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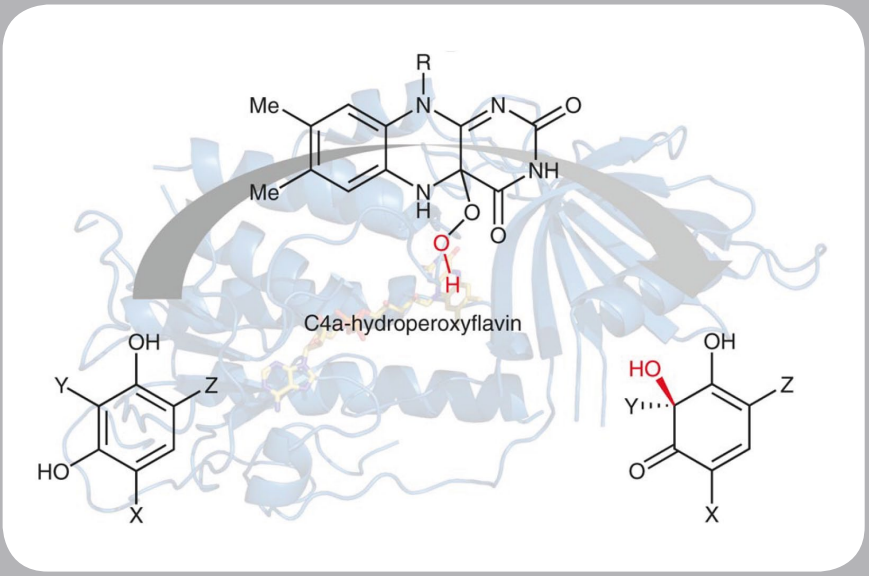
2018/09

Biocatalytic Site- and Enantioselective Oxidative Dearomatization of Phenols

Highlighted article by S. A. Baker Dockrey, A. L. Lukowski, M. R. Becker, A. R. H. Narayan



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Dear Readers,

This summer will always be remembered – at least here in the United Kingdom – as one of the hottest and driest ever. I have been living in Scotland for 9 years now and I can hardly remember a spell of dry and sunny weather longer than seven days in a row, whereas this year we had at least two months of true sunshine, not that heatless orange circle – probably just painted up there in the sky – we usually experience at this latitude. And counting, because the so-called heatwave has no intention of giving up yet! The usually vividly green grass had turned depressingly yellow for weeks owing to the never-experienced-before lack of rain and I have personally seen places in England where the grass literally melted away, incinerated by the implacable action of the sun. I honestly don't know whether this is due to the global warming, and perhaps we should remember that at the beginning of March we were all complaining about the "Beast from the East" that brought inches of snow and nearly paralyzed this country. Whatever the case, it is almost certainly going to be a one-off, truly extraordinary summer and we should strive to enjoy as many barbecues and al-fresco dinners as we possibly can, because I am not sure we will see another summer like this any time soon. Heatwave or not, SYNFORM is always present with its top-notch selection of articles and authors. And this September issue is no different, as we start with the innovative bio-orthogonal ligation process based on an oxime bond formation discovered by Caroline Proulx (USA), which is followed by the groundbreaking biocatalytic oxidative de-aromatization of phenols which occurs with a concomitant enantioselective hydroxylation of the *ortho*-carbon, as described by Alison Narayan (USA). The third article is a YCF interview with Joshua Pierce (USA) who told us about what his group is currently working on and shared his views on chemistry. Finally, a contribution on a new type of conformational isomerism unveiled by Maxwell Crossley and Jeffrey Reimers (Australia).

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

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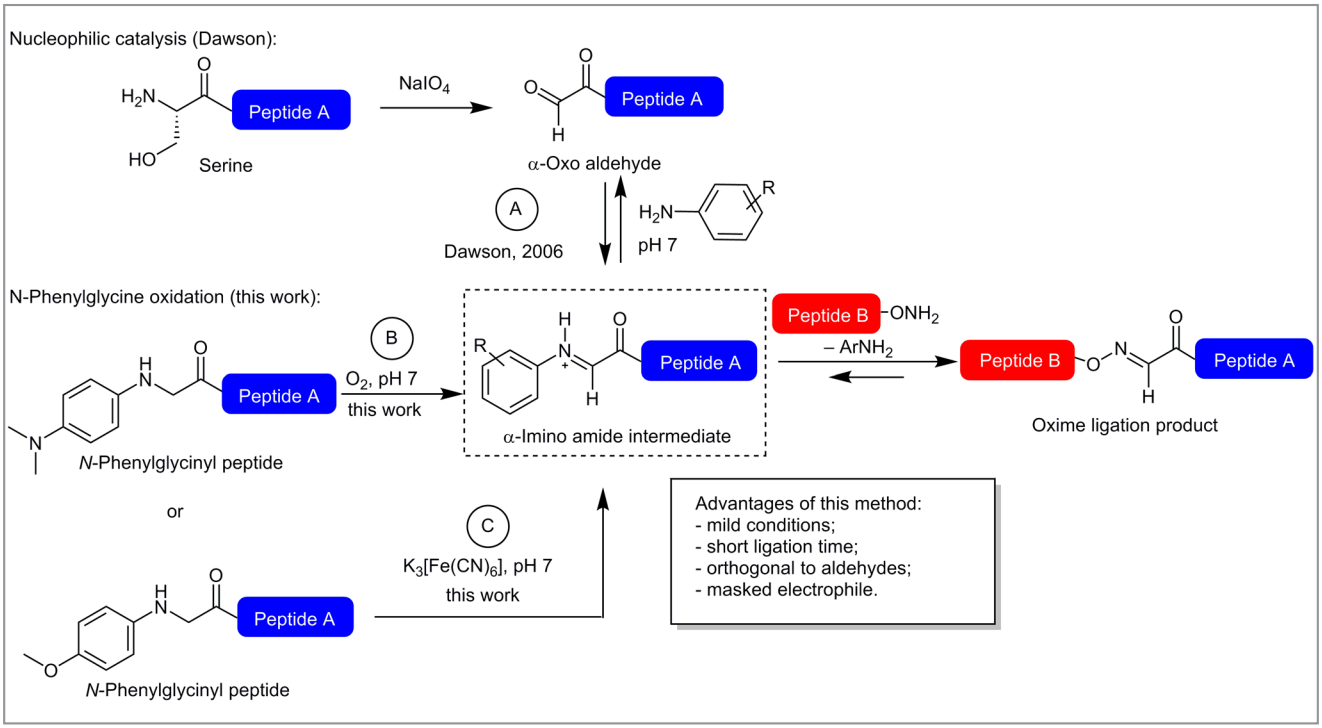
Oxime Ligation via in situ Oxidation of *N*-Phenylglycinyl Peptides

Org. Lett. **2018**, *20*, 2564–2567

The selective formation of covalent bonds in complex biological settings requires the discovery and optimization of high-yielding bio-orthogonal chemical transformations. While many different bioconjugation reactions are available, advances in existing methods are often necessary to increase their scope and utility. In this recent publication, the group of Professor Caroline Proulx at North Carolina State University (Raleigh, USA) sought to address some of the known limitations that exist with oxime ligation reactions, where aminooxy residues react selectively with α-oxo aldehydes to form stable covalent bonds. "Pioneering work from other groups had shown that aniline Schiff base intermediates allowed reaction rate acceleration of up to 40-fold at neutral pH (Scheme 1A). This finding, along with the continued discovery of more efficient aniline catalyst derivatives, has provided significant improvements in terms of biocompatibility for oxime ligations," explained Professor Proulx. She continued: "However, we wanted to see if it was possible to bypass the use of both 1) sodium periodate (to oxidize Ser residues into α-oxo aldehydes) and 2) 10–100 mM aniline catalysts to expand the applications of oxime formation reactions. To do so, we were inspired by several reports of chemoselective oxidative coupling to *N*-phenylglycine residues, where key α-imino amide intermediates have been proposed." Notably, a recent example revealed the use of air as the only oxidant with trace amount of acid (in DCE/MeCN) to enable *N*-phenylglycine oxidation and coupling to indole and styrene derivatives (*Angew. Chem. Int. Ed.* **2014**, *53*, 13544–13547). "We hypothesized that similar mild conditions might be able to generate a reactive α-imino amide intermediate from an *N*-phenylglycine-terminated peptide in water and sought to discover precisely how acidic (what pH range) the buffer would need to be to trigger an in situ oxidation/oxime ligation reaction sequence," said Professor Proulx. She commented: "By tuning the electronics of the



Scheme 1 Strategies for oxime ligation reactions at pH 7.0 using A) aniline catalysis (previous work), B) in situ oxidation of an *N*-(*p*-$Me_2NC_6H_4$)glycine residue using oxygen as the only source of oxidant (this work), and C) unmasking of *N*-(*p*-$MeOC_6H_4$)glycine with potassium ferricyanide (this work)

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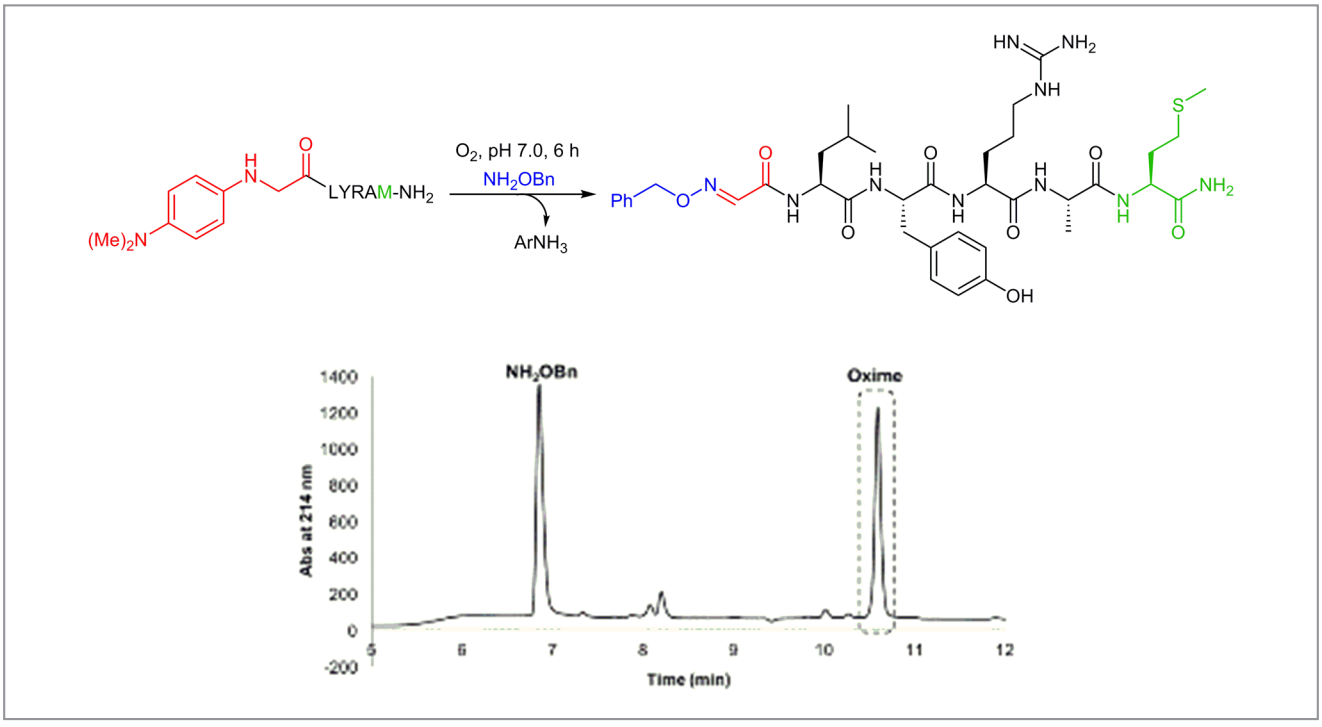
N-arylglycine, we discovered that an *N*,*N*-dimethylamino substituent at the para position of the phenyl ring allowed the tandem oxidation/oxime ligation to occur at pH 7 under oxygen atmosphere (Scheme 1B, Scheme 2). In addition to this, we were curious to see if certain inert *N*-phenylglycines could be unmasked by mild oxidants such as potassium ferricyanide (Scheme 1C, Scheme 3). This proved to be the case, and a previously unreactive *N*-(*p*-$MeOC_6H_4$)glycine residue was able to undergo oxime ligation reactions at pH 7 in the presence of 1–10 mM $K_3[Fe(CN)_6]$."

These advances in oxime ligation alleviate some of the so-called 'biorestrictions' associated with previous methods (e.g. aniline catalysts can react with other aldehydes such as carbohydrates and co-factors). However, Professor Proulx acknowledged that limitations of the group's approach include the competing hydrolysis of the reactive α-imino amide intermediate, which requires a five-fold excess of the aminooxy reaction partner, and the fact that one equivalent of aniline is still liberated during the process.

"Subjecting an *N*-(*p*-$Me_2NC_6H_4$)glycine-terminated peptide with a *C*-terminal methionine residue to our mild conditions revealed no methionine side-chain oxidation over the time period necessary for formation of the α-imino amide and oxime ligation to occur (Scheme 2)," remarked Professor Proulx. This should increase the compatibility of oxime ligation reactions using protein and peptide substrates that contain amino acids that are prone to oxidation, potentially extending beyond those included in this paper (Met, Tyr). "Alternatively, using potassium ferricyanide to selectively unmask *N*-(*p*-$Me_2NC_6H_4$)glycine, we then had a method that allowed the selective formation of the reactive Schiff base intermediate in the presence of other aldehydes," said Professor Proulx. To highlight this functional group orthogonality, the group demonstrated that oxime bond formation with *O*-benzylhydroxylamine could be selective for either their *N*-phenylgycine-terminated peptide or glucose, depending on the reaction conditions (Scheme 3).

"In the future, we hope to elucidate the mechanism of this reaction sequence and increase our understanding of the apparent relationship between substrate pK_a and oxidation rate at different pH values," explained Professor Proulx. "In addition, we would like to expand the use of this chemistry beyond oxime ligation reactions to other transformations involving imine intermediates." She concluded: "Long-term goals include pursuing their unmasking potential in prodrug applications, and embedding an *N*-phenylglycine moiety as an unnatural amino acid side chain for eventual site-specific incorporation into proteins. This should increase the current



Scheme 2 HPLC trace at 214 nm of the oxime ligation reaction between *N*-(*p*-$Me_2NC_6H_4$)G-LYRAM and NH_2OBn after 6 h

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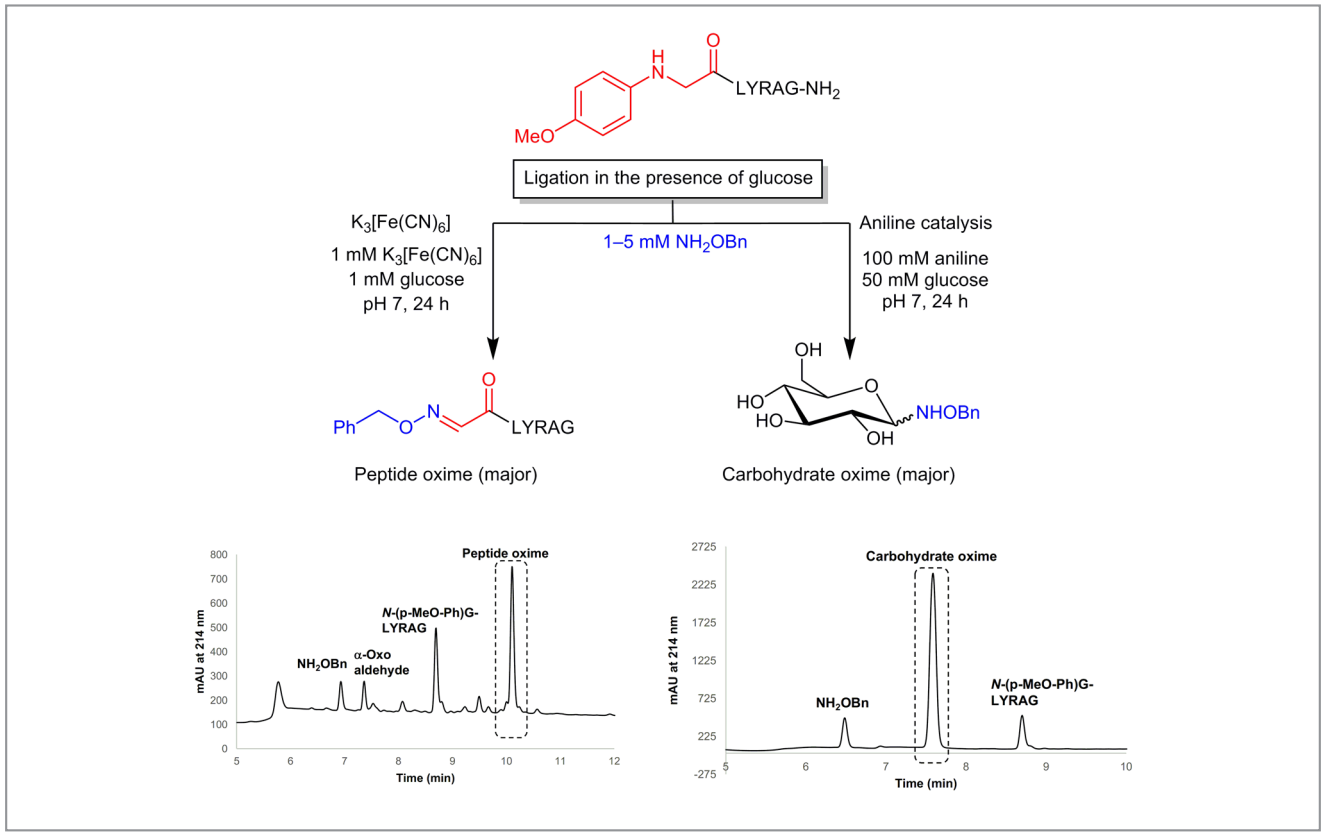

Scheme 3 Selective peptide oxime ligation in the presence of glucose and potassium ferricyanide (left) and carbohydrate oxime ligation in the presence of an *N*-phenylglycine-terminated peptide and aniline catalyst (right) with corresponding HPLC traces at 214 nm

scope and utility of oxime ligations in the toolbox of bioorthogonal ligation reactions."

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About the authors

Prof. C. Proulx

Caroline Proulx grew up in Toronto, Ontario (Canada) and obtained her Hon. B.Sc. in biopharmaceutical sciences, medicinal chemistry, from the University of Ottawa (Canada) in 2007. Subsequently, she obtained her Ph.D. in 2012 from the Université de Montréal (Canada) under the direction of Dr. William D. Lubell, where she developed submonomer methodologies for azapeptide library synthesis and applied them towards the discovery of selective CD36 receptor ligands. Following her graduate studies, she moved to Lawrence Berkeley National Laboratory (USA) from 2012–2016 as an NSERC postdoctoral fellow to study peptoid synthesis and self-assembly under the direction of Dr. Ronald N. Zuckermann at the Molecular Foundry. She began her independent career as an assistant professor at North Carolina State University (USA) in 2016, where she continues to work in the field of peptides and peptidomimetics.

Q. A. E. Guthrie

Quibria A. E. Guthrie grew up in Milwaukee, Wisconsin (USA) and obtained a bachelor's degree in chemistry from the University of Wisconsin – Milwaukee (USA) in 2015, with a focus in biochemistry. As an undergraduate student, she performed research under the supervision of Dr. Xiaohua Peng. She started her graduate studies at North Carolina State University (USA) in 2016 under the leadership of Dr. Caroline Proulx. Her research focus is on mild oxidation of N-phenylglycinyl peptides for bioconjugation reactions.

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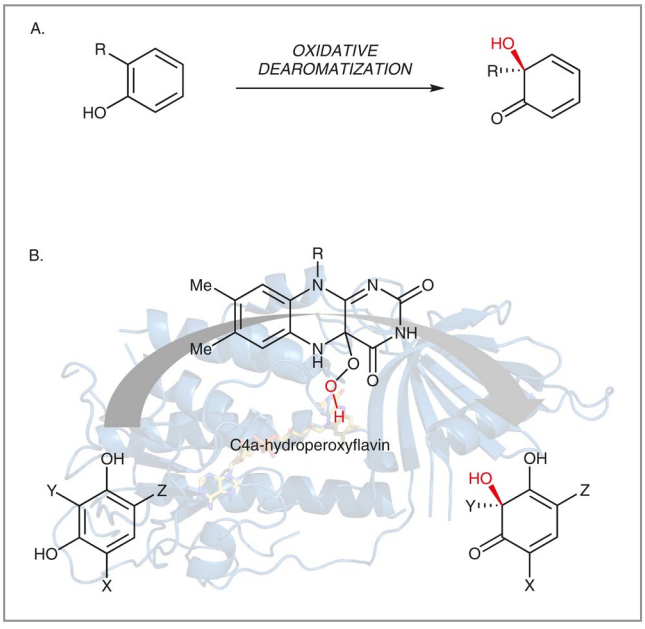
Biocatalytic Site- and Enantioselective Oxidative Dearomatization of Phenols

Nat. Chem. **2018**, *10*, 119–125

Improving selectivity in the oxidation of complex molecules continues to motivate synthetic chemists to devise innovative new strategies and reagents. The oxidative dearomatization of phenols to afford quinol products is one transformation that presents both site- and stereoselectivity challenges, with the opportunity to hydroxylate at either the *ortho*-position or the *para*-position relative to the phenolic hydroxyl group.

The group of Professor Alison Narayan at the University of Michigan (Ann Arbor, USA) recognized the utility of this transformation and sought to develop a selective catalytic method for the generation of quinol products. Prof. Narayan and her team said: "We were inspired by Nature's mechanism for accomplishing oxidative dearomatization using flavin-dependent monooxygenases, which rely on the generation of a hydroperoxyflavin species which interacts with a phenolic substrate (Scheme 1). In enzymatic oxidative dearomatization, both site- and stereoselectivities in the reaction are controlled by the pose of the substrate within the enzyme's active site relative to the hydroperoxyflavin cofactor."



Scheme 1 Site- and stereoselectivities in oxidative dearomatization

April Lukowski, a graduate student in the University of Michigan Program in Chemical Biology, initiated the work in the Narayan lab by expressing and purifying three proteins known to mediate oxidative dearomatization of phenolic intermediates in three unrelated secondary metabolite pathways. Chemistry graduate student Summer Baker Dockrey then evaluated the substrate promiscuity of each enzyme by profiling activity against a panel of sterically and electronically diverse phenolic substrates. "This initial study defined the subset of substrates each enzyme could efficiently oxidize," remarked Professor Narayan. She continued: "While each enzyme demonstrated a substrate scope much broader than the single biosynthetic intermediate it was evolved to process, there was still an outstanding question – were unnatural products being produced with site- and stereoselectivities that matched those of the natural products? Full characterization of products from the enzymatic dearomatization reactions indicated that both the site- and stereoselectivities were preserved across a range of compounds (Scheme 2)."

Initial experiments were carried out using purified protein, which began to constrain the researchers' workflow as the scale of reactions shifted from tens of milligrams to gram scale. "To address this challenge, we explored the use of whole *E. coli* cells used to overexpress each protein directly in reactions, without lysing the cells," explained Professor Narayan. Using this method, the team could store lyophilized cells containing each enzyme in the freezer for months and use these directly in preparative-scale reactions as desired (Figure 1).

"To demonstrate the utility of this biocatalytic oxidative dearomatization, we coupled the generation of reactive quinol products with a second step, either chemical or enzymatic, in the same reaction vessel," said Professor Narayan. She continued: "Using this strategy, Ms. Baker Dockrey, working together with graduate student Marc Becker, completed the one-pot synthesis of three natural products from phenolic starting materials."

Professor Narayan concluded: "We anticipate that the orthogonality and high levels of both site- and stereoselectivities of the method will entice chemists to use these biocatalysts."

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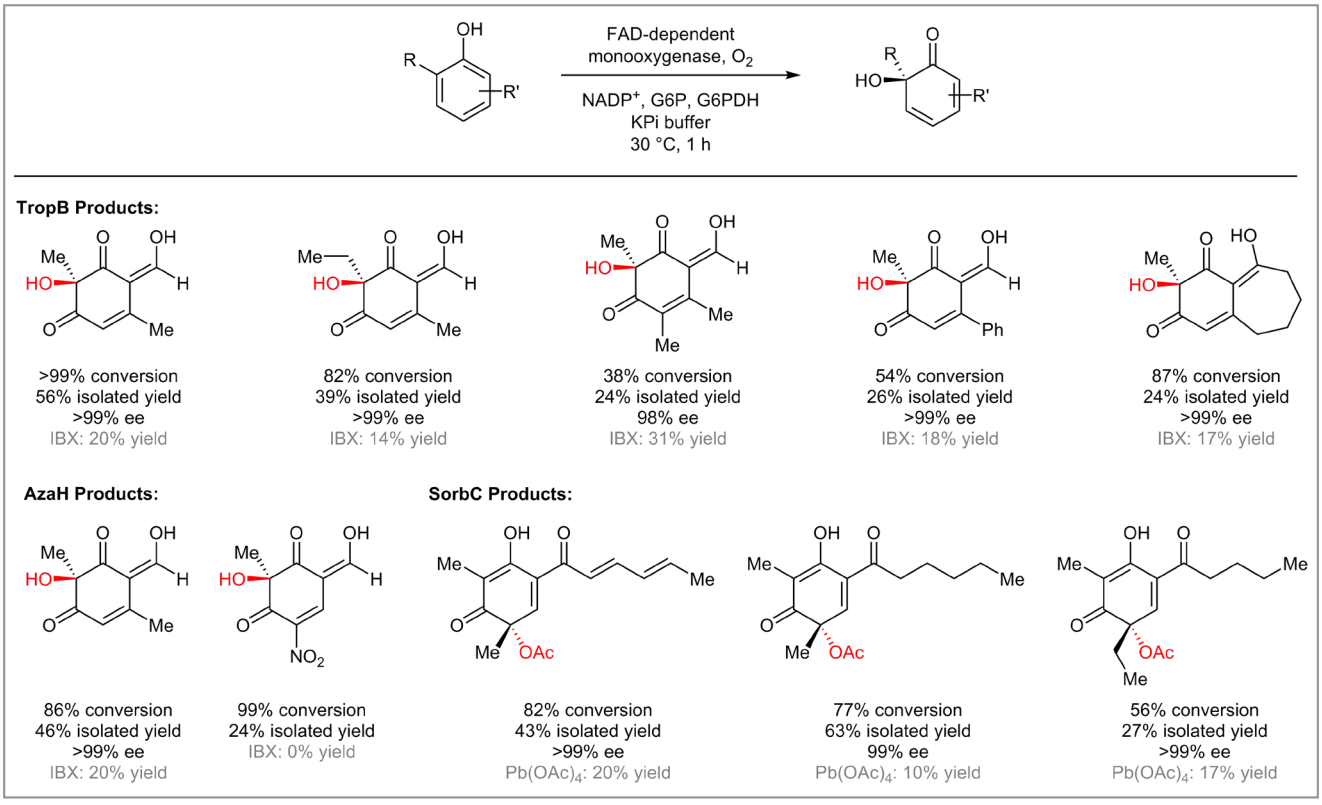

Scheme 2 Substrate scope of enzymatic dearomatization

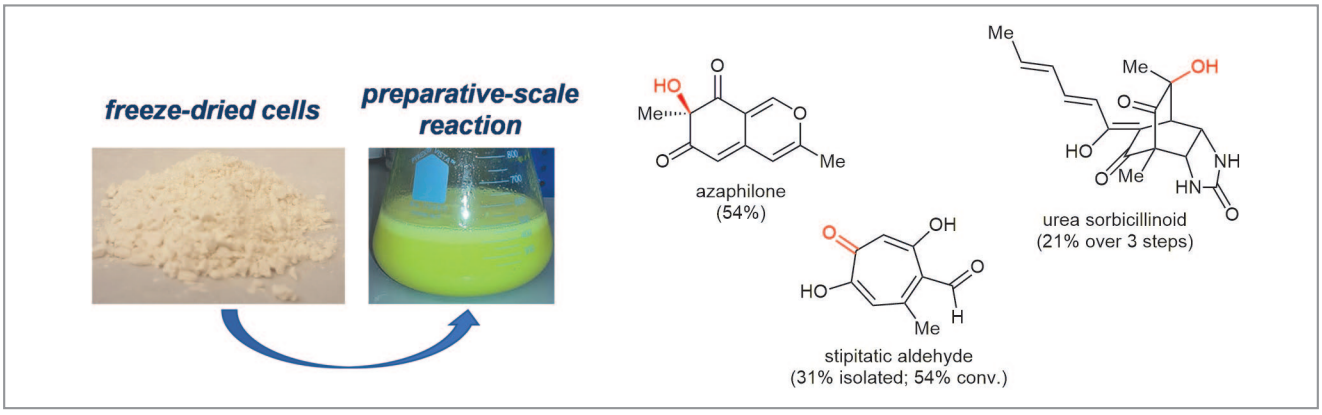

Figure 1 Preparative-scale enzymatic dearomatization using lyophilized *E. coli* cells

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About the authors

S. Baker Dockrey

Summer Baker Dockrey obtained an A.B. in Chemistry from Bryn Mawr College (USA) in 2015, where she worked under Professor Jason Schmink on the development of Corey-Seebach umpolung reagents as nucleophiles in palladium-catalyzed cross-coupling reactions. She joined the Narayan Lab in 2016 where she has focused on identifying enzymes from secondary metabolite pathways with potential synthetic utility and developing methods based on these biocatalysts to enable access to biologically active target molecules.

A. Lukowski

April Lukowski graduated from Saginaw Valley State University (USA) in 2015 with a B.S. in biochemistry where she studied plant enzymology and analytical biochemistry. She worked on projects pertaining to the identification of isoprene synthases in conifers and the quantification of bacterial contamination in local waterways. Inspired by enzymes nature and their abilities to perform complex reactions, she began her doctoral studies in the Program in Chemical Biology and the University of Michigan (USA) in 2015, joining the Narayan lab. Her favorite part of her research is expressing and purifying new proteins and uncovering their activities.

M. Becker

Marc Becker was born in Germany and received his B.S. and M.S. degree in chemistry at the University of Muenster, Germany. In 2016, he started his graduate studies at the University of Michigan (USA), where he is currently pursuing his Ph.D. under the supervision of Prof. Corinna S. Schindler. His research interests are method development and their application in natural product synthesis.

Prof. A. Narayan

Alison Narayan earned a B.S. in Chemistry from the University of Michigan (USA). She completed her Ph.D. at the University of California, Berkeley (USA), where she developed novel methods for the synthesis of nitrogen heterocycles and the total synthesis of complex natural products in the group of Prof. Richmond Sarpong. As a Life Sciences Research Foundation Postdoctoral Fellow, Alison studied natural product biosynthesis and biocatalysis with Prof. David Sherman. In 2015, Alison began her independent career as an assistant professor in the Department of Chemistry and the Life Sciences Institute at the University of Michigan. The Narayan lab is focused on elucidating the function of enzymes involved in natural product biosynthesis and the development of biocatalytic synthetic methods.

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Young Career Focus: Dr. Joshua Pierce (North Carolina State University, USA)

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. Joshua Pierce (North Carolina State University, USA).

Biographical Sketch

Dr. Joshua Pierce

Joshua Pierce was born and raised in northwestern Pennsylvania (USA) and obtained a B.S. with Honors in chemistry from the University of Pittsburgh (USA). Upon graduation he continued with graduate studies at the same university under the direction of Professor Peter Wipf. His research was focused on organometallic methods development, natural product total synthesis and medicinal chemistry.

After defending his thesis in the fall of 2008, Joshua moved across the country to begin postdoctoral studies with Professor Dale L. Boger at The Scripps Research Institute (USA). Research interests centered around complex natural product analogue synthesis, semi-synthesis, and antimicrobial compound development centered on the natural product vancomycin.

Together, these research experiences provided an appreciation of the important role complex molecule synthesis can play in organic chemistry, medicinal chemistry and chemical biology. Since joining NC State's Department of Chemistry (USA) in 2012, the Pierce group has focused on addressing problems in natural products synthesis and organic methods development with a constant goal of high-impact contributions at the chemistry/biology interface. In addition to developing his research program, he also became involved in the Comparative Medicine Institute at NC State where he is an Associate Director of the Emerging and Infectious Diseases Program, was named a NC State University Faculty Scholar in 2017, and in 2018 was promoted to the rank of Associate Professor with tenure.

INTERVIEW

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

Dr. J. Pierce Research in the Pierce group is focused on harnessing the diverse architectures of marine natural products to inspire advances in chemical reaction development, chemical biology and therapeutic lead identification. We have built a program centered on the synthesis of natural products (with a focus on marine natural products) and their use as chemical probes to study biological processes. To accomplish the synthesis of such targets, novel reactions and/or adaptations of existing reactions are required – as well as constant evaluation of innovative synthetic strategies to construct complex organic structures in an efficient and scalable manner. As shown in Figure 1, our program is based on molecule-driven discovery: a constant feedback loop of novel chemistry, chemical biology and biology to generate new projects and exciting discoveries at the chemistry/biology interface.

SYNFORM *When did you get interested in synthesis?*

Dr. J. Pierce I became interested in organic synthesis as a sophomore undergraduate at the University of Pittsburgh. I was a pre-med student and planned to be a biological sciences major until two key things happened: 1) I fell in love with chemistry thanks to amazing professors of both honors general chemistry and organic chemistry and 2) I realized for the first time in my academic training that organic chemistry could directly contribute to the development of treatments for human disease. I was instantly fascinated by the art of organic synthesis and the beauty of complex organic structures – and immediately motivated to begin research in this area. Once in the lab, the rest was history and I have remained fascinated with this area to this day.

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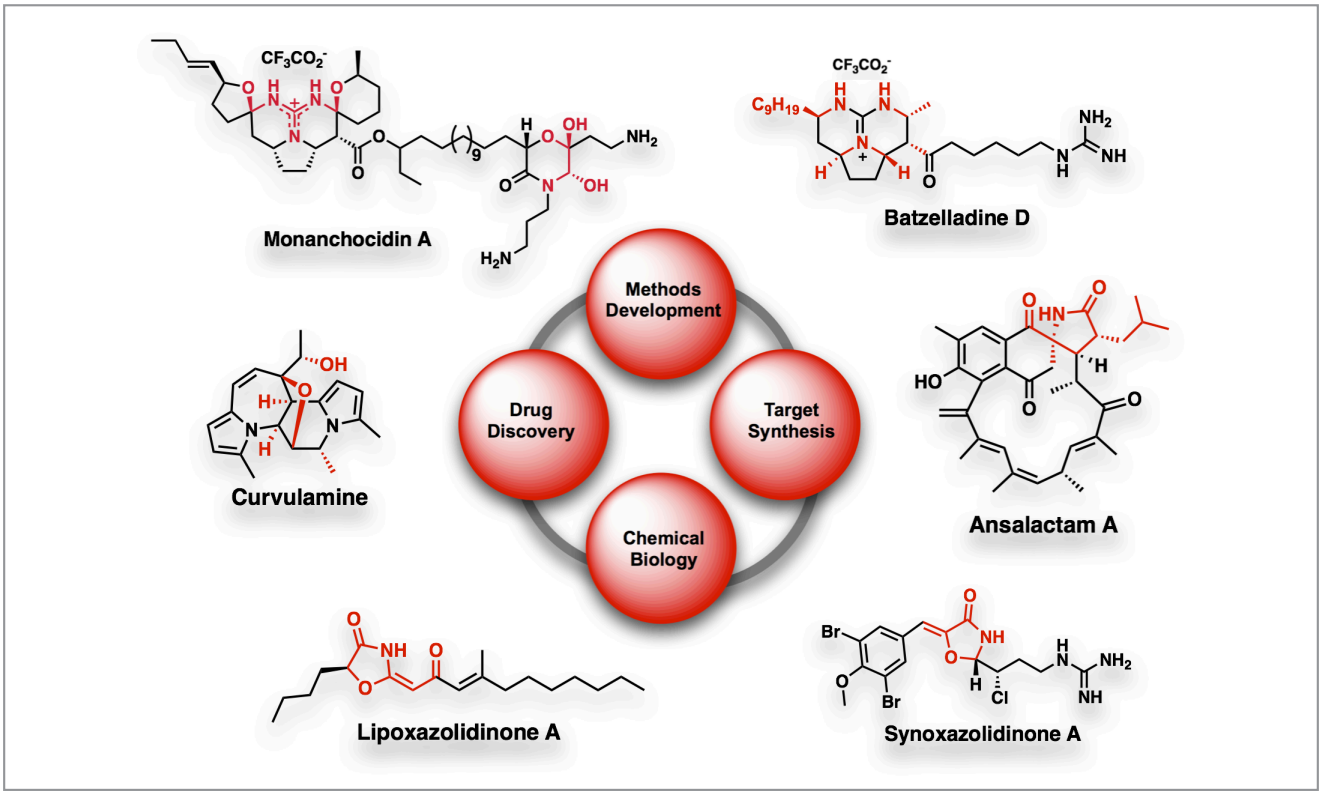

Figure 1 Representative natural products that provide inspiration for a feedback loop of discovery in organic methods, synthetic strategy, chemical biology and drug discovery in the Pierce group

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

Dr. J. Pierce Organic synthesis is thought of as a 'mature' field relative to many of the emerging areas of scientific research, yet every time I teach organic chemistry or embark on a new target molecule it reminds me how much is left to discover. The notion that we can make any molecule if provided enough resources may indeed be accurate – but as a community we are far from the efficiency and practicality that is required to address critical issues related to health, energy and the environment. Innovation in organic chemistry is thriving, and these efforts are in concert with, not in competition with, cutting-edge biosynthetic approaches to both simple and complex molecules. These two areas should work together to find innovative solutions for accessing biologically relevant compounds, as both approaches have inherent strengths and weaknesses – at least for the foreseeable future. It is these novel bioactive compounds, only available through synthesis, that provide value from the innovations in synthetic methods and strategy and thereby provide critical chemical probes for biology, with an ultimate goal of developing novel therapeutics. Synthetic organic chemistry remains the only general approach to install pinpoint modifications on complex molecules and to rapidly access diverse, non-natural molecular architectures. A variety of computational and robotic technologies may influence the approaches taken to design and execute some synthetic efforts in the future; however, organic synthesis will remain vibrant in the coming decades as the practitioners of the field continue to innovate and evolve with the changing times of science and society.

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

Dr. J. Pierce As mentioned previously, our group leverages natural products to inspire innovation in organic synthesis, chemical biology and drug discovery. Of particular interest is the development of novel small molecules for the study and treatment of infectious disease. Natural products have served as a key platform for the development of antimicrobials and the development of new antibiotics is of great importance.

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As an example of our efforts in this area, we have developed novel approaches to oxazolidinone heterocycles in our efforts toward the synoxazolidinone and lipoxazolidinone natural products. In our initial disclosure of the synoxazolidinones,[1] we presented an imine acylation protocol that can be used to prepare either 4-oxazolidinones or pyrrolidinones depending on the conditions employed, we completed a five-step total synthesis, and we revealed simplified analogues with antibiofilm properties via a non-toxic mechanism.[2] These efforts have now been extended to an asymmetric process, the products have been derivatized via rearrangements and oxidative cleavage to prepare valuable building blocks for other classes of natural products, and we now have analogues that are significantly more potent than the natural products themselves.[3–5] Figure 1 shows some of the representative natural products that our group works toward, constantly evolving as new methods arise from our synthetic work and new biological targets are revealed through chemical biology efforts.

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

Dr. J. Pierce Two key achievements stand out and both are related to infectious disease. The first is my contribution as a postdoc to the Boger lab's efforts to develop a novel analogue of vancomycin that overcomes resistance through a single atom change. I was fortunate to be the first to test our key amidine analogue and demonstrate that a long-standing hypothesis in the group was indeed accurate. These efforts have since led to many follow-up studies and may pave the way for a next-generation vancomycin in the years to come. The second is my own group's efforts to develop the lipoxazolidinone family of natural products (Scheme 1).[6] We have developed a rapid approach for their synthesis, optimized novel analogues with improved activity and have demonstrated that these 4-oxazolidinone heterocycles inhibit both protein synthesis and cell-wall biosynthesis in Gram positive bacteria. These efforts, in addition to an array of additional studies, provide the groundwork for a comprehensive effort to advance the 4-oxazolidinones as potential antibiotics. We are extremely excited at the prospect of uncovering the precise mechanisms by which these molecules function and to optimize their properties as drug leads going forward.

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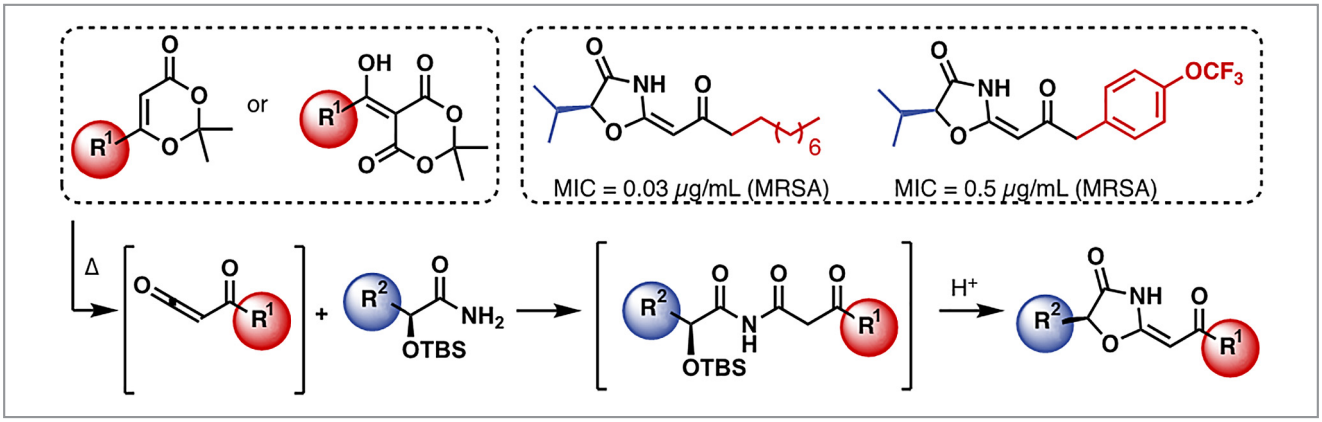

Scheme 1 Synthesis and development of novel antimicrobial agents based on the lipoxazolidinone natural products

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A New Fundamental Type of Conformational Isomerism

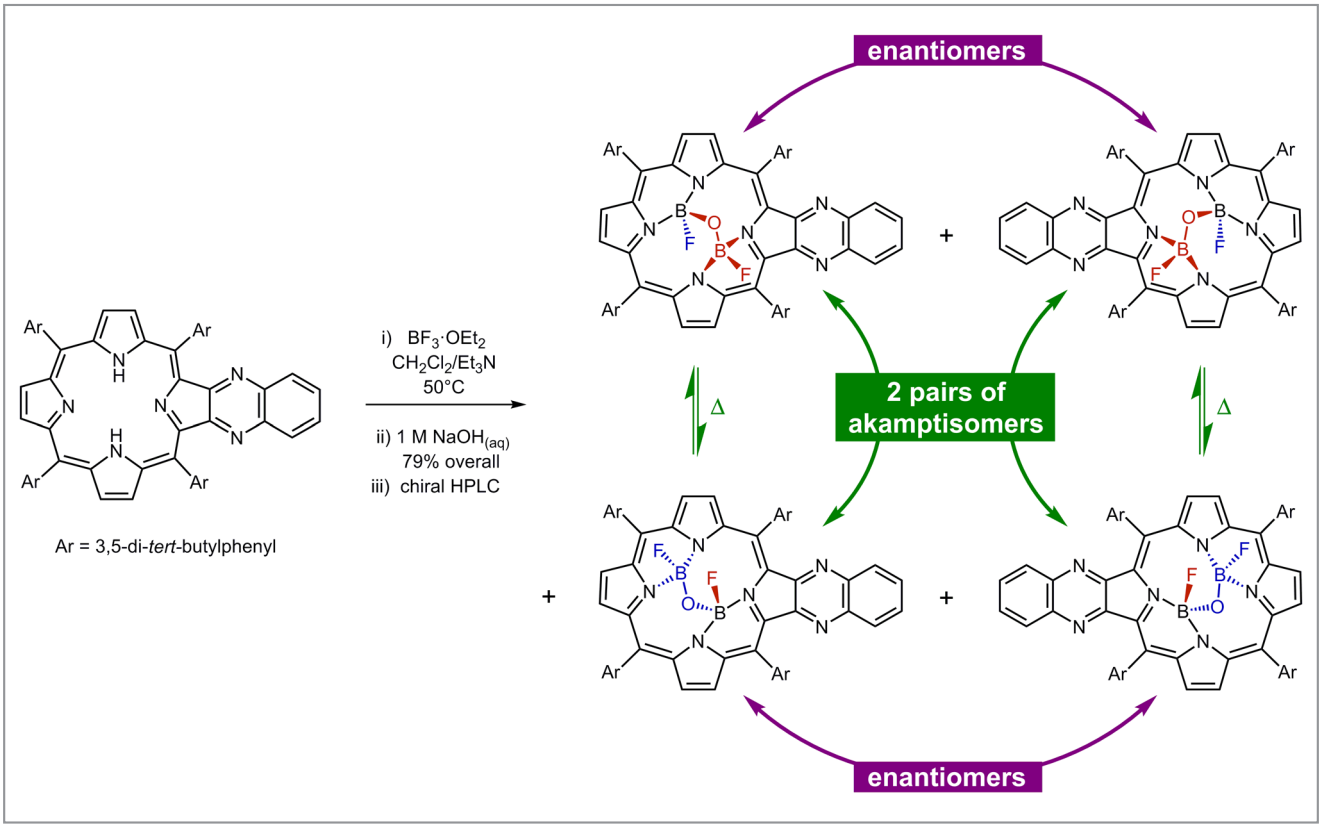
Nat. Chem. **2018**, *10*, 615–624

Isomerism plays a central role in modern chemistry and biochemistry. Its initial discovery in 1830 was followed by the revelation of chirality in 1848, the revelation of *cis–trans* isomerism about double bonds ca. 1890, the isolation of hindered rotamers about single bonds in 1914, and the isolation of hindered invertomers at pyramidal centres in 1961.

Now, in the latest issue of *Nature Chemistry*, Peter Canfield, University of Sydney (Australia) PhD candidate, his research supervisor Professor Maxwell Crossley (University of Sydney), co-supervisor Professor Jeffrey Reimers (University of Technology Sydney and Shanghai University, P. R. of China), and co-workers including Elmars Krausz and Rika Kobayashi (Australian National University) described a new, previously unclassified, fundamental form of conformational isomerism.

Professor Crossley said: "We performed a single 'BOFylation' reaction (a synthetic strategy developed by Penelope Brothers at The University of Auckland, New Zealand) on a free-base quinoxalinoporphyrin, yielding four chiral *transoid* B(F)OB(F)-quinoxalinoporphyrin products (see Scheme 1). When separated by chiral HPLC as enantiopure stereoisomers, we found them to slowly interconvert in a highly stereoselective way that could only be explained by a bond angle inversion (BAI) mechanism. Each reaction involved an intermediate featuring a linear B–O–B geometry as shown in Scheme 2."

Summarizing the results, Mr. Canfield noted: "I always expected four reaction products and knew of BAI as a *possible mechanism* for certain examples of *cis–trans* isomerism of a double bond. However, it came as a surprise that isolable compounds involving only single bonds (in the present case B–O



Scheme 1 Synthesis of the four chiral products showing their stereoisomeric relationships and pattern of unimolecular interconversion.

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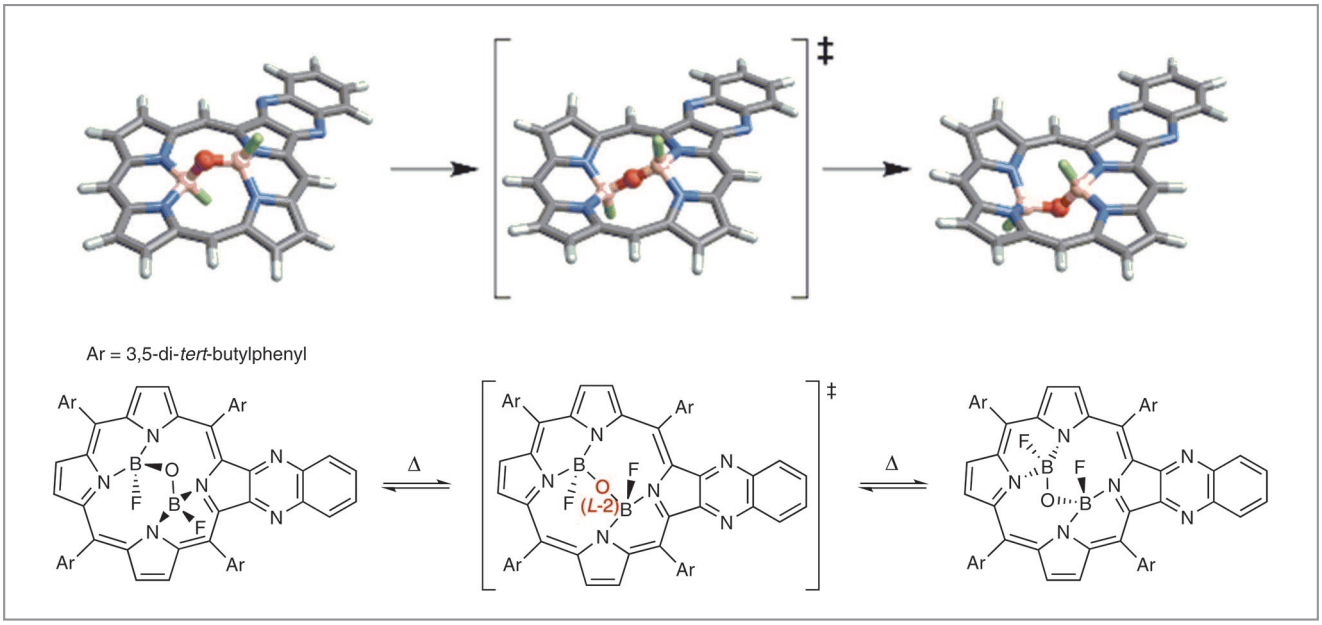

Scheme 2 Models depicting the bond angle inversion mechanism that converts between pairs of akamptisomers via the intermediate transition structure featuring a linear B–O–B geometry. For clarity, the models are of the *meso*-unsubstituted analogues.

bonds) distinguishable in this way had not previously been prepared. After all, the observed process just directly parallels rotamerism about single bonds and pyramidal invertomerism."

Rationalizing this, Professor Reimers explained: "The reason that compounds displaying this feature had not previously been isolated is that, in most molecules, rotation can happen about single bonds extremely quickly. Any BAI reaction can therefore normally be undone by Hula-twist rotations about the two involved bonds, making the reactants and products non-isolable conformational isomers. In the synthesised molecules, an external, low-symmetry porphyrin macrocycle encapsulates the reacting B–O–B system. This bounding macrocycle prevents rotation about the two B–O bonds, allowing unique configurational isomers to be isolated."

The original intent of the synthesis was to design molecules that would yield different spectra to those of normal porphyrins, with focuses on possible technological applications. Professor Krausz said: "We hoped the molecules would yield novel spectral properties so that we could learn more about how magnetic circular dichroism originates and its interpretation for porphyrins and chlorophylls. This is part of our ongoing collaboration on the electronic properties of porphyrins, which are ubiquitous in biochemistry." Dr. Kobayashi added: "My interest was in how well the density functional theory computational methods that I was developing would work given the anticipated high-quality data from Professor Krausz's lab."

"A comprehensive analysis of porphyrin substitution patterns in the context of conceivable isomerisation pathways revealed that the 2,3-disubstituted pattern gave us the simplest and therefore most elegant system with which to unequivocally demonstrate the anticipated phenomenon," said Mr. Canfield. Professor Crossley remarked: "Fortunately, my group has developed the quinoxalino[2,3-*b'*]porphyrin class (Schemes 1 and 2) for numerous applications, so we had the right in-house expertise." "And our long-standing collaboration meant we also had the theoretical tools in place that proved critical for assigning structures based on spectroscopic measurements," added Professor Reimers.

"However, it all worked out very different to expectations," continued Professor Reimers. "Some properties of the molecules were strikingly different to anything seen before. The compounds are soluble in almost everything but 100% water, making crystallization difficult and mounting crystals in X-ray spectrometers even more so. Then the spectra were not as distinctly characteristic as we expected, but we had to rely on them and the associated calculations, along with 2D NMR, to identify which isomer was which."

Focusing on the future, Professor Crossley noted: "In principle, many compounds showing the novel isomerism could be obtained. The essential features are an external environ-

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ment such as a rigid macrocycle used to constrain BAI at some two-coordinate atom linked by only single bonds. Very many macrocycles, and very many reacting groups, could be combined in this way. It does not have to be a porphyrin, it does not have to be B–O–B."

Mr. Canfield emphasised "As Scheme 2 suggests, new isomers should have very different 3D structures. In the compounds synthesised, the fused quinoxalino group makes the porphyrin asymmetric. In this way the diastereomeric pairs of compounds related by BAI are different to each other. Through synthetic control of the asymmetry, the relative stability of the isomers can be adjusted. In a similar way, the barrier height to interconversion, measured at 104 kJ/mol for the BOFylated porphyrins, can be adjusted over a wide range through variation of the inner bridging species and through control of the macrocycle induced compression of this bridge."

Each author had their own reasons for making the molecules. The large differences in the shapes of the isomers would facilitate binding modulation for drug candidates, allow different electrical, magnetic, and optical properties for molecules used in functional materials and devices, and provide basic theoretical insight into chemistry and its spectroscopic techniques. The authors commented: "We believe that exploitation of the synthetic flexibility and accessibility of this new form of isomerism may lead to a wide range of new molecules and materials tailored for specific purposes."

Expounding on their possible pedagogical role, Professor Reimers noted: "The existing IUPAC naming rules are inadequate for the description of the new compounds and their reactions. Hence, we considered a wide range of conceptually feasible isomers using computational means, proposing definitions intended to be proven adequate for naming future compounds and processes."

The isomerism process was named "akamptisomerism", meaning "without bending", in direct analogy to the name "atropisomerism", which means "without turning", that is applied to name hindered rotamers. In addition, the new stereodescriptors "*parvo*" and "*amplo*" were introduced specifying the relationship between the host and its surrounding macrocycle, facilitating unique chemical names for akamptisomers.

"The conceptual basis for understanding akamptisomerism was already known," explained Mr. Canfield. He continued: "Historically, the discovery of new isomerism phenomena came about and was understood somewhat in isolation. Seeking an understanding of processes in complex systems like ML5 and those of higher coordination numbers, Muetterties introduced the geometric concept of polytopal rearrangements in the late 1960s. This unified previous discussions of isomerism and is now utilised by IUPAC as its central concept in classifying stereoisomerism. It was just that this rigorous mathematical approach to stereoisomerism had never been applied to the very simple case of BAI. Now all possible scenarios have been examined, indicating that there are no more fundamental forms of isomerism remaining to be discovered."

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About the authors

P. J. Canfield

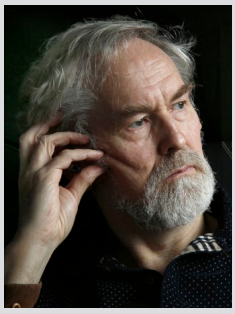
Peter J. Canfield was born in Sydney, Australia. Following an early interest in chemistry, he attended the first Australian Chemistry Olympiad in 1988. He received a BSc at the University of New South Wales (Australia), majoring in chemistry and physics and was awarded first class honours under the guidance of Prof. Michael Paddon-Row in 1994. Following several roles in the public and private sectors, in 2003 he commenced doctoral studies in quantum chemistry with Prof. Reimers at the University of Sydney (Australia). Deferring completion of his PhD, he took on a private sector role heading Research and Development for the aquaculture company, Jewelmer, based in the Philippines. Following time at Shanghai University (P.R. of China), he then returned to doctoral studies at the University of Sydney under the guidance of Prof. Crossley and Prof. Reimers. His research interests centre around the mechanistic underpinnings of chemical processes and how such understanding can be directly applied to beneficial, real-world applications. His latest venture involves the creation of a technology start-up company researching and exploiting the akamptisomerism phenomenon.

Prof. E. Krausz

Elmars Krausz graduated and received his PhD from the University of Sydney (Australia). He held positions at the Australian National University (Australia, 1971–1973, 1978), Oxford University (UK, 1974–1975), the University of Virginia (USA, 1976–1977), and the University of Sydney (Australia, 1979–1980) before being appointed as Research Fellow at the Research School of Chemistry at the Australian National University. He was awarded fellow of the Royal Australian Chemical Institute and was appointed Professor at the Research School of Chemistry in 2002. He is known for his roles in understanding electron-transfer spectroscopy (the "PKS model"), understanding energy capture and water splitting in natural photosynthesis, and the development of laser selective spectroscopies and many novel magnetic circular dichroism measurement and interpretation techniques.

Dr. R. Kobayashi

Rika Kobayashi was born in Sydney, Australia and graduated with a Bachelor of Science (Hons I) from the University of Sydney (Australia) in 1988. She obtained her PhD from the University of Cambridge (UK), under the supervision of Nicholas Handy, where she derived and implemented an analytic gradient for the Brueckner coupled cluster method. Subsequent work has primarily been in programming new methods in various software packages: coupled cluster and response properties in DALTON, the original CCSD(T) module in NWChem and the CAM-B3LYP density functional in Gaussian 09. Since 2001 she has been an Academic Consultant specialising in computational chemistry at the Australian National University Supercomputer Facility with main responsibilities being porting, maintaining and providing user support for a wide range of computational chemistry packages, particularly in the context of high-performance computing. Her research interests are focused around application of these methods to novel problems, recently together with Professor Jeffrey Reimers through the award of a foreign expert travel grant from Shanghai University.



Prof. J. R. Reimers

Jeffrey R. Reimers FAA, FRSN, FRACI studied organic spectroscopy under Ian Ross and Gad Fischer before completing a PhD with Robert Watts on the structure, thermodynamics, and spectroscopy of water and ice. He then studied semiclassical quantum mechanics in USA under Kent Wilson and Rick Heller before returning to Australia to be an ARC Research Fellow from 1985 to 2010 at the University of Sydney. There he collaborated extensively with Noel Hush and Max Crossley on problems involving electron transfer, molecular electronics, porphyrin chemistry, self-assembly, electronic-structure theory, and photosynthesis. In 2014 he moved to a joint appointment at University of Technology Sydney and Shanghai University (P. R. of China), focusing on basic chemistry and molecular electronics. His work spans a wide range of chemical applications, from biochemical function to electronic devices to the origins of consciousness. He has received the RACI Physical Chemistry Division Medal (2014) and the H.G. Smith Medal (2009), the

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About the authors

David Craig Medal of the Australian Academy of Science (2016), and the Shanghai Magnolia Medal (2017); he is a Fellow of the RACI (1999), the Royal Society of NSW (2017), and the Australian Academy of Science (2010).

Prof. M. J. Crossley

Maxwell J. Crossley FAA, FRSN, FRACI is currently Professor of Chemistry (Organic Chemistry) and University Professorial Fellow at The University of Sydney (Australia). He was educated at The University of Melbourne (Australia, Ph.D. advisor Professor Donald W. Cameron). Crossley then became a post-doctoral fellow at the Research Institute for Medicine and Chemistry in Cambridge, Massachusetts (USA) with Professor Sir Derek Barton FRS, then spent two years as a Research Associate at MIT in Cambridge, Massachusetts (USA) with Professor Jack E. Baldwin FRS. In 1978 he moved to Oxford University (UK) where he continued to work with Professor Baldwin and returned to Australia in 1980 as a Research Fellow at the University of Melbourne (Australia). Later that year he moved to Sydney where he has been based since. He has held visiting appointments at the University of Cambridge (UK), the University of Strasbourg (France), the University of Nijmegen (the Netherlands), Osaka University (Japan), and IPC, Chinese Academy of Sciences, Beijing (P.R. of China). Crossley is a Fellow of the Australian Academy of Science (elected 2001). He has received a number of accolades for his research excellence, including the Birch Medal (1998), the H.G. Smith Memorial Medal (2001), a Centenary Medal (2003), the David Craig Medal (2012), the Robert Burns Woodward Career Award (2012), and the Leighton Medal (2013). His main research interests are porphyrin chemistry, functional materials for applications including photochemical upconversion and optics, and molecular electronics.

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