Arylation of Hydrocarbons Enabled by Organosilicon Reagents and Weakly Coordinating Anions

Highlighted article by B. Shao, A. L. Bagdasarian, S. Popov, H. M. Nelson
Dear Readers,

This is one of the very last duties (although it is always a great pleasure to write these SYNFORM editorials) of a very long working year, because holidays are finally looming, yay! I still remember when I was at the beginning of my career and I used to spend most of my time enthusiastically working in the lab, daydreaming about novel exciting reactions and fancy new molecules. At that time holidays didn’t seem to be so attractive; actually I vividly recall thinking that holidays were just a waste of time, an annoying impediment to my next discoveries. But now that – not without regret – I have to spend most of my time managing research (which is basically a euphemism for indicating a lot of paperwork) holidays look much more attractive, I have to admit... Dinners al fresco with relatives and friends, a real yummy Italian pizza (not those abominations available at most local retails), soaking up the sun on my terrace with a cold beer, that’s life! I know that in two weeks I will be missing my job, but now all I have in mind is HOLIDAYS!!! Let’s have a quick look at the August issue of SYNFORM then, before wrapping up everything and going home to pack my luggage. First article: a SYNLETT Highlight about the synthesis of chemicals contained in red wine recently published by L. Cruz and I. Fernandes (Portugal), which somehow reminds me about holidays, again... second article: the ground-breaking hydrocarbons arylation published in *Science* by H. Nelson (USA), third article: the origins of life chemistry investigated by M. Powner (UK), and finally: an interesting Young Career Focus interview with S. H. Cho (Republic of Korea). Time to pack my bags now!

Enjoy your reading!

[Signature]

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Contact

If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com
Synthesis of the Main Red Wine Anthocyanin Metabolite: Malvidin-3-O-β-Glucuronide

Synlett 2017, 28, 593–596

The large diversity of flavonoid metabolites in vivo makes their proper detection and quantification difficult in the absence of pure standards. Indeed, flavonoids are extensively metabolized to different conjugated derivatives (methyl ethers, glucuronides, sulfates) that are likely to be the circulating forms able to reach their metabolic targets. To study the activity of these circulating metabolites, these compounds must be available as standards. However, most of these compounds are not commercially available and hence have to be prepared in the laboratory.

Amongst red-wine flavonoids, anthocyanins are the most difficult to track in vivo. The human metabolism of anthocyanins is poorly described in the literature, with scarce information on the biological effects of their metabolites. A new study led by Dr. Luis Cruz and Dr. Iva Fernandes at the University of Porto (Portugal) has recently investigated this issue.

“Anthocyanins are naturally occurring polyphenols belonging to the group of flavonoid compounds widely found in plants. These pigments are responsible for the color of many flowers, leaves, seeds, fruits and vegetables ranging from red to purple and blue,” said Dr. Fernandes, who added: “In vitro and in vivo studies have demonstrated that anthocyanins may offer potentially beneficial effects to human health because of their biological properties, such as anti-aging, anticancer, anti-inflammatory, anti-infection and anti-diabetes. Epidemiological evidence suggests that the ingestion of high proportions of anthocyanins in the diet may contribute to lowering the risk of cardiovascular events such as hypertension and stroke.”

However, it is recognized that the in vivo anthocyanin bioactive forms do not always correspond to the native forms, but rather consist of conjugates or metabolites originating from the original anthocyanins after absorption. Anthocyanins are rapidly absorbed in the stomach and small intestine and then they appear in plasma and urine as intact, methylated, glucuronono- and/or sulfoconjugated forms. The enterohepatic recycling opens a new field of interest that remains a challenge: unravelling the biological properties of anthocyanin metabolites,” explained Dr. Fernandes.

Dr. Fernandes said: “In 2009, an enzymatic approach to obtain anthocyanin metabolites seemed the best option for this type of flavonoid in order to overcome their low stability under the conditions used for their chemical synthesis (pH and temperature). Some anthocyanin metabolites (methylated, glucuronides and glutathione adducts from cyanidin and delphinidin-3-glucosides) were obtained through that enzymatic approach.”

Some of these standards – such as delphinidin-3-glucoside-, cyanidin-3-glucoside- and petunidin-3-glucoside-methylated metabolites – were then tested against several biological properties, antiradical and reducing properties and also their antiproliferative effects against different cancer cell lines (MKN-28, Caco-2 and MCF-7). “The methylated metabolites were found to still retain significant radical scavenging activity and reducing activity, suggesting that they could act as potential antioxidants in vivo,” said Dr. Fernandes, adding: “The conjugation with methyl groups decreased or did not alter the antiproliferative effect of the native anthocyanins. This report investigated the biological meaning of the new circulating molecules that are produced by the human body in response to the ingestion of phytochemicals.”

Other important cyanidin-3-glucoside metabolites, namely methylated and glucuronylated in positions 4’ and 7, respectively, were chemically synthesized by the same research group, following the strategy of aldol condensation reaction between a salicylic aldehyde and an acetophenone derivative, which had been previously prepared. This strategy allowed the research team to obtain useful amounts of these standards for rapid and correct identification in biological samples.

Dr. Fernandes explained: “Recently, in a crossover trial with healthy volunteers who ingested a blackberry puree, the purified standards allowed our group to identify the position of insertion of the glucuronyl group and methyl group in the metabolites detected in plasma and urine samples. Indeed, cyanidin-7’-O-glucuronyl-3-glucoside was identified for the first time in human plasma and urine samples. Moreover, identification of the attached methyl group’s position was anticipated from comparison with the natural standard peonidin-3-O-β-D-glucoside and the currently available standard cyanidin-4’-O-methyl-3-glucoside, previously obtained by semi-synthesis.”

According to Dr. Fernandes, previous studies evaluating the bioavailability of red-wine anthocyanins had only looked for the main native anthocyanin (Mv3glc) in plasma and urine, underestimating the total anthocyanin content.
the work of Garcia-Alonso et al., where volunteers consumed 180 mg of red wine anthocyanin extract in a sugar-sweetened yogurt,” she said, “the authors were already able to identify some anthocyanin metabolites in plasma.”11

“Identification of the metabolites originating in vivo is often compromised, which restricts the comprehension of the metabolic pathways followed by anthocyanins after absorption,” said Dr. Fernandes. She continued: “Usually, it is only possible to determine the type of conjugation that occurs after anthocyanin absorption, but it is not possible to ascertain the position where that insertion takes place. This is quite important since different molecules may have different biological activities.”

In a work registered in clinicaltrials.gov under the code NCT02975856, a similar human trial was performed with the ingestion of red wine as source of anthocyanins, especially malvidin-3-O-β-glucoside (Mv3glc).12 After analysis of urine and plasma samples, glucuronidation was clearly identified as the main metabolic pathway, although the detailed mechanism was still missing.

“Firstly, and inspired by the in vivo enzymatic assay, the enzymatic hemi-synthesis was performed with the co-addition of glucosidase and UGT protein source in the presence of the main red wine anthocyanin,” explained Dr. Fernandes. This approach was not very successful, since after glucose removal the anthocyanins started to precipitate in the buffer system and degraded rapidly. “The other possibility was to collect the corresponding peak, purify it and perform NMR analysis to ascertain its structure; however, this would be almost impossible due to the low sample quantities and quite hard and time-consuming work,” said Dr. Fernandes, who continued: “To overcome these limitations, synthesis of the most probable main conjugate to be detected after red wine ingestion (malvidin-3-O-β-glucuronide)13 was successfully performed (Figure 1) following the chemical synthesis strategy previously developed by our research group.”6,7

Figure 1 Schematic representation of the metabolic pathway of red wine anthocyanins during absorption and the chemical synthesis approach followed to obtain the main red wine pigments. CGB: Cytosolic-β-glucosidase; UGT: Uridine 5′-diphospho-glucuronosyltransferase; Gluc3AcMe: 2,3,4-tri-O-acetyl-α-D-glucopyranuronic acid methyl ester.
The authors concluded: “The combination of efforts between different areas of knowledge is remarkably fruitful. In this particular case involving our laboratory, knowledge of the chemical and biological behavior of polyphenols allowed us to overcome some of the major limitations associated with the identification of this class of flavonoids in human biological samples.”

REFERENCES

(13) L. Cruz, I. Fernandes, A. Évora, V. de Freitas, N. Mateus *Synlett* 2017, 28, 593.
About the authors

Luís Cruz graduated in chemistry (2004), and obtained his M.Sc. in chemistry (2006) and Ph.D. in chemistry (2010) at the Faculty of Sciences of the University of Porto (FCUP, Portugal) under the supervision of Professor Victor de Freitas. He was assistant professor of the organic chemistry laboratory of the 2nd year of chemistry graduation. He carried out postdoctoral research activities at the Food Chemistry group of REQUIMTE-LAQV Research Center (Portugal) during the period of 2010–2016. He is currently auxiliary investigator in the same group. He has been a team member in several projects funded by national institutions and has been supervising under- and postgraduate students (with M.Sc. and Ph.D. degrees). He is now principal investigator of the project entitled ‘Development of novel anthocyanin-lipophilic bioactives for technological applications’. His research interests include: (a) chemical synthesis of anthocyanin metabolites for biological studies, (b) design of natural and bio-inspired flavlylins as photosensitizers for energetic applications (e.g. dye-sensitized solar cells), (c) recycling and lipophilization of anthocyanins from agro-food wastes towards novel stable colorants for applications in the food, pharmaceutical and cosmetics industries, and (d) study of physical-chemical, antioxidant and biological features of novel anthocyanin-derived pigments.

Iva Fernandes graduated in biochemistry in 2006 and obtained her Ph.D. in chemistry in December 2012, both at the University of Porto (FCUP, Portugal). She is currently a postdoctoral fellow at the REQUIMTE/LAQV at the Faculty of Sciences of the University of Porto since 2010. She is currently an assistant professor at the Department of Chemistry and Biochemistry of the Faculty of Sciences. Her research activities at the Food Chemistry group of REQUIMTE-LAQV Research Center (Portugal) during the period of 2010–2016. She is currently auxiliary investigator in the same group. He has been a team member in several projects funded by national institutions and has been supervising under- and postgraduate students (with M.Sc. and Ph.D. degrees). He is now principal investigator of the project entitled ‘Development of novel anthocyanin-lipophilic bioactives for technological applications’. His research interests include: (a) chemical synthesis of anthocyanin metabolites for biological studies, (b) design of natural and bio-inspired flavlylins as photosensitizers for energetic applications (e.g. dye-sensitized solar cells), (c) recycling and lipophilization of anthocyanins from agro-food wastes towards novel stable colorants for applications in the food, pharmaceutical and cosmetics industries, and (d) study of physical-chemical, antioxidant and biological features of novel anthocyanin-derived pigments.

Ana Évora is an M.Sc. student in biochemistry at the Faculty of Sciences of the University of Porto (FCUP, Portugal), having obtained her B.Sc., also in biochemistry, at the same institution in 2015. Currently, she is working in the Department of Chemistry and Biochemistry (DBQ) of FCUP as a B.Sc. fellow, studying the absorption, stability and bioactivity of new anthocyanin derivatives towards their application in the cosmetics and food industries. More recently, she participated in two national congresses in the field of chemistry with a conference poster, and also in IJUP (the meeting of student researchers from the University of Porto) with an oral presentation. While at college, she concluded her B.Sc. degree in Hungary under the ERAMUS+ program, performing her curricular internship.

Nuno Mateus graduated in biochemistry in 1997 and obtained his Ph.D. in chemistry in 2002, both at the University of Porto (Portugal). He has been teaching (food chemistry and industrial biochemistry, among other courses) at the University of Porto since 2001 and is currently an associate professor at the Department of Chemistry and Biochemistry of the Faculty of Sciences at the University of Porto. Included in the section of organic chemistry of the department, his field of research concerns food chemistry and biochemistry, essentially food polyphenols and in particular red wine chemistry (grape and wine polyphenolic composition; chemical pathways occurring during wine ageing; detection, isolation and characterization of newly formed polyphenols as well as their putative industrial applications, etc.). He has been collaborating with local industrial companies (especially Port wine companies) and has been involved in several research projects funded essentially by the Portuguese government. One of his main areas of research deals with the synthesis and characterization of anthocyanin-derived pig-
ments detected in Port wines and their putative applications as colorants in the food industry. More recently, he has been coordinating projects dealing with biological properties of red wine polyphenols towards some cancers and age-related diseases. He is now also exploring a new research line focused on the application of industrial wastes of the food industry into novel applications in the cosmetics industry.

**Victor Freitas** graduated in chemistry from the Faculty of Sciences of the University of Porto (FCUP, Portugal) in 1989. In 1995, he obtained his Ph.D. in biological and medical sciences from the University of Bordeaux II (France), specializing in oenology. After his Ph.D., he returned to the Department of Chemistry and Biochemistry (DQB) of FCUP where he has been developing his teaching and research activities. He is currently full professor at the University of Porto and member of the REQUIMTE-LAQQ Research Centre where he has been developing an independent area of research involving polyphenol compounds. He is president of the ‘Groupe Polyphénols’ society since July 2016 ([www.groupepolyphenols.com](http://www.groupepolyphenols.com)).
Young Career Focus: Dr. Seung Hwan Cho  
(Pohang University of Science and Technology, Republic of Korea)

**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. Seung Hwan Cho (Pohang University of Science and Technology, Republic of Korea).

**Biographical Sketch**

Seung Hwan Cho obtained his B.Sc. (2006) and Ph.D. (2011) degrees from the Korea Advanced Institute of Science and Technology (KAIST), under the guidance of Professor Sukbok Chang. During his Ph.D. studies, he focused on two different research topics: (1) copper-catalyzed three-component couplings with terminal alkynes, sulfonyl azides, and nucleophiles, and (2) transition-metal-free or transition-metal-catalyzed C–C and C–N bond formation reactions via a C–H activation strategy. After spending one more year at KAIST for his military service, he joined the group of Professor John F. Hartwig at the University of California, Berkeley (USA) as a Cheongam postdoctoral fellow (2012–2014). There, he was engaged in research to develop silane-directed secondary C–H borylation reactions. He began his independent career in July 2014 at Pohang University of Science and Technology (POSTECH), Pohang, Republic of Korea. His research involves chemo- and stereoselective transformations using 1,1-diborylalkanes as coupling reagents. He received the Cheongam Science Fellowship for Young Investigators, the ACP Lectureship Award (Hong Kong and Singapore) and the Thieme Chemistry Journals Award (all in 2017).

**INTERVIEW**

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

**Dr. S. H. Cho** Research in our group aims to discover, develop and understand new organic transformations which will result in a rapid increase in molecular complexity. In particular, we are highly interested in the design and synthesis of new types of organoboron compounds such as 1,1-diborylalkanes and their/utilizations in transition-metal-free C–C and C–B bond-formation reactions. Moreover, we are interested in developing transition-metal-catalyzed diastereoselective and enantioselective organic transformations of 1,1-diborylalkanes with suitable electrophiles to generate chiral organoboron compounds.

**SYNFORM** When did you get interested in synthesis?

**Dr. S. H. Cho** During my undergraduate years I majored in chemistry, but I was not interested in studying it. I could not find the motivation to study chemistry, and I had no confidence in myself. But, after I met Professor Sukbok Chang, my life completely changed. He encouraged me to do experiments in his lab, and I started my undergraduate research in his group.

Professor Chang gave me the opportunity to experience independent research and I was able to discover the real research process. There, I luckily had a chance to be involved in a project to develop a copper-catalyzed multicomponent reaction with terminal alkynes, sulfonyl azides and suitable nucleophiles. During the research, I observed that the ketene-imine intermediate, which was generated by the reaction between a terminal alkyne and a sulfonyl azide in the presence of a copper catalyst, could react with water to form an amide. This result was an unconventional approach to the synthesis of amides and I was fortunate to publish my undergraduate
thesis in J. Am. Chem. Soc. I felt great pleasure while performing and organizing experiments. After much consultation with Professor Chang, I decided to continue studying organic chemistry.

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

Dr. S. H. Cho Organic synthesis is a vast area in science because there are an infinite number of molecules that can be synthesized. I think this intriguing point drives chemists to devote themselves to creating new molecules and to understanding Nature in terms of reactivity and mechanism. These efforts ultimately lead to breakthroughs in related fields such as medicinal chemistry, chemical biology, and materials science. Over the past decades, impressive advances have been made in the area of synthetic methodology. There have been many breakthroughs in organic synthesis over the last few decades, but there are still many unsolved problems that are affecting the development of other research areas (materials, biomedicine, environment, etc.). I believe it is our job to use our endless creativity to find new molecules and reactions and to increase our mechanistic understanding. These efforts will definitely expand the area of organic synthesis explosively and constantly, thus supporting the overall development of society.

SYNFORM Your research group is active in the area of organic catalysis and new synthetic methodology. Could you tell us more about your research and its aims?

Dr. S. H. Cho Since the start of my independent research in 2014, my group has been interested in two main topics using 1,1-diborylalkanes as coupling reagents (Scheme 1). Specifically, we developed the transition-metal-free alkylation of N-heteroaromatic N-oxides using 1,1-diborylalkanes as methylation or alkylation sources. In this reaction, we have shown that the α-boryl carbanion generated in situ from the reaction between a 1,1-diborylalkane and an alkoxide base can attack the electrophilic C2 position of an N-heteroaromatic N-oxide; subsequent elimination and re-aromatization delivers C2-alkylated N-heteroaromatic compounds. We also developed the transition-metal-free borylation of aryl and vinyl halides using 1,1-diborylalkanes as boron sources. While 1,1-diborylalkanes are typically used for the formation of C–C bonds, our example offered unique reactivity and selectivity. Moreover, we also developed the copper-catalyzed chemoselective reaction of 1,1-diborylalkanes with suitable electrophiles. In particular, we developed copper-catalyzed allylic substitution and 1,2-addition reactions to form synthetically useful organoboron compounds. We are still continuing this research and aim to design new types of 1,1-diboron compounds that can be used in regio-, diastereoselective and enantioselective organic transformations.2–6
SYNFORM  What is your most important scientific achievement to date and why?

Dr. S. H. Cho  Personally, the copper-catalyzed three-component coupling reaction of a terminal alkyne, a sulfonyl azide and water, which provides unconventional amide synthesis, is one of the most meaningful papers in my career. As I mentioned above, I was able to continue studying organic chemistry because of this research experience. Since I have only spent three years in academia, it is hard to choose my most important scientific achievement. Of course, I hope that it still lies ahead of me. However, if I were to choose some contributions to the field during my independent career, I would pick the transition-metal-free methylation of N-heteroaromatic N-oxides. Because the introduction of a methyl group into N-heteroarenes is challenging and their separation from the starting material is quite difficult, our developed protocol offers a convenient method for the methylation of N-heteroarenes with a simple purification process.

REFERENCES

Aryl carbocations are not frequently used for intermolecular arylation and alkylation reactions, owing to their high energy, challenging controlled generation and difficulties in taming their reactivity. However, if these problems could be overcome, the use of phenyl carbocations and related intermediates could represent a very efficient and straightforward way to synthesize biaryls and alkyl arenes. Recently, the group of Professor Hosea Nelson from the University of California, Los Angeles (USA) reported in Science a breakthrough method for generating and reacting β-silicon-stabilized aryl cation equivalents having very weakly coordinating anions, that can be generated via silylium-mediated fluoride activation.

"The chemistry is built on a mountain of foundational work by Siegel, Reed, Ozerov and others," explained Professor Nelson, "while we added a bit of an organic methodology twist. Specifically, we looked at ways to make phenyl cation equivalents that were more competent intermolecular reaction partners." Through β-silicon substitution, Professor Nelson and co-workers were able to achieve this and enable a cationic chain reaction that required substoichiometric amounts of silane. "We were quite surprised to observe the halogen selectivity inherent in the system," said Professor Nelson. "We were even more surprised to see that we could arylate methane, and that n-alkyl nucleophiles react at the terminal CH3 group! Arylation of alkanes is very rare, and we feel that our chemistry forms a nice conceptual foundation for moving this area forward."

Interestingly, Professor Nelson revealed that this project was fuelled by a team of ‘rookies’. In fact, Professor Nelson was a brand-new faculty member, who had been trained in organic methodology and total synthesis, while the two co-first-authors, Brian Shao and Alex Bagdasarian, were 1st year graduate students and the third author, Stasik Popov, was a summer rotation student who hadn’t even officially started graduate school at UCLA. Professor Nelson said: "We found ourselves making advances in a field that was completely new to us…quite exciting and unexpected."

The new methodology can be used to achieve intermolecular arylation (Scheme 1) as well as alkylation reactions (Scheme 2), affording respectively biaryls and alkyl arenes.

In terms of future potential, the group is trying to expand the chemistry in two areas. "Firstly, we are looking to develop new initiators and phenyl cation precursors that allow for greater substrate compatibility. Our roots are in organic methodology and total synthesis, so we would love to be able to do reactions with more complex substrates," explained Professor Nelson. He continued: "Secondly, we are also pursuing a better mechanistic understanding. We feel that will also allow us to improve the chemistry with respect to efficiency and cost in the area of simple hydrocarbon functionalization."

Professor Nelson concluded: "Finally, the hunt for unambiguous evidence (crystallographic evidence) of a phenyl cation intermediate is an ongoing project in the group."

Figure 1: The novel synthetic methodology
Scheme 1 Arylation reactions

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Scheme 2 Alkylation reactions

A. Alkanes

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B. Methane

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About the authors

Brian Shao was born and raised in Alhambra, California (USA). He obtained his B.Sc. degree at the University of California, Davis (USA) in 2015 and continued his studies at the University of California, Los Angeles (USA) as a Ph.D. candidate that same year. Joining Professor Hosea Nelson’s group, his research focuses on silylium-mediated catalysis.

Alex Bagdasarian was born in Cupertino, California (USA) in 1993. He completed his B.S. in Pharmaceutical Chemistry at the University of California, Davis (USA) in 2015. During his time there, he worked under the supervision of Professor Mark J. Kurth focusing on the synthesis of biologically active heterocyclic scaffolds through novel methodologies. During the summer of 2015, he joined the lab of Professor Hosea Nelson where he has been working on developing new reactions using main-group catalysts.

Stasik Popov was born in Kazakhstan in 1994. He obtained his B.S. degree in Chemistry and Mathematics from Brandeis University (USA) in 2016. In the same year, he joined Professor Nelson’s group at University of California, Los Angeles (USA) as a graduate researcher. His research focuses on the development of new synthetic reactions utilizing silylium catalysis.

Hosea Nelson earned a B.S. in Chemistry from the University of California at Berkeley (USA) in 2004 and a Ph.D. from the California Institute of Technology (USA) in 2012 (advisor Professor Brian Stoltz). After postdoctoral training at the University of California at Berkeley (advisor Professor Dean Toste), Professor Nelson joined the UCLA faculty in 2015. His research focuses on the discovery of new chemical reactions.
Divergent Prebiotic Synthesis of Pyrimidine and 8-Oxo-purine Ribonucleotides

*Nat. Commun. 2017, 8, 15270*

According to Dr. Matthew Powner from University College London (UK), a central issue for origins of life research is to elucidate the roots of biochemical information transfer, which underpins Darwinian evolution, inheritance, replication, and genetically encoded catalysis in life.

Dr. Powner believes that RNA is the leading candidate for the first biopolymer of life, due to its dual biological role in information transfer and catalysis, as well as the deep-seated evolutionary history of non-coding RNAs (for example, 16S and 23S ribosomal genes, tRNA genes and nucleotide binding domains are amongst the most conserved genomic regions in both microbial and non-microbial taxa). “Accordingly,” said Dr. Powner, “the ‘RNA World’ – an evolutionary period, before DNA and coded proteins, when biological genotype and phenotype were both maintained in RNAs – is the leading model for the origin of Darwinian evolution on Earth, but this model is contingent upon realizing the prebiotic synthesis of a pool of activated RNA monomers – The ‘Molecular Biologist’s Dream’.”

Dr. Powner added: “Although prebiotic nucleotide synthesis has been investigated for more than 50 years, an adequate solution to this problem remains elusive. Recently, remarkable progress has been made towards this challenge, but to date all syntheses have only accounted separately for pyrimidine or purine nucleotides.”

He continued: “During my PhD with Professor John Sutherland at the University of Manchester (UK), we developed a chemical strategy to synthesize the canonical pyrimidine nucleotides, cytidine and uridine, by a robust prebiotically plausible route (Powner et al. *Nature* 2009, 459, 239). This was an important step towards understanding the origins of RNA; however, two classes of RNA monomer are required to synthesize RNA: pyrimidines and purines.

Although we had elucidated a robust synthesis of the pyrimidine nucleotides, there was no complementary purine synthesis. In fact, all reported purine syntheses are contingent on unstable complex sugars, low-yielding reactions, unselective transformations, large pH fluctuations, and, importantly, all operate under conditions that are incompatible with pyrimidine synthesis.”

The issue of selectivity, rebranded as clutter, has surfaced as a major concern for those working in the area of prebiotic chemistry. Recently, however, Dr. Powner’s group has resolved several major outstanding selectivity issues inherent to their previous work by demonstrating that their pyrimidine synthesis (as well as proteinogenic amino acid synthesis) can be controlled by the sequential crystallization of the essential prebiotic precursors, even from highly complex aqueous mixtures (Islam et al. *Nat. Chem.* 2017, 9, 584). “Remarkably, we found that the order of crystallization of nucleotide precursors predicted the order of reactions required to selectively build the canonical nucleotides, and these discoveries further emboldened us to revisit and revise our pyrimidine synthesis strategy,” remarked Dr. Powner.

**Scheme 1** Divergent synthesis of pyrimidine (4C, 4U) and 8-oxo-purine (5A, 5I) nucleotides on a single oxazole sugar scaffold (1)
An essential element of the selection strategy required to orchestrate nucleotide assembly from complex mixtures was the in situ synthesis of a molecular chaperone, 2-aminothiazole, which contains a key sulfur atom that allows it to tracelessly direct ribonucleotide synthesis. Dr. Powner explained: “Exploiting the same rationale, that sulfur compounds or moieties could act as traceless directing groups, we considered how sulfur might be used to introduce the plasticity, controlled and site-specific activation required to divergently synthesize both purine and pyrimidine heterocycles on one single sugar scaffold. We focused our strategy on conformationally restricted, tethered purine assembly (Powner et al. J. Am. Chem. Soc. 2010, 132, 16677; Powner et al. J. Am. Chem. Soc. 2012, 134, 13889) to overcome the chemo-, regio- and stereoselectivity problems inherent to nucleotide synthesis.”

According to Dr. Powner, the paper in Nature Communications resolves the mutual incompatibility of purine and pyrimidine synthesis for the first time (Stairs et al. Nat. Commun. 2017, 8, 15270), by recognizing that 8-oxo-purines, rather than the canonical purines, reveal an underlying generational parity to pyrimidine nucleotides. “We then exploited this equivalence to develop, through a single set of congruent reactions, a divergent synthesis of pyrimidine and 8-oxo-purine nucleotides from a common oxazoline precursor (1, Scheme 1),” explained Dr. Powner. He continued: “Our divergent synthesis concurrently delivers regiospecific N1-pyrimidine and N9-purine glycosidation, and the β-ribo-stereochemistry of RNA to both purine and pyrimidine nucleotides.”

“The simplicity and parity of our divergent reaction pathways attest to the unrealized potential of 8-oxo-ribonucleotides (5),” said Dr. Powner. He concluded: “The generational relationship between pyrimidine (4) and 8-oxo-purine (5) nucleotides opens the exciting possibility that 8-oxo-ribonucleotides may have acted as information carriers at the outset of biology (Figure 1). Accordingly, we provide a new perspective on the original RNA molecules that would have harbored the first step of biology, and a simple chemical solution to delivering both purine and pyrimidine nucleotides at the origins of life.”

**Biographical Sketch**

**Shaun Stairs** was born in the UK and received his undergraduate degree from the University of Cambridge (UK). He continued at Cambridge for his Ph.D. under Dr. Finian Leeper developing new click chemistry methodologies for cell surface glycan labelling. He later undertook postdoctoral research with Dr. Matthew W. Powner at University College London (UK) where he worked on the prebiotic chemistry of purine nucleotides. His research interests encompass the origins of life, nucleotide and carbohydrate chemistries, green chemistry, click and bioconjugation chemistries, and medicinal chemistry.

**Arif Nikmal** was born in Kabul (Afghanistan) in 1989 and came to the UK in 2004. He received his B.Sc. in chemistry in 2011 and M.Sc. in chemical research in 2012 at Queen Mary University of London (UK). He then joined University College London (UK) to conduct his doctoral studies under the supervision of Dr. Matthew W. Powner. His scientific interests include prebiotic chemistry and organic chemistry.
**Dejan-Krešimir Bučar** obtained a B.Sc. in chemistry under the supervision of Dr. Ernest Mestrović at the University of Zagreb (Croatia), and a Ph.D. in chemistry from the University of Iowa (USA) under the guidance of Professor Leonard R. MacGillivray. He then started his independent research career as a Royal Society Newton International Fellow at the University of Cambridge (UK), where he was kindly hosted by Professor William Jones. While in Cambridge, he was also a Bye-Fellow at Sidney Sussex College. He recently joined the Department of Chemistry at University College London (UK) as UCL Excellence Fellow and Lecturer. His research interests mainly evolve around molecular co-crystals and their applications.

**Shao-Liang Zheng** received his Ph.D. in inorganic chemistry under the supervision of Professor Xiao-Ming Chen at Sun Yat-Sen University (P. R. of China) in 2003. He then worked with Professor Phillip Coppens at the State University of New York at Buffalo (USA) as research scientist, emphasizing photocystallographic studies of host-guest crystals. He joined Harvard University (USA) in 2009, where he is currently the Director of the X-ray Laboratory and Lecturer in the Department of Chemistry & Chemical Biology. His interests are applications of advanced crystallography in chemistry and materials science, and crystallography education.

**Jack W. Szostak** received his B.Sc. from McGill University (Canada) in 1972, and then under the supervision of Professor Ray Wu his Ph.D. from Cornell University (USA) in 1977. He moved to the Sidney Farber Cancer Institute and Harvard Medical School (USA) in 1979, and then to Massachusetts General Hospital (USA) in 1984. He is an Investigator of the Howard Hughes Medical Institute, Professor of Genetics at Harvard Medical School, Professor of Chemistry and Chemical Biology at Harvard University, and the Alex Rich Distinguished Investigator at Massachusetts General Hospital. He is a member of the National Academy of Sciences and the American Philosophical Society, and a Fellow of the New York Academy of Sciences, the American Academy of Arts and Sciences, and the American Association for the Advancement of Science and has been awarded the National Academy of Sciences Award in Molecular Biology, the Sigrist Prize from the University of Bern (Switzerland), the Medal of the Genetics Society of America, Harold Urey Medal from the International Society for the Study of the Origin of Life, the Albert Lasker Basic Medical Research Award and the Nobel Prize in Physiology or Medicine.

**Matthew W. Powner** obtained his MChem in chemistry at the University of Manchester (UK) in 2005, and then his Ph.D. in organic chemistry working with Professor John D. Sutherland in 2009. He continued his research at Manchester as an EPSRC Doctoral Prize Fellow, before moving to the laboratory of Professor Jack W. Szostak as postdoctoral fellow at Massachusetts General Hospital (USA). He joined University College London (UK) in 2011, where he is currently Reader in Organic Chemistry. His research interests include the origins of life, photochemistry, nucleotide, peptide, lipid, and carbohydrate chemistries, green chemistry, ribozymes, multicomponent reactions, chirality and crystal engineering.
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