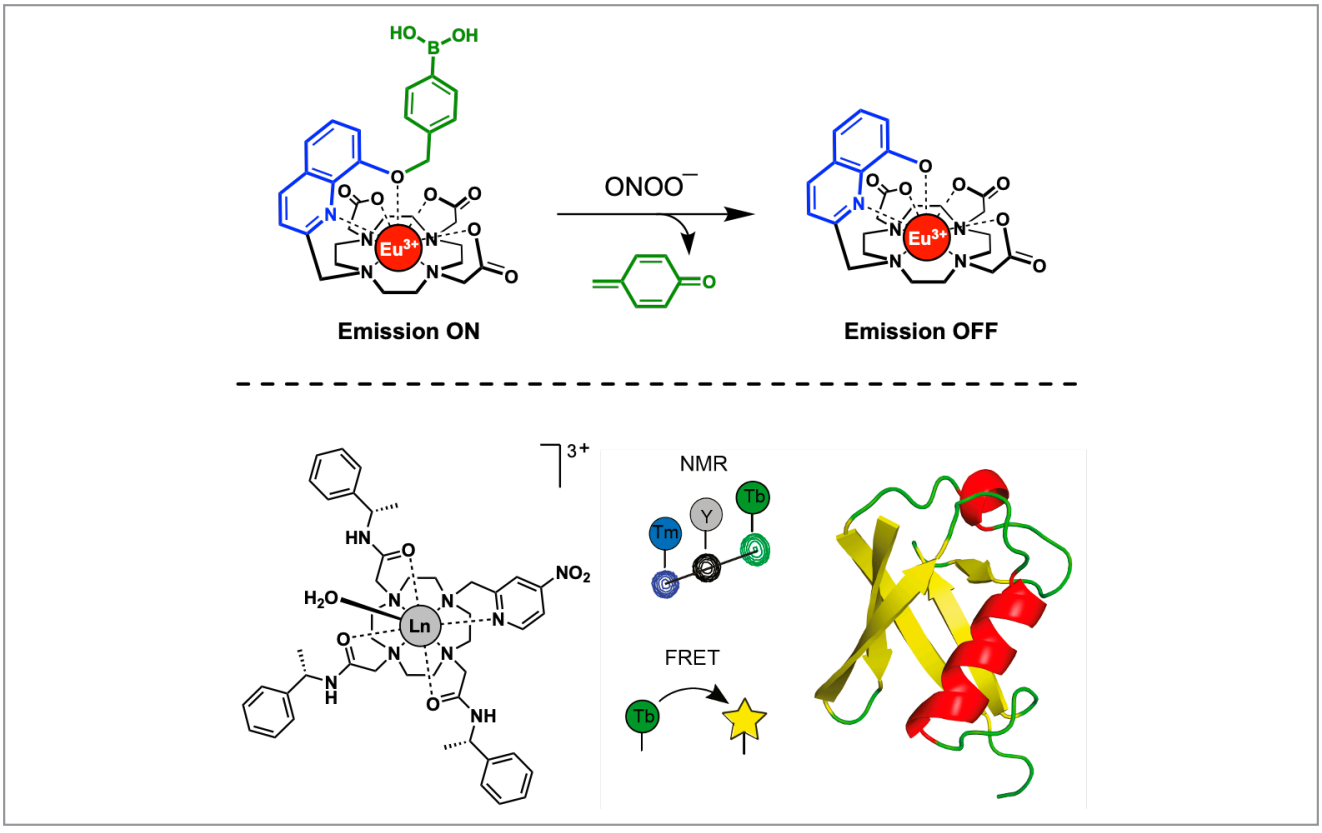

Figure 2 Reactivity-based probe for selective detection of peroxynitrite (top). Chiral paramagnetic tag for site-selective attachment to proteins (bottom).

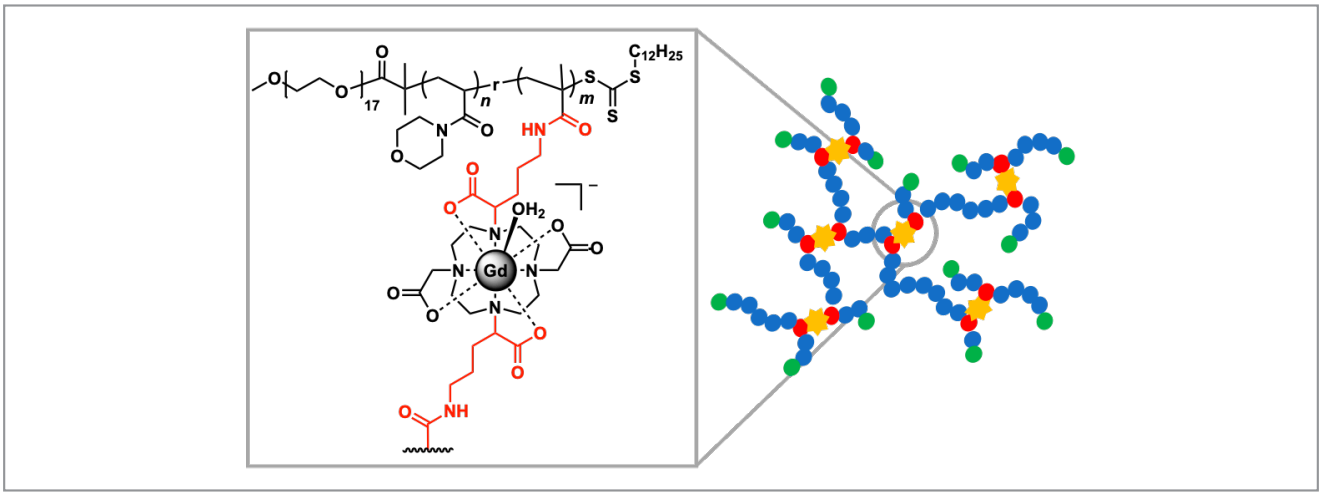

Figure 3 Gd(III) building blocks for macromolecular MRI contrast agents

way to optimise our supramolecular receptors for eventual 'real-world' applications. There is no doubt that my scientific achievements are only possible because of the talented and enthusiastic group of researchers that I've had the pleasure to work with in our lab over the past 5 years. Thanks to their drive and talent, we also have more exciting projects in the pipeline.

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Illuminating the Dark Conformational Space of Macrocycles Using Dominant Rotors

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Macrocycles can target complex protein interfaces that are not readily tractable through traditional small-molecule approaches. "Perhaps the most significant and enabling feature of macrocyclic drugs and biological probes, in contrast to their small molecule counterparts, is their intricate three-dimensional shape, or conformation," said Professor Andrei Yudin, from the University of Toronto (Canada): "Apart from relatively small rings such as cyclohexane, deciphering conformation–activity relationships in larger molecules is substantially more complicated.[1] As a result, there is substantial interest in technologies that allow systematic studies of the effect of macrocyclic conformational changes on biological activity."

In a recent paper, Professor Yudin et al. used the term 'dark conformational space' to describe the metastable states in peptide structures observed by NMR and X-ray crystallography. "The concept of dark space becomes intuitive when a parallel is made to less structurally complex small molecules," explained Professor Yudin, who continued: "The twist-boat conformation in cyclohexane is approximately 5.5 kcal mol^{-1} higher in energy than the chair form, making it challenging to detect and directly study its physicochemical properties. Interestingly, the replacement of four hydrogens in cyclohexane with cyclohexyl groups destabilizes the chair conformation significantly to exclusively reveal the twist-boat form.[2]"

Due to coupled bond rotations, macrocycles belong to a class of challenging structures in which slight alterations in dihedral angles can propagate through the ring and trigger conformational changes at distal position(s). "In the case of lorlatinib, an anticancer drug developed by Pfizer," said Professor Yudin, "a methyl group five atoms away from the biaryl linkage results in severe allylic 1,3-strain and effectively destabilizes the non-bioactive conformer by 8.5 kcal mol^{-1}.[3] Remarkably, a single methyl group in a 12-membered ring provides more stabilization than the *tert*-butyl group on cyclohexane (Figure 1A). Removing the methyl group in lorlatinib leads to a macrocyclic structure that exists as a mixture of two atropisomers separated by a conformational interconversion barrier of 24.6 kcal mol^{-1}."

The authors reasoned that coupling among bond rotations within a macrocycle might be controlled by a 'dominant rotor', whose rotational barrier is substantially higher than the rest of the system (Figure 1B). Professor Yudin said: "We hypothesized that this feature might remodel the accessible conformational space of a macrocycle into two non-interconverting ensembles we refer to as a two-well system. Rotors originating from amino acid amides generally display a *cis–trans* amide rotation barrier of about 18–20 kcal mol^{-1}, which is too low of a barrier for maintaining control of a given system under ambient conditions. To explore the energetic landscape of constrained peptides, we speculated that the dominant rotor candidates should possess a rotational energy barrier of at least 25 kcal mol^{-1}."

The group evaluated a collection of N-protected biaryl amino acids and uncovered a particular class of phenylene–triazolyl rotors to meet their energetic requirements (Figure 1B). "We prepared the tunable atropisomeric building blocks **1–8** that were predicted to span a range of rotational barriers and introduced them into cyclic peptides," said Professor Yudin. He continued: "This simple approach has allowed us to correlate conformational changes in a wide range of rings with the nature of the dominant rotor and led to the creation of two-well systems with controlled conformational behavior. Figure 2A depicts a representative two-well macrocycle (**9**) isolated. What is especially significant is that the two atropodiastereomers have completely different conformations, evidenced by different hydrogen-bond networks and differences in solubility."

"Ordinarily, conformational isomers such as S_a-**9** and R_a-**9** cannot be isolated because the barrier to interconversion is easily surmountable at room temperature. This result underscores that staying away from equilibrium offers a fascinating possibility to control complex molecules," remarked Professor Yudin, who added: "We also considered larger macrocycles that are composed mainly of amino acid residues and showed that higher-energy conformations could be enforced using dominant rotors. These units effectively remodel the conformational landscape of 16- to 22-membered rings and enable observation of peptide conformations that are uncommon because of their irregular geometrical features (Figure 2B)."

According to Professor Yudin, control over conformation in macrocycles is an unsolved problem. "Had mastery of this kind been possible, one could easily design a potent and selec-

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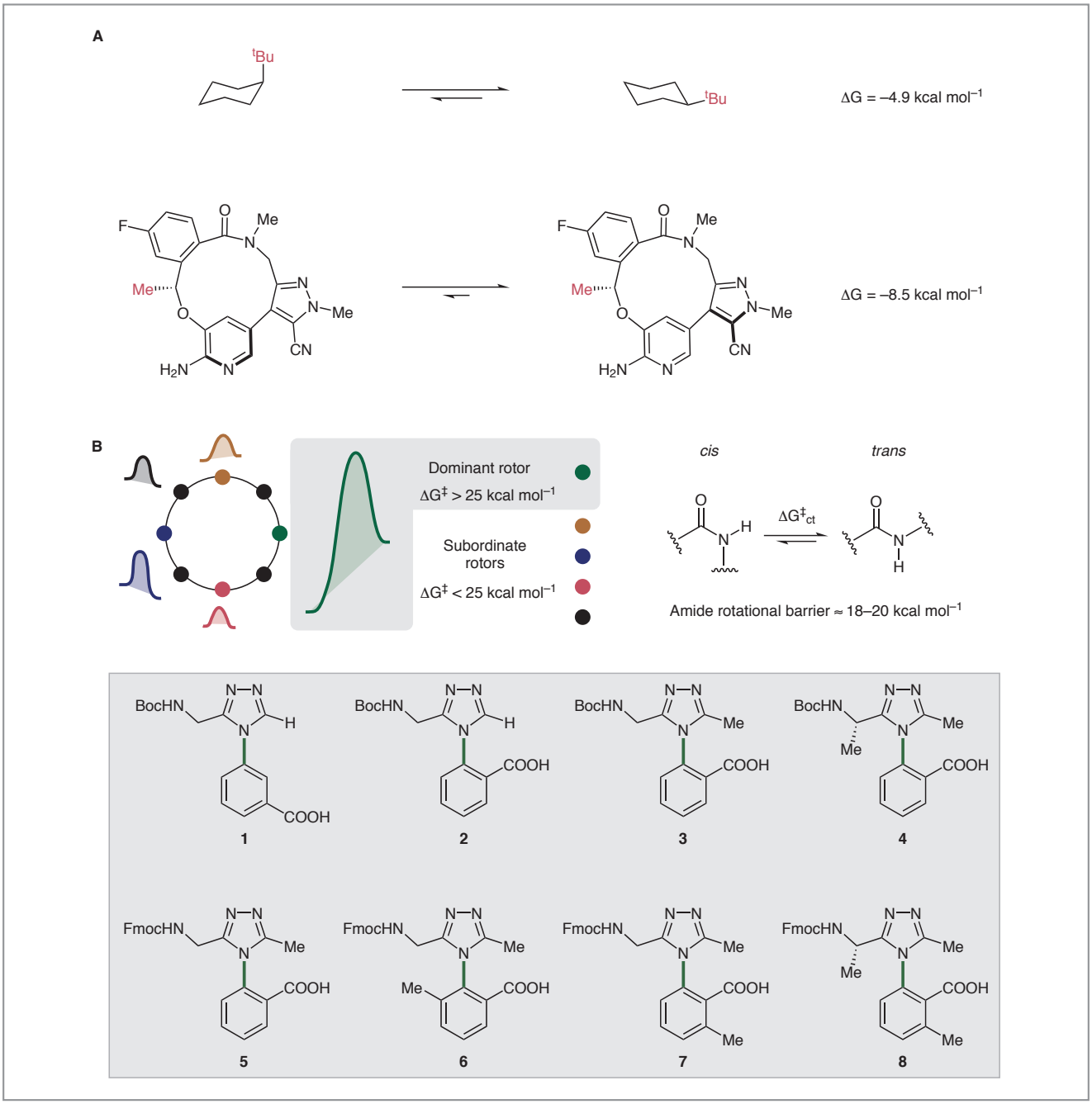

Figure 1 **A.** A methyl group in the appropriate environment of lorlatinib provides more stabilization than a *tert*-butyl group on cyclohexane. Both cyclic structures represent conformationally biased systems with a strong preference for one conformer. **B.** Tunable atropisomeric constituents with relatively high barriers termed 'dominant rotors' as a means to control complex energy landscapes of constrained chains of 'subordinate rotors'.

tive binder to any protein surface. While RNA and phage display technologies have contributed to the discovery of bioactive macrocycles, they have not advanced our understanding of the conformational factors that drive recognition at biological interfaces," remarked Professor Yudin, who continued: "In the area of polypeptides, it is known which amino acid sequences result in the formation of an α-helix, a β-turn, and β-sheet structures. Other than formation of canonical motifs, there is little understanding of how to induce the formation of unusual conformations and irregular turn motifs in peptide macrocycles.[4]" Professor Yudin concluded: "The dominant rotor method should now allow exploration of a wide range of structures, opening the tantalizing possibility that some molecular properties might have remained veiled because of the difficulties in generating and stabilizing conformational ensembles that are energetically unfavorable. We also recognize that a drastic increase in the rate of synthesis is needed to facilitate exploration of the dark conformational space. Current efforts are directed toward addressing this challenge."

Professor Giorgio Colombo, an expert in biomolecular simulation and computational chemistry from the University of Pavia (Italy) commented: "The paper by Yudin and co-

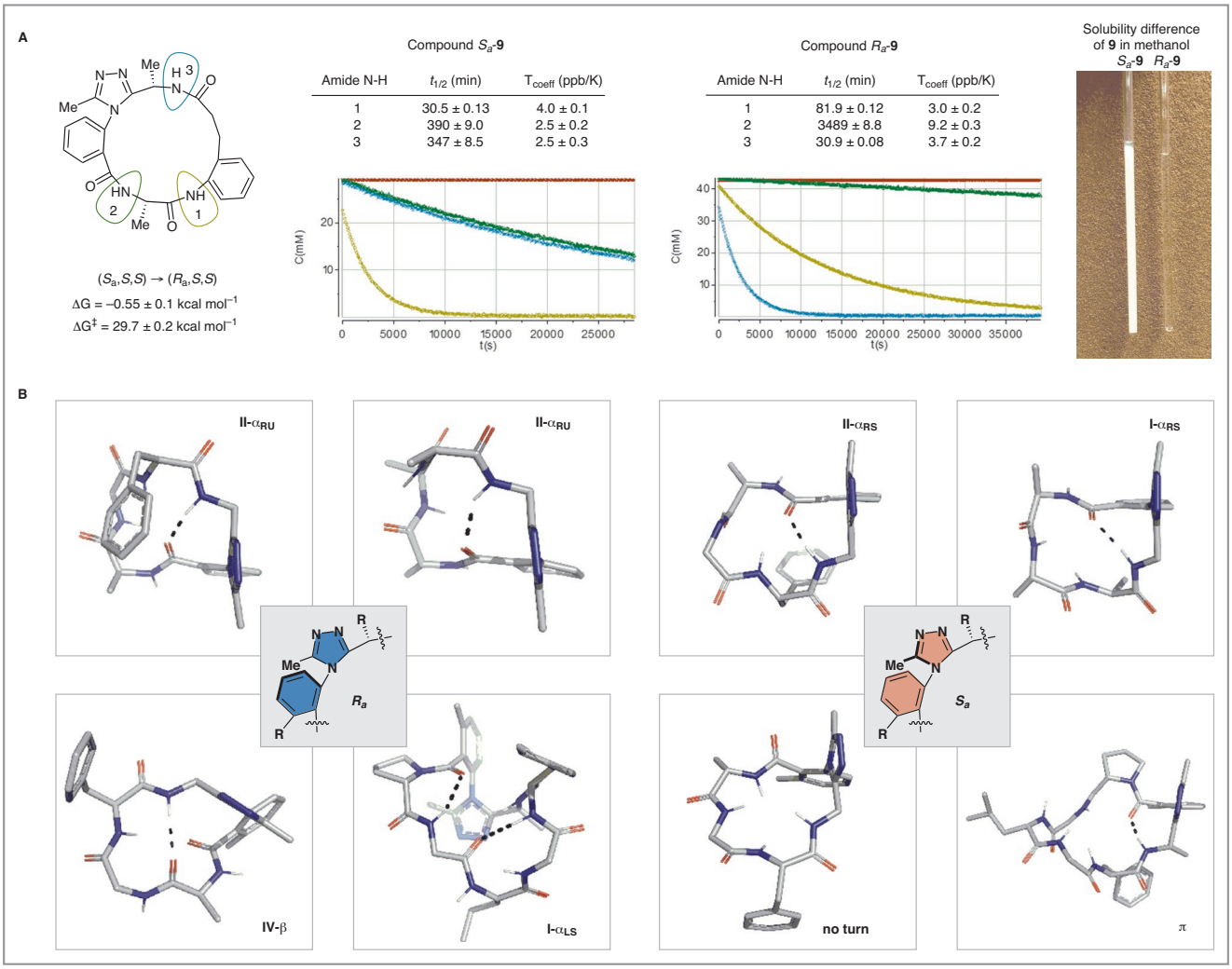

Figure 2 **A**. Differences in amide NH hydrogen–deuterium exchange rates and chemical shift/temperature coefficients show that dominant rotors can stabilize distinct solution conformations. The solubility of dominant rotor peptide ***R*$_a$-9** in methanol at 20 mM suggests a more compact conformation with reduced polar surface area and higher lipophilicity relative to ***S*$_a$-9**. **B**. Examples of dominant rotor-containing macrocycles with amino acid residues forced into rare turn motifs not observed in their linear counterparts or homodetic rings with all-natural connectivity.

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workers represents an interesting breakthrough in a difficult and problematic field, such as that of cyclic peptides. The possibility given by the dominant rotors method to unveil transient hidden conformations opens up new possibilities for the design of new active biomolecules. In this context, one of the main hurdles has often been that active conformations are not the dominant ones observed in solution. This new approach has the potential to enrich our design arsenal of an important new weapon to generate new structures with observable activities in a rational manner."

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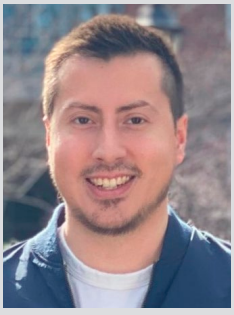
Prof. A. K. Yudin

Andrei K. Yudin is a Professor of Chemistry at the University of Toronto (Canada). He received his B.Sc. from Moscow State University (Russia) in 1992 and a Ph.D. from the University of Southern California (USA) in 1996. After a postdoctoral stay at The Scripps Research Institute (USA) between 1996 and 1998, he joined the faculty at the University of Toronto, where he and his students have been working on fundamental problems of organic chemistry.



Dr. D. B. Diaz

Diego B. Diaz is currently an NSERC Postdoctoral Fellow at Harvard University (USA). He received an H.B.Sc. degree from the University of Toronto Mississauga (Canada) in 2014 and a Ph.D. from the University of Toronto (Canada) in 2020. Diego made numerous contributions during his Ph.D. under the supervision of Professor Andrei K. Yudin, from investigating boron's chameleonic behavior in both synthetic and biological settings to developing methods for controlling the conformation of complex peptides.

Solomon Appavoo received his B.Sc. degree in chemistry from Carleton University (Ottawa, Canada) in 2016, where he carried out research with Professor Jeffrey Manthorpe on the design of kinase inhibitors. In 2016 he joined the research group of Professor Andrei K. Yudin at the University of Toronto (Canada) where he is currently pursuing a Ph.D. degree in chemistry. His research interests involve the synthesis and conformational analysis of medicinally relevant organic molecules.

A. F. Bogdanchikova

Anastasia F. Bogdanchikova received an H.B.Sc. degree in chemistry from the University of Toronto (Canada) in 2017. She then joined *Encycle Therapeutics Inc.* and worked on macrocycle synthesis to target integrin alpha-4-beta-7, which is involved in the pathogenesis of inflammatory bowel disease. In 2019, Anastasia joined Professor Andrei K. Yudin at the University of Toronto to explore the application of atropisomeric building blocks in peptide-based macrocycles.

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Dr. Y. Lebedev

Yury Lebedev studied chemistry at Ivanovo State University of Chemistry and Technology (Russia). His Ph.D. research on organometallic synthesis was done with magna cum laude at the University of Bonn (Germany) under the supervision of Professor A. C. Filippou. This was followed by postdoctoral stays at RWTH Aachen University (Germany) and King Abdullah University of Science and Technology (Saudi Arabia) under the guidance of Professor Magnus Rueping. His other postdoctoral appointments were held at the University of Toronto (Canada) with Professor Andrei K. Yudin and the University of Vienna (Austria) with Professor Nuno Maulide, where he received the Lise Meitner scholarship. Since 2021 he occupies the position of discovery scientist at the biotech startup *Solgate* (Austria).

T. J. McTiernan

Timothy J. McTiernan received his B.Sc. from the University of Guelph (Canada) in 2019, where he focused on the synthesis of several Gal-(1,4)-GlcNAc disaccharide backbones of the Lewis B carbohydrate antigen under the guidance of Professor France-Isabelle Auzanneau. In 2019, Timothy joined Professor Andrei K. Yudin's research group at the University of Toronto to pursue a Ph.D. in chemistry. He currently holds an Ontario Graduate Scholarship with research interests in cyclic peptides, particularly on the effects of structural modification and conformational restriction on their properties.

Dr. G. P. Gomes

Gabriel dos Passos Gomes (Gabe) received his B.Sc. in chemistry from the Federal University of Rio de Janeiro (Brazil), under the supervision of Professor Pierre Mothè Esteves, in 2013. He earned his Ph.D. in 2018 from Florida State University (USA), under the guidance of Professor Igor V. Alabugin, where he also was awarded the LASER Fellowship in 2014 and the 2016–2017 IBM Ph.D. Scholarship. At FSU, Gabe's research was centered on the relationship between molecular structure and reactivity, focusing on the development and applications of stereoelectronic effects. For his work at FSU, Gabe was awarded: the FSU's Graduate Student Research and Creativity Award for his work in Computational Chemistry; the ACS COMP Chemical Computing Group Excellence Award for his work on the mechanism of the Gold-Catalyzed Bergman Cyclization; selected for the CAS SciFinder Future Leaders Program. In 2019, Gabe joined the University of Toronto (Canada) as a Postdoctoral Research Fellow in the Matter Lab, led by Professor Alán Aspuru-Guzik. In 2020, Gabe was awarded the prestigious NSERC Banting Postdoctoral Fellowship with the project „*Designing Catalysts with Artificial Intelligence*" and was featured on the „*Next Great Impossible*" series by Merck/Millipore-Sigma. Gabe joined the *Journal of Chemical Information and Modeling* as an Early Career Board member in 2021. His research rests at the interface between machine learning and organic chemistry, where he aims to develop new platforms for reaction discovery, with emphasis on catalysis.

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Regioselective Activation of Benzocyclobutenones and Dienamides Leads To Anti-Bredt Bridged-Ring Systems by a [4+4] Cycloaddition

Nat. Commun. **2021**, *12*, 3022; DOI: 10.1038/s41467-021-23344-0

Bridged-ring systems are common structural motifs in many functional molecules, including bioactive natural compounds. The anti-Bredt rule has been used to qualitatively define bridged-ring systems with olefins at the bridgehead position. "Bridged skeletons are characterized by their size (e.g. we focus on bicyclo[m.n.1]) and ring strain (hybridization form of the bridgehead carbon, BC)," said Professor Tao Xu, from the Ocean University of China (Qingdao, P. R. of China), who added: "While the sp^2-hybridized BC underpins certain limitations on both the ring size (m + n ≥ 7) as well as ring strain, examples can still be found in a number of natural products. However, benzo-fused BC-bearing [m.n.1] systems are unusual (m + n > 8) and, to the best of our knowledge, unknown to chemists when confined in a small ring (m + n ≤ 8) framework." The research group of Professor Xu wanted to address this challenge and try to expand the anti-Bredt rule (Figure 1a).

Professor Xu went on to explain that there are two state-of-the-art cycloaddition methods for accessing anti-Bredt bicyclo[5.3.1] scaffolds: "The first is the type II intramolecular Diels–Alder (IMDA) reaction developed by Shea; and the second is the Ni-catalyzed type II [4+4] intramolecular cycloaddition by Wender (Figure 1b)" (for references see the original article). However, according to Professor Xu, a general, catalytic and diversifiable cycloaddition strategy remained

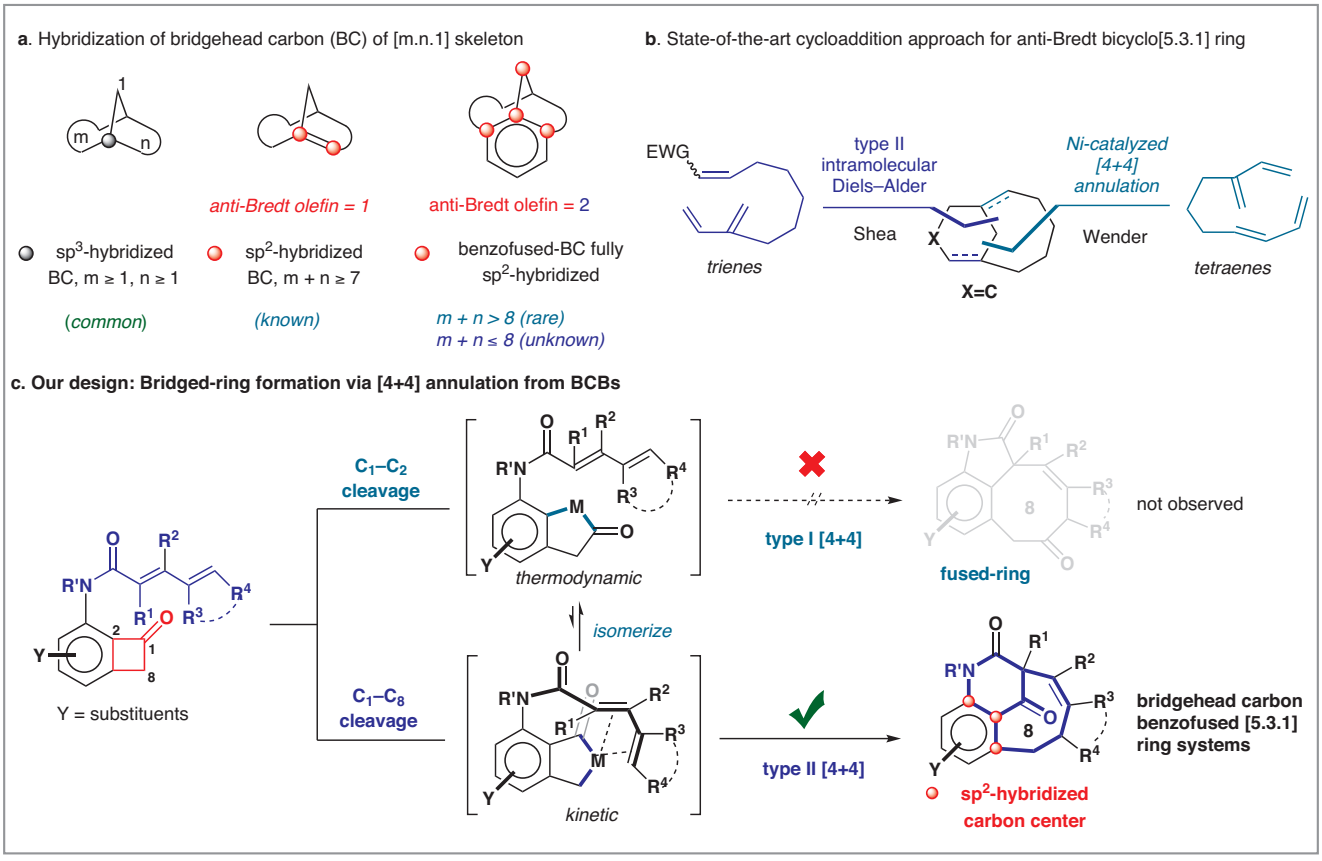


Figure 1 Design of a [4+4] annulation approach to access double anti-Bredt skeleton. a. Hybridization of bridgehead carbon of [m.n.1] systems. b. State-of-the-art cycloaddition approaches. c. Our design.

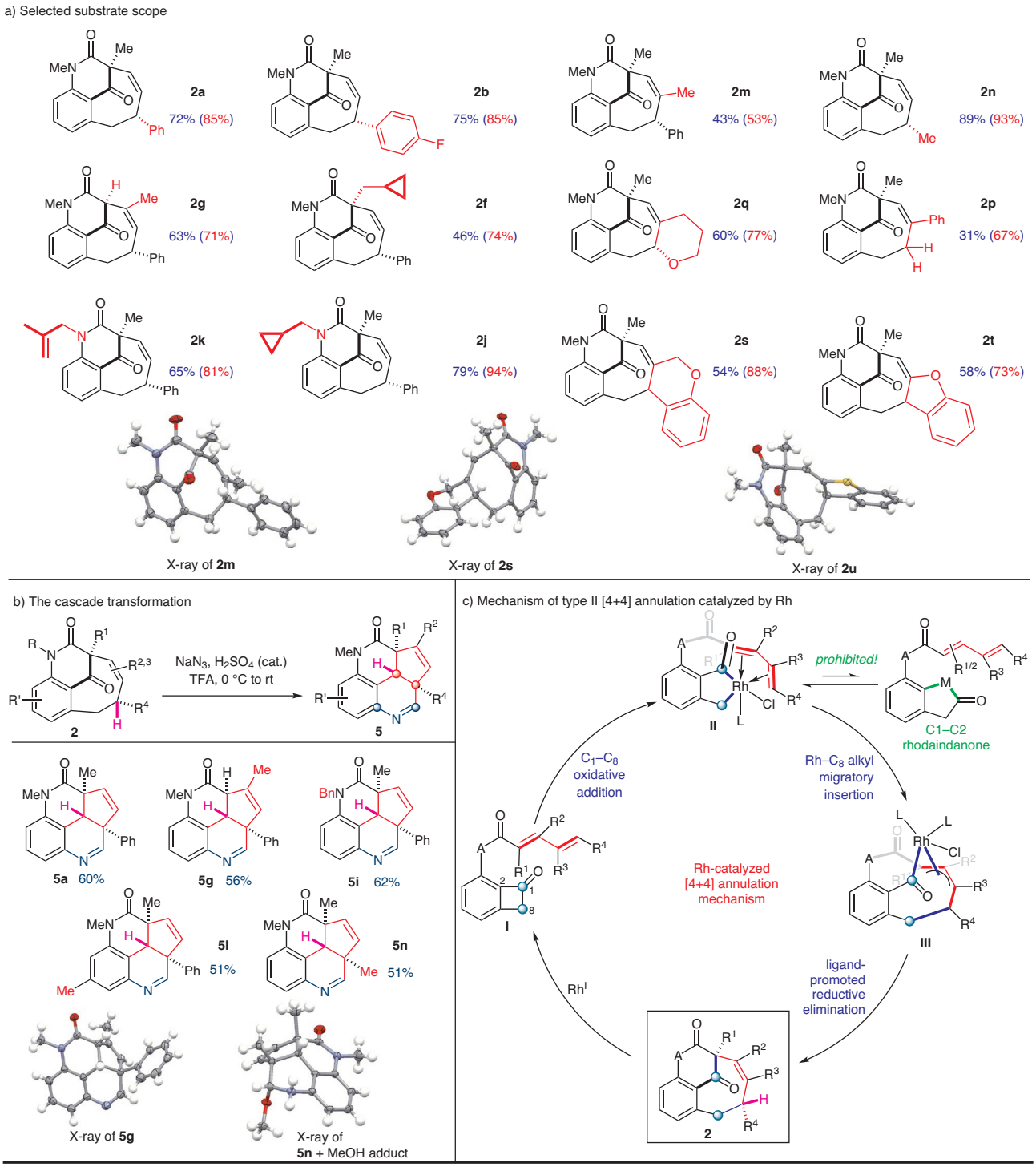
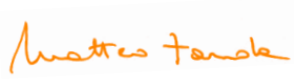


Figure 2 Broad substrate scope: a. Selected examples of the type II [4+4] annulation. b. Examples of the cascade transformation leading to polyfused rings. c. Proposed mechanism.

elusive, especially for the bridged ring systems that bear highly strained, consecutive double bonds surrounding the bridgehead carbon. Professor Xu explained: "We designed a formal [4+4] annulation reaction starting from regioselective C1–C8 activation of a benzocyclobutenone (BCB) using Rh(I) as catalyst. The normal 'cut and sew' chemistry coined by Guangbin Dong and co-workers won't happen here, because the isomerization to its thermodynamic C1–C2-cleaved counterpart is inhibited by the excess amount of phosphine ligands. The former rhodacycle will participate in a migratory insertion and reductive elimination leading to benzo-fused bridgehead bicyclo[5.3.1] ring systems (Figure 1c)."

The chemistry proved to be viable through screening many conditions. "In addition, a very broad substrate scope was examined (Figure 2), demonstrating that the methodology is robust and that it can be applied in a number of complex settings," remarked Professor Xu, who continued: "What's more, a cascade transformation consisting of through-space 1,5-hydride transfer, cation-induced cyclization and Schmidt reaction was serendipitously discovered, which led to the formation of complex fused-ring skeletons. This cascade reaction also fills the gap of converting complex bridged rings into their fused counterparts. During this transformation, one allylic C–H bond and one benzylic C–C bond are chemoselectively disconnected, which leads to recombination of one C–C bond and two C–N bonds." Professor Xu concluded: "We look forward to its application in functional molecule synthesis in the near future."



About the authors

J. Zhang

Jianyu Zhang was born and raised in Shandong, P. R. of China. He earned both his Bachelor's and Master's degrees at Liaocheng University (P. R. of China). He joined Professor Xu's lab in 2016, where he started transition-metal-catalyzed diene and benzocyclobutenone coupling. He has just passed his doctoral defense and will earn his doctoral degree of pharmacy in June 2021. He has decided to pursue an industrial career in the near future.

X. Wang

Xi Wang was born in Anhui, P. R. of China. She obtained an undergraduate degree from the University of Jinan in Shandong province (P. R. of China) in 2019. Currently, she is a second-year student in Prof. Tao Xu's group at the Ocean University of China (P. R. of China). Her research interest is photocatalytic free-radical cycloaddition and its application in complex marine natural product synthesis.

Prof. T. Xu

Tao Xu was born in Handan, Hebei province, P. R. of China. He obtained a B.Sc. degree from Dalian University of China (P. R. of China) then in 2011, a Ph.D. degree from Peking University (P. R. of China). In the same year, he started postdoctoral training with Guangbin Dong (University of Texas at Austin, now at University of Chicago, USA). In 2015, he joined Ocean University of China (P. R. of China) as a full professor and was promoted to tier III in 2018. His research group is focused on transition-metal-catalyzed reactions involving inert bond activations and their application in marine natural product total synthesis.

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