

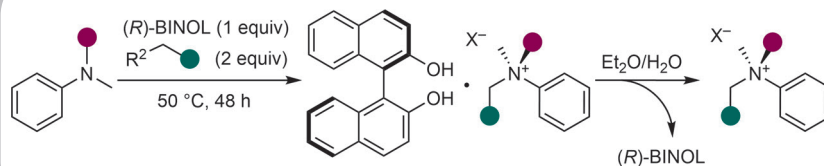
Synform

People, Trends and Views in Chemical Synthesis

2022/03

Enantioselective Synthesis of Ammonium Cations

Highlighted article by M. P. Walsh, J. M. Phelps,
M. E. Lennon, D. S. Yufit, M. O. Kitching



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Dear Readers,

Uncertainty is never good for any business, and this includes research. Some time ago, the UK government promised UK-based researchers who had successfully applied to Horizon Europe grants “safety net funding”, meant to cover the “first wave” of seven EU calls – including European Research Council (ERC) starting grants – in case the country failed to associate with Horizon Europe in time. Last month, 46 UK-based ERC starting grant winners were announced, but the UK has not yet activated the promised back-up funding system and these successful applicants were told to move to the EU (or an associated country) to be sure of keeping their multimillion grants. This situation is certainly detrimental for the researchers, but it is even more detrimental for the UK research system, as it is becoming increasingly clear that ERC funding – and in general all Horizon Europe funding – has the potential of luring away from the UK some of the brightest and most successful researchers. Research needs stability and open frontiers for enabling effective collaborations among scientists; my feeling is that the UK is drifting away from the rest of Europe, and from the European funding system, thus risking a progressive marginalisation and isolation. There is still some time for the UK to sign on the dotted line of the Horizon EU association, but “political” issues – such as the Northern Ireland Protocol – which have very little to do with science, need to be resolved first, and perspectives are not too encouraging. Joint research programmes and collaborations between EU- and UK-based researchers are critically important, let’s just hope that for once common sense will prevail over politics, because global challenges and threats – such as the COVID 19 pandemic and climate change – are not impressed by borders, let alone by Brexit.

Switching to the content of this new SYNFORM issue, the first literature coverage article deals with the Ni(II)-catalyzed syn- δ -aryl- γ -amination of allyl, homoallyl

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and bishomoallyl-amines protected as picolinamides, reported by C. Wang (P. R. of China). The second article covers a powerful strategy – developed by J. S. M. Samec (Sweden) – for better exploiting the potential of lignin, the second-most abundant organic material on earth, by using a novel oxidative cleavage of C–C bonds to generate simple and valuable products, such as *p*-benzoquinone derivatives. The third article is a Young Career Focus interview with H. J. Yoon (Republic of Korea) about his research interests, especially the emerging area of polymer mechanochemistry. Last but certainly not least, a report on the ground-breaking *Nature* article by M. Kitching (UK) describing the stereo-controlled preparation, isolation and characterisation of hitherto elusive chiral non-racemic ammonium cations.

Enjoy your reading!

Matteo Zanda

Contact

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

Directed Nickel-Catalyzed Regio- and Diastereoselective Arylamination of Unactivated Alkenes

Nat. Commun. **2021**, *12*, 6280

Professor Chao Wang's group, from Tianjin Normal University (P. R. of China), has been interested in transition-metal-catalyzed difunctionalization of unactivated alkenes via a directing group strategy for some time. Previously, the group reported a regioselective Ni-catalyzed 2,1-diarylation and aryl-alkylation of homoallylic amine derivatives, bearing a picolinamide (PA) auxiliary, with commercially available arylboronic acids and organohalides.¹ "Transition-metal-catalyzed three-component, dicarbo-functionalization of alkenes, which enables the expeditious construction of molecular complexity, has drawn tremendous attention in recent years," said Professor Wang.²⁻⁴ "Although intermolecular three-component dicarbo-functionalization of alkenes has achieved some success in recent years, carbohetero-functionalization of olefins remained underexploited and rare. C–C and C–N bonds are two of the most ubiquitous bonds in nature, and arylamination of olefins represents a powerful and attractive synthetic tool for the simultaneous introduction of aryl and amino groups across alkenes, to enable the rapid increase in molecular complexity from abundant and readily available materials," explained Professor Wang. He continued: "Intramolecular arylamination with an alkene acceptor tethered to either the aryl halide or active nitrogen functionality using transition-metal catalysts has been developed for the synthesis of nitrogen-containing cycles. In comparison, intermolecular arylamination providing access to aryethylamine-based acyclic molecules is particularly difficult and remains rare, owing to its high entropic cost and the problem of controlling the chemoselectivity of multicomponent reactions."

This project emerged when Professor Wang discussed with his students the possibility of achieving the challenging arylamination by replacing organohalides with aminating electrophiles (Scheme 1A). "To the best of our knowledge, intermolecular olefin arylamination of unactivated alkenes with arylboronic acids and N–O electrophiles was rather elusive," said Professor Wang. He continued: "Indeed, the development of this protocol for arylamination of unactivated alkenes was limited by three fundamental issues: (1) undesired competitive cross-coupling between arylboron reagents and O-benzoylhydroxylamines, (2) the low binding affinity of unactivated alkenes to metal centers, especially for internal alkenes, and (3) the difficulty to control regioselectivity, such as arylamin-

ation vs aminoarylation, and 1,2-arylamination vs 1,n-arylamination via chain-walking isomerization."

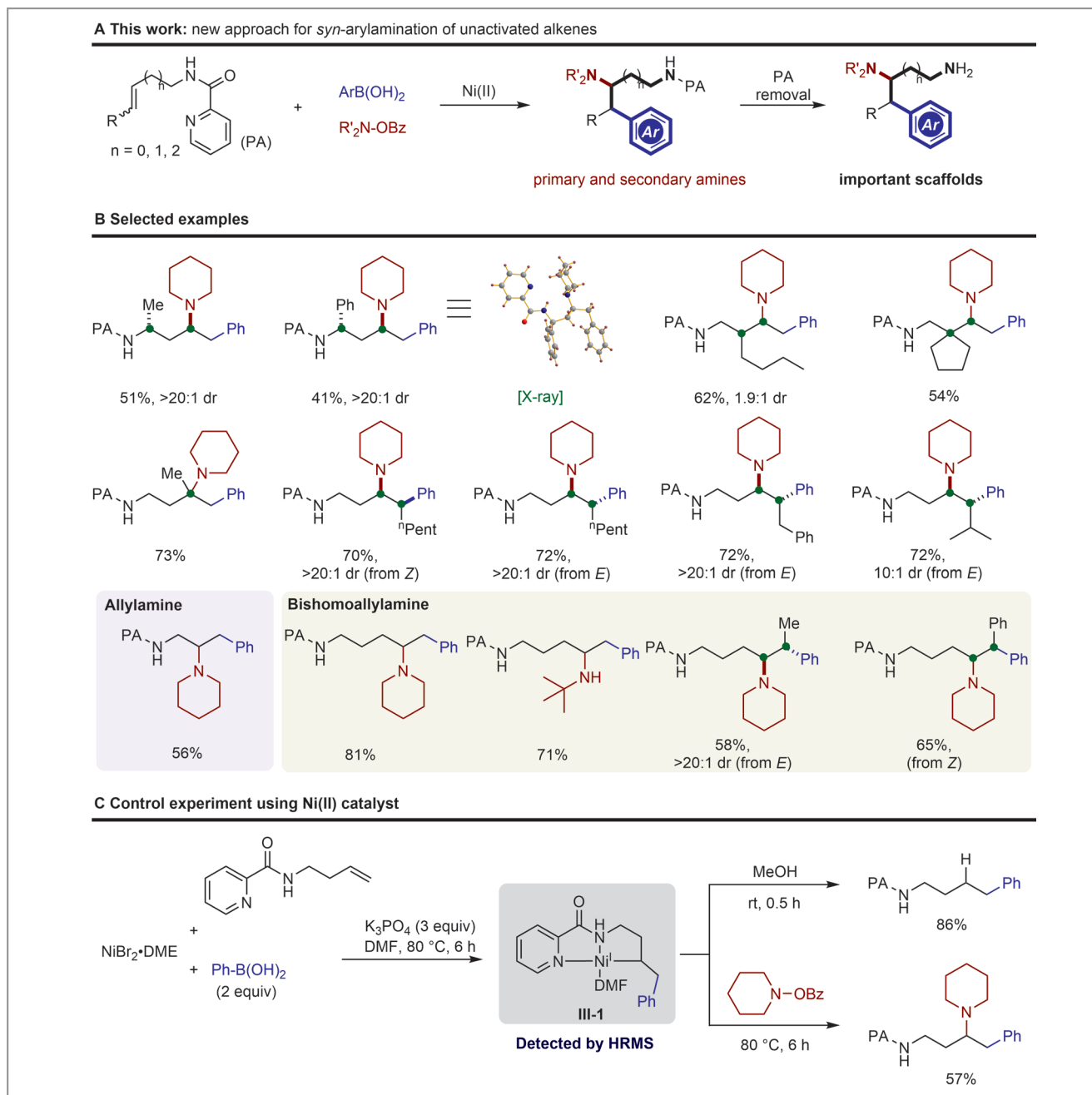
Professor Wang recalls that the group started this investigation with an extensive optimization campaign to enable Ni-catalyzed arylamination of homoallylic amine substrates containing a directing group with phenylboronic acid and piperidino benzoate and the results indicated the coordination of the PA directing group and NiBr₂·DME was an excellent catalytic system to afford the product of 1,2-arylamination of unactivated alkenes. "This new protocol was compatible with terminal and internal alkenyl amines of different chain lengths, a broad range of primary and secondary amine sources, and exhibited excellent functional group tolerance (Scheme 1B)," said Professor Wang. Interestingly, the reaction of α -substituted terminal alkenes led to the formation of *trans*-isomeric products with high levels of diastereoselectivity, in which two skipped stereocenters were established. "To the group's delight, PA protected allylic amines and a variety of terminal and internal bishomoallylamines underwent arylamination to regioselectively provide the desired products, indicating four- and six-membered nickelacycles were formed and these can be stabilized in the catalytic system. In addition, our protocol was suitable for large-scale synthesis and the synthetic utility of this method was further demonstrated by the modification of pharmaceutical agents," recalled Professor Wang.

To elucidate the mechanism, a series of control experiments were conducted. For example, stoichiometric reaction of the alkene substrate with NiBr₂·DME followed by treatment with phenylboronic acid was conducted to generate Ni(I)-Ar complex (Scheme 1C). Addition of methanol to the solution of complex furnished the hydroarylation product in 86% yield upon alcoholic protonation, and the complex reacted with piperidino benzoate to afford the expected product in 57% yield. Professor Wang commented: "These results demonstrated that the reaction could be initiated by transmetalation of arylboronic acid with Ni(II) precatalyst and subsequent alkene insertion occurred prior to engagement with an electrophile to give the observed regiochemical outcome. While attempts to isolate and identify the intermediate failed, the proposed nickel intermediate ligated with DMF was detected by HR-MS (ESI) analysis." As such, Professor Wang proposed

that the reaction proceeds via a Ni^I/Ni^{III} catalytic cycle rather than a Ni⁰/Ni^{II} cycle.

Professor Wang concluded: "We have disclosed a methodology for the regio- and diastereoselective intermolecular arylamination of unactivated alkenes with a base-metal catalyst and readily available reagents, under simple conditions.

The removable bidentate PA auxiliary facilitated the formation of stabilized 4-, 5-, or 6-membered nickelacycles and enabled the difunctionalization of both terminal and internal alkenyl amines, leading to the concomitant introduction of important aryl groups and structurally diverse amino groups across the C=C bonds, with good functional group compatibility. We be-



Scheme 1 Directed nickel-catalyzed regio- and diastereoselective arylamination of unactivated alkenes

lieve our work will open a new avenue for the regioselective difunctionalization of unactivated alkenes, and facilitate progress in drug discovery. The expansion of this strategy to other electrophiles for alkene carbohetero-functionalization is currently underway in our lab.”

Mattias Fenech

REFERENCES

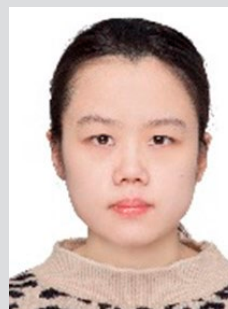
- (1) S. Wang, C. Luo, L. Zhao, J. Zhao, L. Zhang, B. Zhu, C. Wang *Cell Rep. Phys. Sci.* **2021**, *2*, 100574.
- (2) J. Derosa, O. Apolinar, T. Kang, V. T. Tran, K. M. Engle *Chem. Sci.* **2020**, *11*, 4287–4296.
- (3) S. O. Badir, G. A. Molander *Chem* **2020**, *6*, 1327–1339.
- (4) L. M. Wickham, R. Giri *Acc. Chem. Res.* **2021**, *54*, 3415–3437.

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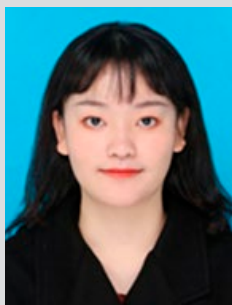
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Chao Wang received his Ph.D. from Soochow University (P. R. of China) in 2015 under the supervision of Yingming Yao and Yingsheng Zhao. After postdoctoral studies with Professor Shaozhong Ge (2015–2018) at National University of Singapore, he started his independent career as a full professor at the College of Chemistry at Tianjin Normal University (P. R. of China) in 2018. Wang's research interests focus on base-metal-catalyzed (asymmetric) functionalization of alkenes.

Oxidative Cleavage of C–C Bonds in Lignin

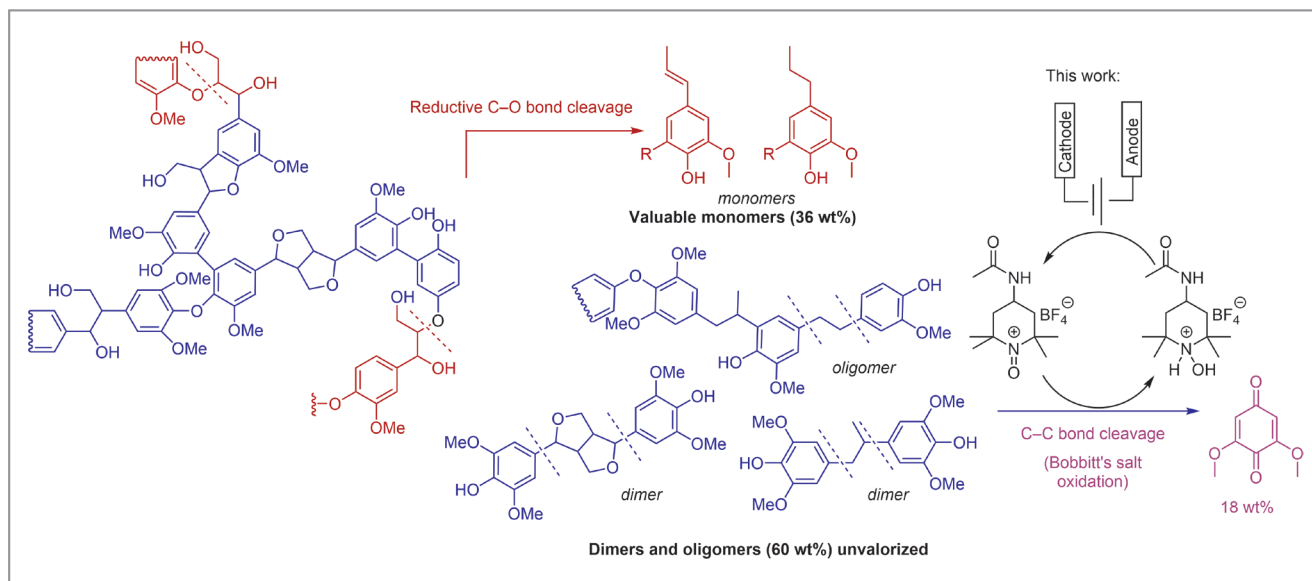
Nat. Chem. **2021**, *13*, 1118–1125

Lignin – which is second only to cellulose as the most abundant organic material on earth – is a complex water-insoluble polymer, composed largely of phenylpropane units which are generally linked through ether bonds (predominantly the aryl-aryl ether-type). Lignin is present mostly in plants' cell walls, representing a key constituent in the support tissues of all terrestrial plants. Industrially, the conversion of cellulose and hemicellulose into fuels and chemicals leaves lignin as a byproduct. To date, relatively few uses have been found for lignin, other than as a fuel. Professor Joseph S. M. Samec, from Stockholm University (Sweden), has a longstanding interest in lignin chemistry, within the group's broader research interests in green chemistry and biomass conversion. "In 2018 we had a whole day seminar in our research group and tried to think of research problems within our field that needed addressing further by the community of lignin chemistry. It's as true now as it was then that lignin chemistry was mainly focused on cleaving β -ether bonds (Scheme 1)," explained Professor Samec. He continued: "These bonds are prevalent in lignin; however, methods that can cleave 100% of these bonds still limit the yield to around 40% of desired aromatic monomers.¹ To enable higher yields, one would need to cleave C–C bonds, which requires pressures and temperatures found in oil refin-

eries (above 360 °C and 60 bars). Thus, there was an obvious unexplored research direction, albeit very challenging."

Examples of oxidative cleavage of aryl–C bonds can be traced back to the works of Joseph Bozell,² where Co-salen catalyzed oxidation of *p*-substituted phenols led to the formation of *p*-benzoquinones. "Oxidative cleavage of C–C bonds in lignin to generate simple and valuable products – e.g. derivatives of *p*-benzoquinone – seemed a very attractive, yet challenging approach, as an oxidation of phenols is generally complex and unselective,"³ explained Professor Samec, who noted that oxidation of lignin and lignin model compounds using TEMPO and its derivatives were comprehensively investigated by Stahl's group.^{4,5} "However, the main focus of these studies was on the β -ether bonds, and the fate of other types of linkages was largely unaddressed," commented Professor Samec, adding: "As we were interested in the cleavage of other types of bonds in lignin structure (C–C bonds) which remain intact during the vast majority of lignin depolymerization methodologies, we performed our studies on the residual 'unvalorized lignin', possessing no β -ether bonds, and the corresponding model compounds."

4-Substituted TEMPO-derivatives, such as 4-acetamido-TEMPO, are oxidants that are relatively cheap and easy to



Scheme 1 The novel oxidative cleavage of C–C bonds in lignin

handle. Moreover, the oxidant can be regenerated electrochemically. Professor Samec said: "Initial results on the lignin model compounds were very promising, as we observed a facile formation of 2,6-dimethoxy-*p*-benzoquinone at room temperature, using Bobbitt's salt – an oxidized form of 4-acetamido-TEMPO. However, in order to achieve high selectivity, we had to go through optimization of reaction conditions and mechanistic studies. The mechanism shed light on the importance of having a nucleophilic reagent present to prevent condensation reactions and also significant difference in reactivity of mono-methoxy and dimethoxy phenolic models. Even though upon optimization of the reaction conditions the product was generated in high selectivity from both the model compounds and 'unvalorized lignin' (lignin possessing no β -ether bonds), usage of a stoichiometric amount of oxidant was still a disadvantage. We joined forces with Prof. Mats Johansson at Stockholm University in order to re-oxidize the reduced form of Bobbitt's salt. Fortunately, this collaboration worked very well, and together we were able to perform the reaction in a catalytic fashion, where the reduced form of the oxidant was isolated from the reaction mixture and subjected to electrochemical oxidation. We were able to perform five consecutive cycles with a minimal loss in conversion."

Professor Samec concluded: "We are very excited about these results, not only that we can cleave C–C bonds in lignin but also that we generate dimethoxybenzoquinone, which is a precious fine chemical, in near perfect selectivity using benign reaction conditions. We hope these results will inspire more scientists to continue developing benign methods for other C–C bonds in lignin and other polymers."

Mats Johansson

REFERENCES

- (1) M. M. Abu-Omar, K. Barta, G. T. Beckham, J. S. Luterbacher, J. Ralph, R. Rinaldi, Y. Román-Leshkov, J. S. M. Samec, B. F. Sels, F. Wang *Energy Environ. Sci.* **2021**, *14*, 262–292.
- (2) J. J. Bozell, B. R. Hames, D. R. Dimmel *J. Org. Chem.* **1995**, *60*, 2398–2404.
- (3) D. Schilter *Nat. Rev. Chem.* **2018**, *2*, 0129.
- (4) A. Rahimi, A. Azarpira, H. Kim, J. Ralph, S. S. Stahl *J. Am. Chem. Soc.* **2013**, *135*, 6415–6418.
- (5) M. Rafiee, M. Alherech, S. D. Karlen, S. S. Stahl *J. Am. Chem. Soc.* **2019**, *141*, 15266–15276.

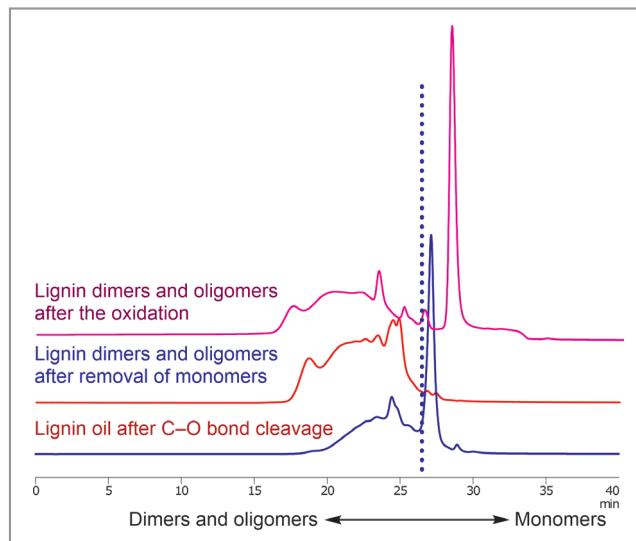
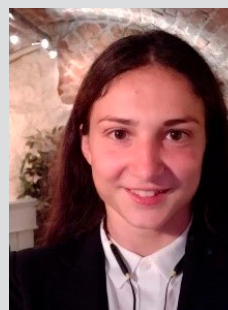


Figure 1 HPLC analysis of treated lignin samples. See Scheme 1 for the structures of monomers, dimers and oligomers.

About the authors



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Elena Subbotina received her B.Sc. and M.Sc. degrees in organic chemistry from Lomonosov Moscow State University (Russian Federation) in 2014 and her Ph.D. in organic chemistry from Stockholm University (Sweden) in 2020 under the supervision of Prof. Joseph Samec. During her PhD studies she worked as a visiting PhD student in ITQ (Valencia, Spain) under the supervision of Prof. Avelino Corma. She is currently a postdoctoral fellow at KTH Royal Institute of Technology (Stockholm, Sweden) under the supervision of Prof. Lars Berglund and Prof. Martin Lawoko. Dr. Subbotina has received a Marie Curie fellowship and will go to Yale University (USA) and pursue a postdoc under the supervision of Prof. Paul Anastas. Her research interests include biomass valorization and bio-based materials.

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Dr. T. Rukkijakan

Thanya Rukkijakan was born and raised in Saraburi, Thailand. He obtained his B.Sc. in biochemistry from Kasetsart University (Thailand) in 2005 and worked as a scientist in microbiology at CPF (Thailand) PCL. In 2009, he started his M.S. in organic chemistry under the supervision of Assoc. Prof. Pitak Chuawong at Kasetsart University and received his Ph.D. in chemistry in 2018. During his doctoral studies, he participated in a research exchange program at Uppsala University (Sweden) supervised by Prof. Joseph S. M. Samec, and Nagoya University (Japan) supervised by Prof. Toshio Nishikawa. Since 2019, he has worked as a postdoctoral researcher in Prof. Joseph S. M. Samec's group at Stockholm University.



Dr. M. D. Márquez Medina

Maria Dolores Márquez Medina received her PhD in June 2019 at the University of Córdoba (Spain). Prior to this, in 2015 she spent time in the Christian Doppler Laboratory for Microwave Chemistry of Prof. C. O. Kappe at the University of Graz (Austria), and for four months in 2018 she had a doctoral stay at the University of Stockholm under the direction of Professor Joseph S. M. Samec, working in the field of catalysis. After completing her Ph.D., she worked in the CSIC catalysis and petrochemical center (ICP) to carry out a research project under the responsibility of the ENAGAS company. At present, she is developing her scientific work in the research group Supramolecular Analytical Chemistry Research Group (FQM-186) at the University of Córdoba. Her entire career has been focused on the use and transformation of plant waste using green chemistry.



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Xiaowen Yu was born in Baoji, Shaanxi, P. R. of China. She received her B.Eng. in polymer science and engineering from Beijing University of Chemical Technology (P. R. of China) in 2013 and Ph.D. in chemistry from Tsinghua University (P. R. of China) in 2018. She was a postdoctoral researcher at Stockholm University (Sweden) under the supervision of

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Prof. M. Johnsson

Mats Johnsson received his Ph.D. in 1993 from Stockholm University, Sweden. He has been guest researcher at CEMES/CNRS in Toulouse, France working with Prof. Jean Galy. He is now professor of inorganic chemistry at Stockholm University and has led several projects on ceramic materials, synthesis of ceramic whiskers, and synthesis and physical properties of low dimensional materials. His research has focused during the last few years on electrocatalytic water splitting and alcohol oxidation. He is Director of Studies at the Department of Materials and Environmental Chemistry at Stockholm University and he is actively involved in teaching.



Prof. J. S. M. Samec

Joseph S. M. Samec received his Ph.D. in 2005 from Stockholm University, Sweden. He was a visiting researcher for Professor Charles P. Casey at the University of Wisconsin (USA) in 2002. During 2006–2007, he joined the California Institute of Technology, USA as a postdoctoral researcher with Robert H. Grubbs (Nobel Laureate). In 2009, he started his independent research career at Uppsala University (Sweden) where he was promoted to associate professor in 2011. In 2015, he moved to Stockholm University and was then promoted to full professor in 2017. His research interest focuses on green chemistry in organic synthesis and biomass conversion and its applications. In 2013, he founded RenFuel AB, a spin-off company from his academic research that produces biofuels from lignin, and in 2020 he founded RenFuel Materials that produces lignin-based materials.

Young Career Focus: Professor Hyo Jae Yoon (Korea University, 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 Professor Hyo Jae Yoon (Korea University, Republic of Korea).

Biographical Sketch



Professor H. J. Yoon

Hyo Jae Yoon obtained his BSc in chemistry from Sogang University (Korea). He then went on to pursue his PhD in materials chemistry at Northwestern University (USA) under the supervision of Professor Chad A. Mirkin. After a stint at Harvard University (USA) as a post-doctoral researcher in the group of Professor George M. Whitesides, he took up a position at Korea University in 2014.

mechanophores, and unveil detailed mechanisms of mechanochemical reactions.

SYNFORM *When did you get interested in synthesis?*

Professor H. J. Yoon My first experience in synthesis was during a master course where I was fascinated by asymmetric synthesis of biologically active molecules. This interest was further consolidated at Northwestern University where I was trained as an organometallic and coordination chemist, concerned with synthesizing supramolecular complexes as allosteric enzyme mimics. At Harvard, I utilized my synthesis skills and knowledge for the research of materials and surface chemistries.

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

Professor H. J. Yoon Organic synthesis in the last century has been predominantly explored under thermal or photochemical conditions. Reactions under conditions other than these traditional ones can offer new and/or greener synthetic routes. For example, part of our research concerns force-induced structural transformation of mechanophores. Mechanochemical conditions can allow one to steer chemical reactions toward routes that are inaccessible under the traditional conditions. Another example involves organic synthesis by means of electrochemistry – electrosynthesis and electric field-assisted catalysis. Electrosynthesis has a huge potential for efficient and sustainable synthetic methodologies and can be useful for industrial applications; electric field-assisted catalysis has been recently demonstrated in molecular tunneling devices. Indeed, these research areas have emerged in recent years and can pave the way for new applications.

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

INTERVIEW

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

Professor H. J. Yoon My research group is concerned with resolving challenges in electronics and energy applications. Recently, we focused on three separate areas: molecular electronics and thermoelectrics and polymer mechanochemistry. In molecular thermoelectrics, we design and synthesize molecules and examine the Seebeck effect – conversion of heat into electricity – of them using our own metrology technique, which is based on a liquid metal electrode. In molecular electronics, we employ 2,2'-bipyridine-terminated *n*-alkanethiol, as a molecular diode, for drawing inferences on structure-tunneling relations. In polymer mechanochemistry, we are interested in discovering new mechanophores and mechanochemical reactions. We develop synthetic methodologies to incorporate new mechanophores into polymers, explore force-induced structural transformations of the

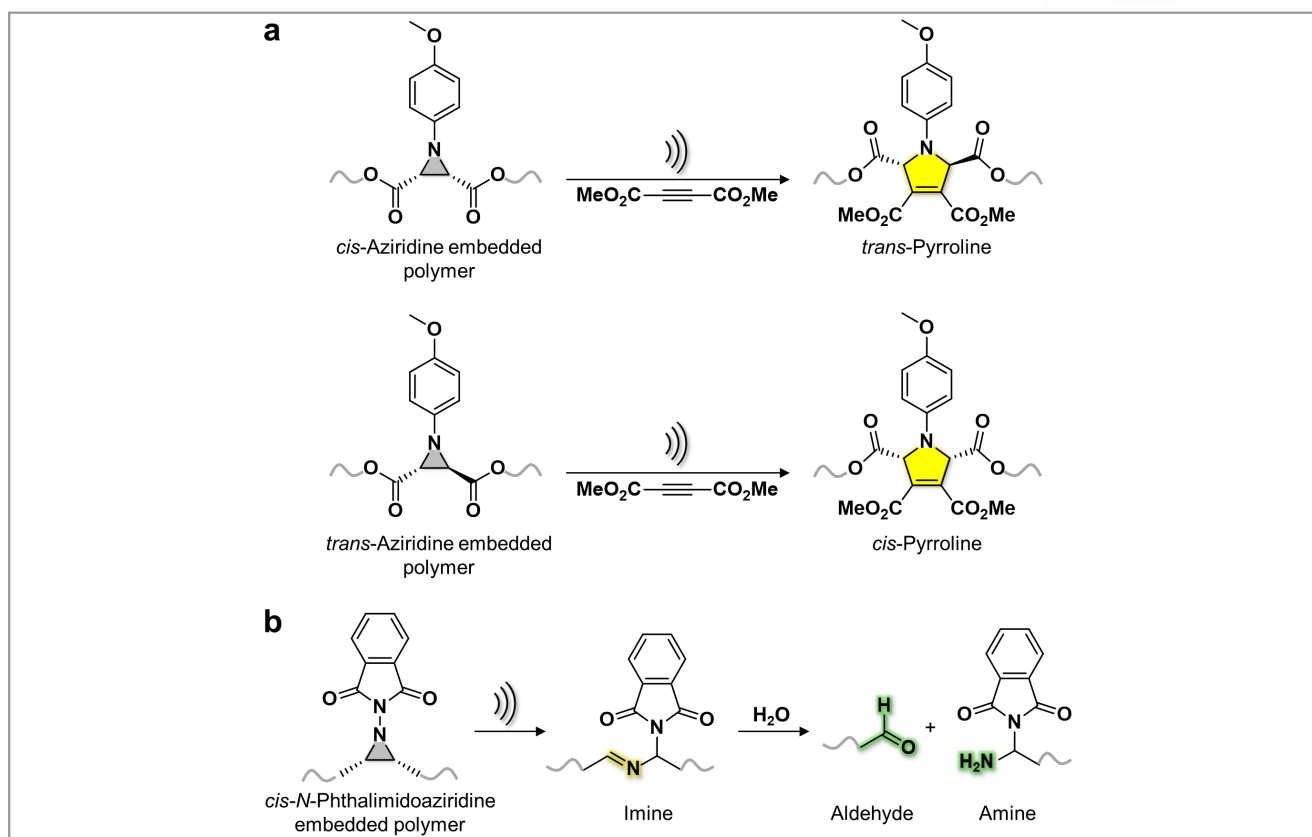
Professor H. J. Yoon Our research is fundamental in nature and based mainly on a physical-organic approach. Namely, one component in a system – it can be a chemical reaction or a solid-state device – is varied while keeping others constant. This approach permits one to draw structure–property relations and gives some hints as to solving problems of our interest; to quote Whitesides' words, it is like “a Swiss Army knife”. Recently, our research group focused on investigating charge movement and energy conversion in well-aligned organic and organometallic molecules, and polymers on surface. Some of the currently ongoing projects aim to i) decipher mechanisms of charge transport, caused by external electric field or thermal gradient, at the organic-electrode interfaces, and ii) develop new mechanochemical reactions, which may be useful for tackling environmental problems caused by polymers.

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

Professor H. J. Yoon In polymer mechanochemistry, we demonstrated the potential of aziridine for a new mechano-

phore. Last year, we successfully synthesized polymers containing *trans*- or *cis*-aziridines and found that the aziridines react with a dipolarophile under mechanochemical conditions based on ultrasound sonication although they are robust in structure – they do not undergo *cis*–*trans* isomerization under the same conditions (*Angew. Chem. Int. Ed.* **2020**, *59*, 4883) (Scheme 1a). This year, we synthesized a polymer containing aziridine with a different *N*-substituent, *cis*-*N*-phthalimidoaziridine. Interestingly, the aziridine undergoes migration of the *N*-phthalimido group to yield imine under mechanochemical conditions, but not thermal (*Angew. Chem. Int. Ed.* **2021**, *60*, 23564) (Scheme 1b). In the presence of water, the resulting imine is easily hydrolyzed, bifurcating into amine and aldehyde. In molecular thermo-electrics, we reported a new, efficient large-area technique to measure the Seebeck coefficient of molecular monolayers (*Nano Lett.* **2018**, *18*, 7715). Using this technique, we explored how the Seebeck coefficient is related to the (supra) molecular structure of the active component in molecular-scale tunneling devices (*Adv. Mater.* **2021**, *33*, 2103177; *ACS Cent. Sci.* **2019**, *5*, 1975).

Mattias Farnik



Scheme 1 Mechanochemical reactions of aziridine mechanophores embedded in polymers

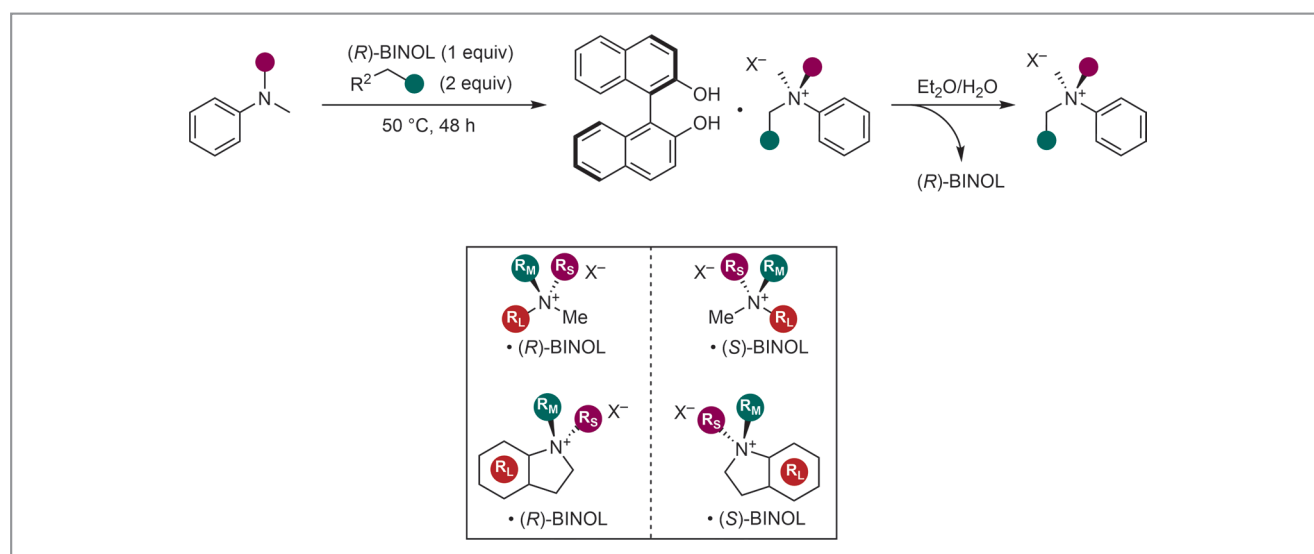
Enantioselective Synthesis of Ammonium Cations

Nature 2021, 597, 70–76

Recently the group of Dr. Matthew Kitching at Durham University (UK) reported in *Nature* a fascinating and groundbreaking achievement: the enantioselective synthesis of elusive stereogenic ammonium cations. “Chirality has always fascinated synthetic chemists. Given that the biological world is one rich in sources of chiral information, the importance of enriched stereocentres on the activity and selectivity of organic molecules has been of longstanding interest to the organic chemistry community,” said Dr Kitching. “To date, the attention of the synthetic community has been focused on the enrichment of carbon stereocentres, with successful strategies for their construction being realised by many generations of synthetic chemists. However, the construction of stereochemical information at heteroatomic centres has received less attention. Whilst phosphorus and sulphur have seen solutions to controlling the stereochemistry of these centres, nitrogen heteroatoms have been avoided due to this atom’s reputation for stereochemical lability.” Dr. Kitching commented further: “As most undergraduate chemists learn, nitrogen is difficult to isolate in an enriched form due to this centre’s tendency to undergo rapid inversion enabled by quantum tunnelling. We wondered whether we could use this rapid inversion as a way to access ammonium cations in an enriched form through supramolecular recognition.”

According to the authors of this research, nitrogen stereocentres can be set in the context of other stereochemical information, such as in the tropane alkaloids, but preparation of the nitrogen epimer is cumbersome and examining the effect of inversion of the ammonium cation’s stereochemistry is difficult to untangle from the rest of the stereochemical framework of these chiral systems. Dr. Kitching said: “We were genuinely surprised by the lack of processes capable of setting this common heteroatom – the oldest known heteroatomic stereocentre – a problem we thought would be interesting to explore.”

Dr. Kitching went on to explain how co-author Mark Walsh’s PhD project, which was aimed at exploring how the stereochemistry of nitrogen centres could affect chemical transformations, was central for this work. “It was during this work we realised that there really weren’t any good ways to prepare these stereocentres in a synthetically useful way,” explained Dr. Kitching. He continued: “All previous methods relied on resolution which made accessing material to study the stereochemistry of these transformations exceedingly laborious and we realised that this problem – synthesising an enriched nitrogen stereocentre – would have to be solved before any meaningful progress could be made in examining the importance of nitrogen stereochemistry.”



Scheme 1 Reaction conditions and selectivity rules for the enantioselective synthesis of ammonium cations

Dr. Kitching recalls that this was not an easy undertaking and it wasn't until the second year of Mark's PhD that the first results of recognition of a chiral ammonium cation by BINOL were obtained (Scheme 1). "Taking this initial result to a dynamic asymmetric synthesis would take a further two years of study, finally being unambiguously proven in May 2019," explained Dr. Kitching. He went on: "Delaying the communication of the recognition process, to allow the development of the dynamic asymmetric synthesis, was difficult as this would be the first publication from the group, and we felt significant pressure to communicate results early – but we knew that if we could achieve a dynamic process it would be well received by the community."

Dr. Mark Walsh commented: "The initial hit for the recognition experiments came from trying to replicate Eiji Tayama's work (*Tetrahedron: Asymmetry* **2009**, *20*, 2600 and references therein). In his work, recognition of an ammonium cation by BINOL could be achieved through supramolecular recognition. I tried Tayama's prep on the ammonium cations I was investigating and found a ternary complex was formed, precipitating from chloroform. Later, after a more thorough reading of Tayama's manuscript and its footnotes, I realised this was quite unexpected as Tayama's approach relied on recognition through a hydroxyl group present within the cation's structure."

Dr. Walsh further commented that many of the experiments were fairly laborious to conduct, although they gave important information. He said: "Manually recording optical rotation through polarimetry over an eight-hour period at two-minute intervals was maddening, but necessary."

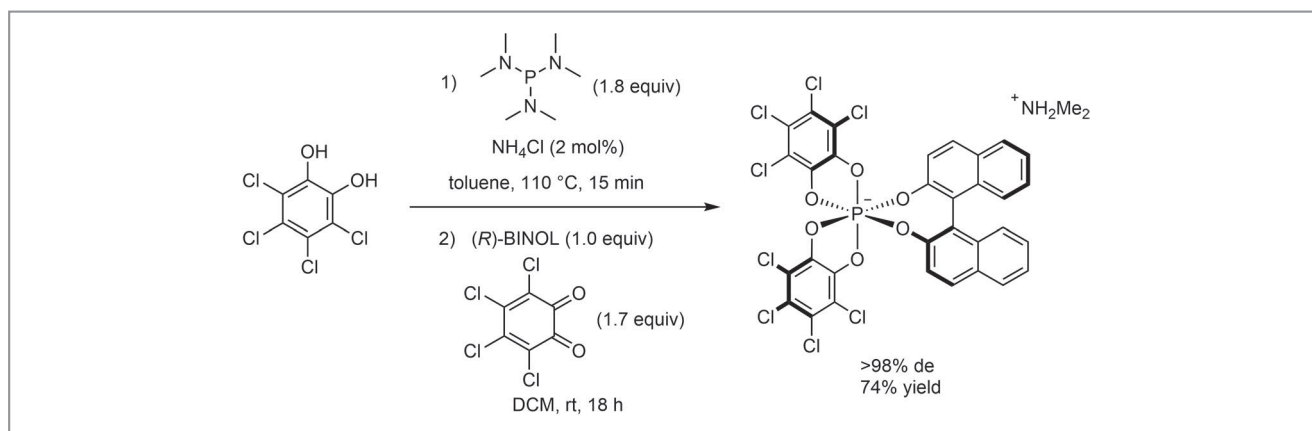
Dr. Kitching praised Dr. Walsh's dedication: "It was, on occasion, difficult to ask Mark to perform some of the experiments that would be required from reviewers, but he always

went into the lab ready to put on new reactions that would give us the information we'd need to develop the process further."

The authors explained that one of the most difficult parts of this work was determining the enantiomeric excess of the ammonium cations they'd isolated. Despite extensive HPLC screening, no column/solvent combinations allowed separation of the ammonium cation enantiomers. Dr. Walsh revealed: "After about six months of screening various processes we found an NMR chiral shift reagent that was capable of revealing the enantiomeric enrichment (Scheme 2). This was all made much harder without authentic enriched samples to interrogate."

Dr. Kitching also paid tribute to the crystallography unit at Durham University: "This excellent service, led by Dmitry S. Yufit, was fundamental to this project. We're incredibly lucky to have such a capable crystallography unit in the department to train PhD students like Mark and provide the unambiguous confirmation of the assignment of the stereocentres we've set (Figure 1). We'd be lost without him!"

Dr. Kitching also revealed some unforeseen results found during the work: "The enrichment of the ammonium cations over time was totally unexpected. It required a bit of work to prove that there wasn't some form of autocatalysis happening, but ultimately we're pretty sure that this gives evidence that there's a reversible process that leads to an enrichment of the cation by preferential complexation to BINOL." He continued: "Another unexpected result was a tentative rule that allows the prediction of the sense of enrichment of an ammonium cation using our process. These sorts of empirical rules are often viewed with some uncertainty by the synthetic community. However, they seem to hold ... for now!" Dr. Kitching revealed some further work being undertaken by his group:



Scheme 2 Synthesis of the NMR chiral shift reagent used to assess the enantiomeric enrichment of ammonium cations

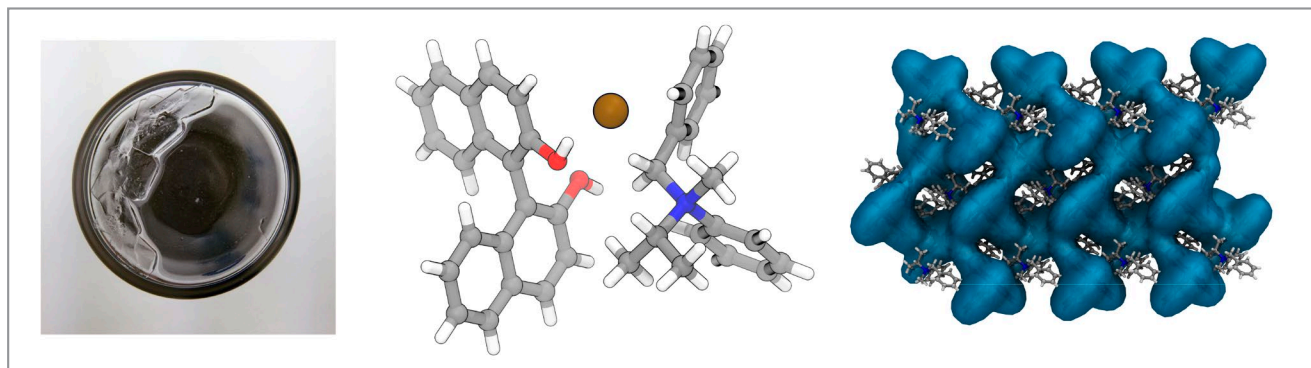


Figure 1 Slow evaporation of EtOH solutions of chiral ammonium cations provides single crystals (left) which after crystallographic analysis provide ultimate proof of the sense of chirality installed in the ammonium cations (centre). Analysis of the crystal packing of these structures shows hydrogen bonding networks key to the selectivity in the synthesis of these compounds.

“Whilst we can predict the sense of enrichment, which ammonium scaffolds will participate in the recognition is still beyond us. Our group is currently exploring this and we hope to report these results imminently.”

“Having access to enriched chiral ammonium cations is only the first step,” said Dr. Kitching, who concluded: “Everywhere that chemists have found chirality, we know that it has important implications for the reactivity and selectivity of processes that they are involved in. With access to enriched nitrogen cations, we hope that those interested in the stereochemistry of organic molecules will have a new stereogenic centre to explore.”

Mattias Forsell

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Mark P. Walsh received his BSc (2016) from Dublin City University (Ireland). He then moved to Durham University (UK) to pursue a PhD (2020) under the supervision of Dr Matthew Kitching. His research interests include X-ray crystallography and supramolecular chemistry. He is currently conducting postdoctoral research under Prof Jonathan Clayden at the University of Bristol (UK).

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Matthew O. Kitching completed his degree in Natural Science at the University of Cambridge (UK) in 2006. Following this, he joined Prof. Steven V. Ley's group for his doctoral studies on the use of enabling technologies in organic synthesis. In 2010, he joined Prof. Victor Snieckus' group at Queen's University in Kingston (Canada) to conduct postdoctoral studies on combined directed-ortho-metalation/cross-coupling approaches for the synthesis of polysubstituted heterocycles. In 2013, Matt returned to the UK to study under direction of Prof. David Leigh FRS, investigating the use of molecular machines in chemical synthesis. In 2016, Matt was appointed as a Lecturer at Dublin City University (Ireland), before moving to Durham in 2017 where he now occupies the position of Assistant Professor, running a research group focused on the use of dynamic processes in chemical synthesis.

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