Synform

People, Trends and Views in Chemical Synthesis

2020/05

Formyl-Selective Deuteration of Aldehydes with D₂O via Synergistic Organic and Photoredox Catalysis

Highlighted article by J. Dong, X. Wang, Z. Wang, H. Song, Y. Liu, Q. Wang

Contact

Your opinion about Synform is welcome, please correspond if you like: marketing@thieme-chemistry.com



Dear Readers,

Sadly, we are all in lockdown, and as much as I am enjoying spending some time with my family, I must admit that working from home for me is not as productive as being in my office. I am glad for all the colleagues who are tweeting about how productive they are while working from home, and frankly I am also a bit jealous of their efficiency and capacity to concentrate. To be honest, I have no excuses, as my children are grown-ups and the main distraction is my cat Zorro, who occasionally jumps on the laptop looking for cuddles, but the truth is simply that I have too many thoughts, too many worries, too many questions on how the future might be after this unprecedented epidemic. How the hell is one supposed to work in a situation like this??? Kudos to you, my productive friends and colleagues, but I am struggling, I am distracted, I am just totally out of focus. I am just glad that I managed to write something in this editorial, because 10 minutes ago my brain was in a situation of high vacuum. Luckily, there is some consolation in SYNFORM and some very exciting science that brightens up these bleak days a bit. We start with a Young Career Focus interview with the brilliant organic electrochemist Kevin Lam (UK), followed by Q. Wang (P.R. China) and his clever and selective strategy to perform deuteration of the aldehyde CHO function. The next article comes again from P. R. of China and specifically from the group of G. Yin, with a very original Ni-catalyzed version of the Suzuki-Miyaura cross-coupling. The last article comes from the place where I have been working recently – which is completely unprecedented in the history of SYNFORM – and is a contribution from the groups of A. Malkov and B. Buckley (UK) with their elegant electrochemical β-hydrocarboxylation of substituted olefins.

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Enjoy your reading, my friends, and stay safe and healthy!!!



Contact

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

Young Career Focus: Dr. Kevin Lam (University of Greenwich, UK)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Kevin Lam (University of Greenwich, UK).

Biographical Sketch



Dr. K. Lam

In 2010, **Kevin Lam** received his PhD in Medicinal and Synthetic Organic Chemistry from the Catholic University of Louvain in Belgium, under the supervision of Professor István Markó. His doctoral work explored the use of electrochemistry and photochemistry as green alternatives to activate organic molecules. This work resulted in the development of a new radical-based deoxygenation reaction (the Markó–Lam reaction).

After his PhD, he moved to the University of Vermont (UVM, USA). His research focused on applying analytical/physical electrochemistry alongside spectroscopy to study the complex redox behaviour of organometallic compounds.

This work bolstered the use of weakly coordinating electrolytes/solvents as an electrochemical medium to allow for the generation and characterisation of highly reactive and unstable 17e⁻ organometallic radical cations. Additional work at UVM led to the pioneering of a new method to modify electrode surfaces through an ethynyl linkage. The covalent attachment of molecules to an electrode surface is fundamental to the field of molecular electronics and numerous materials applications.

In 2013, he accepted a position of Assistant Professor at Nazarbayev University in Astana (Kazakhstan). During his time there, Kevin developed a new research program in the field of Molecular Electrochemistry. His work led to the development of new organometallic anticancer compounds as well as to the discovery of novel, efficient and green electrocatalysts for CO_2 recycling.

In 2017, Kevin accepted an Associate Professor position in Medicinal Chemistry at the University of Greenwich (UK) where he continues his interdisciplinary research.

INTERVIEW

SYNFORM What is the focus of your current research activity?

Dr. K. Lam Our current research is centred around the study of electron transfers across the fields. We are a curiosity-driven research group and as a consequence, we perform research in fields that might seem to be completely unrelated at first sight (Scheme 1). For instance, we have been using electrochemistry in materials chemistry for surface modification, in organometallic chemistry for the elucidation of complex redox mechanisms, in organic synthesis for the preparation of highly reactive intermediates and more recently even in medicinal chemistry!

SYNFORM When did you get interested in synthesis?

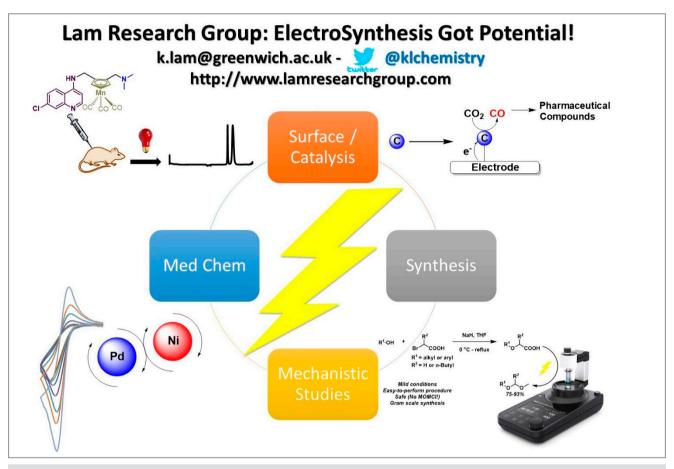
Dr. K. Lam I developed an interest in organic chemistry during my first year at the Université Catholique de Louvain in Belgium where we were taught synthesis by my friend and mentor, Prof. István Markó who has passed away recently. He was a fantastic lecturer who taught us organic chemistry the 'old way' using a blackboard and chalk without ever relying on any notes! This is when I became fascinated with organic synthesis that is both a science and an art!

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

Dr. K. Lam Organic synthesis is everywhere, it might not always be visible, but it is literally taking part, in the background sometimes, in projects across the fields from biochemistry where one has to prepare specific peptides to materials chemistry where researchers need to synthesise new molecules to tune the physical properties of their new materials. Organic synthesis has definitely a bright future!

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Scheme 1 The Lam research group's areas of interest

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

Dr. K. Lam As mentioned earlier, we have a broad area of research with a special focus on organic and organometallic electrosynthesis. Readers might be surprised to learn that this is an extremely old discipline. Indeed, the first organic electrosynthesis was conducted by Faraday himself! We are using electrochemistry not only as a way to generate highly reactive organic intermediates (carbanion, carbocations, radicals, carbenes, etc.) but also as a unique approach to study electron transfers in organic molecules and to shed light on reaction mechanisms.

Our main goal is to demonstrate the use of electrochemistry in organic chemistry by making synthetic chemists' lives easier and showing them how toxic and expensive reagents could be replaced by the cheapest and the greenest source of electrons available to date: electricity itself!

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

Dr. K. Lam My major achievement is probably the fact that people named, much to my surprise, a reaction after István and me! The 'Markó–Lam deoxygenation' (Scheme 2) and at the same time, this is a great tribute to the fantastic chemist that István was.

Scheme 2 The Markó-Lam deoxygenation

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Formyl-Selective Deuteration of Aldehydes with D_2O via Synergistic Organic and Photoredox Catalysis

Chem. Sci. 2020, 11, 1026-1031

In recent years, interest in the incorporation of deuterium atoms into patented drugs and drug candidates to enhance their metabolism and pharmacokinetic properties has burgeoned. "In 2017, the US Food and Drug Administration approved the first deuterated drug, deutetrabenazine (Austedo), and the increasing demand for new deuterium-labeled drugs

Scheme 1 Strategies for synthesizing deuterated aldehydes. A) Previous methods to produce formyl-deuterated aldehydes through FG transformation. B) Hydrogen isotope exchange (HIE) to produce deuterated aldehydes. C) Hypothesis for the proposed deuteration. D) This work.

has motivated the development of efficient deuteration methods," said Professor Qingmin Wang, from the State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University (P. R. of China).

"The development of an efficient protocol for constructing formyl-deuterated aromatic aldehydes can be expected to increase the availability of deuterated lead compounds," said Professor Wang. Aromatic aldehydes selectively labeled at the formyl position are traditionally produced from (1) the corresponding esters by means of reduction with LiAlD₄ followed by oxidation. (2) from the corresponding amides by reaction with deuterated Schwartz's reagent, (3) from aryl halides via Pd/Rh-cocatalyzed reductive carbonylation or (4) from carboxylic acids via deoxygenative deuteration (Scheme 1A, for references see the original paper). A few protocols for Ir- and Ru-catalyzed hydrogen isotope exchange (HIE) at the formyl moiety have been reported, although there is an intrinsic difficulty in controlling the reactivity of aryl ring moiety and formyl moiety (Scheme 1B). Recently, MacMillan's group reported direct HIE at α -amino C(sp³)-H bonds via a pathway involving abstraction of a deuterium atom from a deuteriumlabeled thiol catalyst by an α -amino radical. "We hypothesized that generation of acyl radicals from aldehydes by a hydrogen atom transfer (HAT) photocatalyst in the presence of D₂O and a thiol catalyst would produce deuterated aldehydes," said coauthor Dr. Jianyang Dong.

Professor Wang continued: "Decatungstate anion $([W_{10}O_{32}]^{4-})$, an efficient HAT photocatalyst, has bond dissociation energies (BDE) of up to 100 kcal mol⁻¹ (for cyclohexane).

To our knowledge, visible-light polyoxometalate-facilitated HAT has not previously been synergistically merged with thiol catalysis. Because aldehydes have relatively low BDEs (94 kcal mol⁻¹), we envisioned that such a combination of catalytic processes would afford access to a considerable variety of acyl radicals and deuterated aldehydes from abundant aldehyde feedstocks (Scheme 1C). Moreover, owing to the gaps between the BDEs of C(=O)H bonds (94 kcal mol⁻¹), arvl C-H bonds (113 kcal mol⁻¹), and S-H bonds (80-88 kcal mol⁻¹), decatungstate anion would be unable to abstract a hydrogen atom from the arvl C-H bond, allowing us to achieve formyl labeling without the formation of aryl-labeled by-products (Scheme 1C)." The group recognized that the choice of a suitable thiol catalyst would be heavily influenced by thermodynamic factors, particularly the BDE of the thiol bond relative to that of the acyl C–H bond, as well as its pK, relative to that of water.

Professor Wang emphasized that this general strategy for formyl-selective deuteration of aldehydes with $\rm D_2O$ mediated by the synergistic combination of light-driven, polyoxometal-ate-facilitated HAT and thiol catalysis has a broad substrate scope, excellent functional group tolerance and selectivity (Scheme 1D). "We provided a practical method for late-stage modification of synthetic intermediates in medicinal chemistry and for generating libraries of deuterated compounds (Figure 1). We hope that this method can help the development of novel deuterium-labeled drugs," concluded Professor Wang.

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Figure 1 Structurally complex deuterated aldehydes prepared by using the alkylation protocol

About the authors



Prof. Q. Wang

Qingmin Wang is currently a professor at the State Key Laboratory of Elemento-Organic Chemistry, Nankai University (P. R. of China). He obtained his B.Sc. (1994) from Lanzhou University (P. R. of China) and Ph.D. (2000) from Nankai University under the supervision of Prof. Runqiu Huang. His research interests mainly focus on the isolation, total synthesis, structural optimization, and bioactivity research of natural products and

the design, synthesis, and structure–activity relationships of pesticides and drugs.



J. Dong

X. Wang

Jianyang Dong obtained his B.S. (2016) under the supervision of Prof. Jianhan Huang at Central South University (P. R. of China). He then pursed a Master's degree in 2016 under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China) and in 2018 he began his PhD studies. His research focuses on photoredox-catalyzed radical chemistry.

Xiaochen Wang obtained her B.Sc. (2017) at Changchun University of Science and Technology (P. R. of China). She then started her M.Sc. studies under the superision of Prof. Qingmin Wang at Nankai University (P. R. of China) in 2018. Her research focuses on photoredox-catalyzed radical chemistry.



Z. Wang



Dr. H. Song



Prof. Y. Liu

Zhen Wang obtained his B.Sc. (2017) under the supervision of Prof. Kunxian Shu at Chongqing University of Posts and Telecommunications (P. R. of China) before starting his current M.Sc. studies under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China). His research focuses on photoredox-catalyzed radical chemistry.

Hongjian Song obtained his B.S. in 2008 at Qufu Normal University (P. R. of China). He then obtained his M.S. (2011) and Ph.D. (2014) under the supervison of Prof. Qingmin Wang at Nankai University (P. R. of China), majoring in organic chemistry. Currently he is a lecturer at Nankai University. His research focuses on natural pesticide discovery.

Yuxiu Liu obtained her B.Sc. (1994), Master's (1997) and Ph.D. (2003) from Nankai University (P. R. of China). She is currently an associate professor at the State Key Laboratory of Elemento-Organic Chemistry, Nankai University. Her research interests mainly focus on the isolation, total synthesis, structural optimization, and bioactivity research of natural products.

Reaction Scope and Mechanistic Insights of Nickel-Catalyzed Migratory Suzuki-Miyaura Cross-Coupling

Nat. Commun. 2020, DOI: 10.1038/s41467-019-14016-1

Metal-catalyzed cross-coupling reactions have revolutionized carbon–carbon bond disconnections in synthetic chemistry. In this context, β -hydrogen–containing sp³-carbon electrophiles are generally recognized to be more challenging than their sp²-carbon analogues owing to the possibility of β -hydride elimination taking place as side reaction. During the past several decades, extensive efforts have been devoted to avoiding β -hydride elimination and constructing chemical bonds at the sp³-carbon through metal-catalyzed cross-coupling. Recently, migratory cross-coupling reactions have been emerging as a new research field, as these reactions allow the generation of products through an iterative migratory insertion/ β -H elimi-

nation process (Scheme 1). The net result of this process is the controlled functionalization of a carbon atom different from the one originally carrying the metal.

Since the group of Professor Yin (Wuhan University, P. R. of China) began their research in this field in 2017, they have been committed to expanding the scope of migratory cross-coupling reactions and have conducted an in-depth study on the mechanism of these reactions. The migratory Suzuki-Miyaura cross-coupling represents the latest progress of the Yin group in this field. Electrophilic alkyl reagents (including alkyl chlorides, bromides, iodides and tosylates) have given satisfactory results (Figure 1a) when engaged in the reaction.

Scheme 1 Nickel-catalyzed migratory cross-coupling

Figure 1 Scope of the reaction

Professor Yin explained: "Our method offers a protocol to rapidly access diarylalkanes and allylbenzenes from a series of aryl/vinyl-bearing alkyl electrophiles and sp²-C boron-based nucleophiles. This approach is characterized by a broad substrate scope and excellent migratory regioselectivity. Interestingly, this strategy can serve as a platform for the synthesis of terminal, partially deuterium-labeled molecules from readily accessible starting materials (Figure 1b). These kinds of compounds are difficult to obtain by common synthetic methods."

Professor Yin's group has studied the reaction mechanism by a combination of experimentation and calculation. Experimental studies suggest that migratory cross-coupling products are generated from a Ni(0/II) catalytic cycle. Theoretical calculations indicate that the chain-walking occurs at a neutral nickel complex rather than at a cationic one. Interestingly, Professor Yin and co-workers found that the classical Suzuki–Miyaura coupling reaction and the migratory Suzuki–Miyaura coupling reaction proceed through distinctly different pathways. "We believe that the study of the reaction mechanism will help us in understanding the reaction process and is of great significance to further expanding the scope of this particular migration reaction," remarked the authors.

Professor Yin concluded by mentioning some future prospects: "Our research group will continue to carry out research in this field and develop more practical synthesis methods."

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About the authors



Prof. G. Yin

Prof. Guoyin Yin received his Ph.D. from Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS, P. R. of China) in 2011, under the supervision of Prof. Guosheng Liu. Starting in late 2011, he conducted postdoctoral research at Technical University of Munich (Germany) with Prof. Thorsten Bach as an Alexander von Humboldt Postdoctoral Fellow, at RWTH Aachen University (Germany) with Prof. Franziska

Schoenebeck, and at the University of Delaware (USA) with Prof. Donald A. Watson. In 2016, he began his independent career at the Institute for Advanced Studies (IAS) of Wuhan University (P. R. of China). His research interest currently focuses on transformations involving metal migration.



Prof. Y. Lan

Prof. Y. Lan completed his Ph.D. in 2008 at Peking University (P. R. of China) under the supervision of Professor Yun-Dong Wu. From 2009 to 2012, he worked as a postdoctoral fellow at the University of California, Los Angeles (USA) with Professor K. N. Houk. He then joined the faculty of Chongqing University (P. R. of China). In 2016, he received the Chinese Chemical Society Award for Outstanding Young Chemist. His cur-

rent research interest focuses on the mechanism and selectivity of transition-metal-mediated coupling reactions with DFT calculations.



Y. Li



Y. Luo

Yuqiang Li was born in Anhui Province (P. R. of China) and received his B.Sc. degree from Central South University in 2016. Subsequently, he pursued his Ph.D. under the guidance of Prof. Guoyin Yin at Wuhan University (P. R. of China). His research topic focuses on cross-coupling reactions involving metal migration.

Yixin Luo received her BS degree at Chongqing Normal University (P. R. of China) in 2016. Currently, she is pursuing her PhD under the supervision of Prof. Yu Lan at Chongqing University. Her current research interests are focused on the mechanistic study of transition-metal-catalyzed crosscoupling reactions.

Harnessing Applied Potential: Selective β -Hydrocarboxylation of Substituted Olefins

J. Am. Chem. Soc. **2020**, 142, 1780–1785

The carboxylate moiety is prevalent in nature, and a wide range of biologically active drugs and bioactive compounds are carboxylic acids or derivatives. However, the incorporation of a carboxylic function in a selective manner, from low-value materials such as alkenes, remains a significant challenge for organic chemists. In particular, sustainable and straightforward methods for selective carboxylation are underdeveloped. Dr. Benjamin Buckley, Professor Andrei Malkov and team from Loughborough University (UK) have recently reported a new electrosynthetic approach to the selective β-hydrocarboxylation of alkenes with inexpensive and abundant carbon dioxide, thus avoiding the use of toxic, flammable carbon monoxide that is the current reagent of choice for this purpose. The reported method allows direct access to carboxylic acids derived from terminal, di-, tri-, and tetra-substituted alkenes, in a highly regioselective manner. Interestingly, the authors observed a selectivity which is opposite to that reported utilizing transition-metal complexes1 and complementary to the photochemical approaches reported to date.²

Dr. Buckley noted: "There are a number of electrochemical processes reported that allow for CO₂ incorporation into organic molecules. In the majority of cases, these rely on a sacrificial electrode – such as magnesium – and this presents several difficulties, including the limited sustainability of the approach, the challenges in translation to industrial applications and implementation of continuous processes."

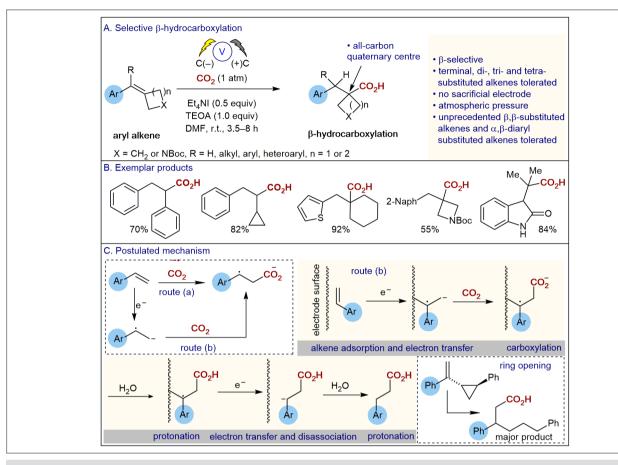
After reporting the use of a sacrificial electrode system for the formation of cyclic carbonates from epoxides and oxetanes, the team set themselves the target of developing a nonsacrificial electrochemical system in which they could utilize CO₂.3 "This was inspired by our unpublished findings on the nature of a precipitate that we observed during the original cyclic carbonate reaction," explained Dr. Buckley. He continued: "Depending on the sacrificial electrode employed, we could isolate oxalic acid (after acidic work-up) and this now became really interesting from a C-C bond-forming point of view. Our interest increased even further following the publication of a paper by Bouwman and co-workers highlighting the importance of catalysts for oxalate synthesis.4" Prof. Malkov, Dr. Buckley and co-workers eventually found that this was not a unique process, as there was a precedent reported more than two decades before by Vasil'ev, although at much higher tem-

perature and pressure. In that interesting paper, the authors also added ethylene and observed C-C bond formation.5 "We adapted our process and added styrene, which provided good vields of dicarboxylation across the double bond, similar to that reported by Duñach, 6" said Dr. Buckley. From that point, the team implemented a regime to replace the sacrificial electrode, finally settling on a system that contained two carbon electrodes, tetraethylammonium iodide as electrolyte, and triethanolamine as a proton source with CO₂ at ambient pressure (Scheme 1A). Dr. Buckley remarked: "Surprisingly, under these conditions, we observed mono-carboxylation at the β-carbon of styrene, and not dicarboxylation. On further investigation we found that triethanolamine is essential for selectivity and a recent report has highlighted triethanolamine's non-innocent role in activating CO₂. Excitingly, further substrate screening revealed that our system works well for substrates that previously were challenging for metal-catalyzed and photochemical approaches. For example, we could successfully carboxylate stilbenes, tri- and tetra-substituted alkenes (Scheme 1B). This gives unprecedented access to allcarbon quaternary carboxylic acids, which are also challenging to prepare using the traditional metal-catalyzed carbonvlation processes.7"

Delineating the mechanism of these reactions is somewhat challenging given the similar reduction potentials of alkenes and CO₂ (Scheme 1C). Dr. Buckley said: "Collaboration with the Wright group enabled cyclic voltammetric analysis of the reaction process indicating formation of the radical anion of the alkene as a preferred approach, indeed we also observed the ring opening of a cyclopropane-derived alkene, suggesting the formation of a radical at the benzylic position. However, further studies in this area are required to fully understand the process."

Dr. Buckley concluded: "We are currently examining the potential of this approach to a wide variety of carboxylation chemistries and expect this to inspire many other electrosynthetic approaches that will no longer need to rely on a sacrificial electrode approach."





Scheme 1 (A) General approach to the hydrocarboxylation process. (B) Example products from the process. (C) Postulated routes towards the mono-carboxylated products.

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About the authors



Dr. B. Buckley

Benjamin Buckley is currently a Reader at Loughborough University (UK). In 2003 he received his PhD with Prof. Philip C. Bulman Page on organocatalytic asymmetric epoxidation. He then took up a post-doctoral position in the Page group for a further five years, working on a range of projects with industrial and academic partners. In late 2007 he was appointed to a Research Councils UK Fellowship at Loughborough and

initiated independent research in the areas of catalysis, electrosynthesis and carbon dioxide utilisation. He was promoted to a Senior Lectureship in 2014 and also moved to the University of Utah, USA on sabbatical leave for a year with Professor Matthew S. Sigman's group. In February 2020 he was appointed to a Readership in Chemistry at Loughborough.



Prof. A. Malkov

Andrei Malkov started his career with the award of MSs (Hons) from the Moscow State University (Russia) in 1982, which was followed by PhD studies at the Institute of Organo-Element Compounds (Moscow, Russia), successfully completed in 1986. He continued his work in the area of organometallic synthesis and catalysis, which intensified with his move to the UK in 1992 where he had two postdoctoral spells at the UEA

(1992–1995) and the University of Leicester (1995–1999). He started his independent career in the UK at the University of Glasgow (UK) in 1999 where he rose through the ranks to become Reader. In 2008 he was appointed as Professor of Organic Chemistry at Loughborough University (UK). He is currently active in the following research areas: Asymmetric organocatalysis: new catalysts, new methodology, synthetic applications; Catalytic functionalization of C–H bonds: method development, synthetic applications; Electrosynthetic methods for utilisation of carbon dioxide; Total synthesis of bioactive natural products, biological investigations.



Dr. A. Alkayal

Anas Alkayal obtained his B.Sc. in 2006, and his M.Sc. degree in chemistry in 2011 at Al-Baath University (P. R. of Syria). He then began his Ph.D. research under the supervision of Doctor Ayman Karam also at Al-Baath University focusing on drug discovery. He received his PhD in 2016, and in 2018, moved to Loughborough University (UK) to conduct postdoctoral research with Dr. Buckley which centres around reducing our reliance on

fossil-fuel-based raw materials, utilising electrosynthesis and carbon dioxide.



Dr. V. Tabas

Volodymyr Tabas received his M.Chem in chemistry from Loughborough University (UK) in 2014. He then started his PhD in the group of Dr. Buckley and Prof. Malkov, focusing on electrosynthesis and CO₂ utilisation. In 2016 he won the RSC Catalysis Science and Technology Poster award at the 14th International Conference on Carbon Dioxide Utilization (ICCDU) and in 2017 the Outstanding Young Researcher Award at the 15th ICCDU in Shanghai, China. In 2019 he was awarded his PhD in chemistry.



Dr. I. Wright

lain Wright pursued his undergraduate degree at the University of Strathclyde (UK) where he stayed to complete his PhD in 2011 advised by Professor Peter Skabara and focused on oligothiophene-based materials. This was followed by postdoctoral appointments at Universität Basel (Switzerland) with Professors Ed Constable and Catherine Housecroft and Durham University (UK) with Professor Martin Bryce. In Novem-

ber 2016 he was appointed as a Lecturer (Assistant Professor) in Chemistry at Loughborough University (UK). His research streams concern the synthesis, photophysics and electrochemistry of new organic and organometallic materials for optoelectronic devices.

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Stephanie Montanaro received her M.Chem degree from Durham University (UK) in 2016. In 2017 she started her PhD at Loughborough University (UK) in the group of Dr. Wright, focused on the synthesis and study of organic electronic materials.

S. Montanaro

Coming soon

SYNLETT Highlight

Electrochemical C(sp³)-H Fluorination

Literature Coverage

Photosensitized Intermolecular Carboimination of Alkenes through the Persistent Radical Effect

Literature Coverage

Ligand-Promoted Cobalt-Catalyzed Radical Hydroamination of Alkenes

Further highlights

Synthesis Review: Recent Advances in Photocatalytic

Decarboxylative Coupling Reactions in Medicinal Chemistry
(by L. McMurray and co-workers)

Synlett Account: C–H Insertion Reactions of Donor/Donor Carbenes: Inception, Investigation, and Insights (by J. T. Shaw)

Synfacts Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs":

Synthesis of (–)-Canataxpropellane

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Impressun

Edito

Matteo Zanda, Chair in Biomolecular Imaging, Centre for Imaging Science, Department of Chemistry, School of Science, Loughborough University, Leicestershire, LE11 3TU, UK and

C.N.R. – Istituto di Chimica del Riconoscimento Molecolare Via Mancinelli, 7, 20131 Milano, Italy Editorial Assistant: Alison M. Sage synform@outlook.com; fax: +39 02 23993080

Editorial Office

Managing Editor: Susanne Haak,

susanne.haak@thieme.de, phone: +49 711 8931 786

Scientific Editors:

Stefanie Baumann, stefanie.baumann@thieme.de, phone: +49 711 8931 776 Selena Boothroyd, selena.boothroyd@thieme.de Michael Binanzer, michael.binanzer@thieme.de, phone: +49 711 8931 768 Giuliana Rubulotta, giuliana.rubulotta@thieme.de, phone: +49 711 8931 183

Kathrin Ulbrich, kathrin.ulbrich@thieme.de, phone: +49 711 8931 785

Senior Production Editors:

Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778 Thorsten Schön, thorsten.schoen@thieme.de, phone: +49 711 8931 781

Production Manager: Sophia Hengst,

sophia.hengst@thieme.de, phone: +49 711 8931 398

Production Assistant: Tobias Brenner,

Tobias.brenner@thieme.de, phone: +49 711 8931 769

Editorial Assistant: Sabine Heller,

sabine.heller@thieme.de, phone: +49 711 8931 744

Marketing Director: Julia Stötzner,

julia.stoetzner@thieme.de, phone: +49 711 8931 771

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