

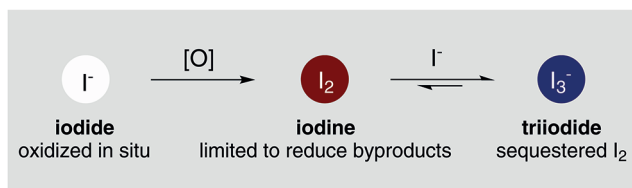
Synform

People, Trends and Views in Chemical Synthesis

2016/11

Triiodide-Mediated δ -Amination of Secondary C–H Bonds

Highlighted article by E. A. Wappes, S. C. Fosu,
T. C. Chopko, D. A. Nagib



Contact

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



Thieme

Dear Readers,

Feeling blue because of the November rain and a bit down because holidays are long gone with still a long way to go until the next ones? That would be normal, but not for me! In fact, November is my favorite month – yes, you understood well – because I love fog and mist, Scottish drizzle, and the cozy atmosphere of being home with the loved ones with that kind of weather outside. And, I forgot, I love Halloween too! So, when most people feel a little bit blue because of the November weather, I actually feel really well and upbeat when November comes! So, don't be surprised if this SYNFORM issue adds further excitement to my usual November good mood. And how could it be any different considering the poker of chemistry aces we have in hand this month? The incipit is a Young Career Focus interview with S. Dhar (USA) who tells us about her interests, achievements and career goals. Runner-up article is photoredox synthesis of cationic organic dyes designed by J. C. Scaiano (Canada). Next in line is the clever total synthesis of the natural tetramic acid aurantoside G developed by R. Schobert (Germany). Dulcis in fundo, the very original synthesis of cyclic amines via δ -amination of secondary C–H bonds recently described by D. Nagib (USA). I am confident this excellent SYNFORM issue will have the effect of a mouthful of chocolate on every organic chemist currently dealing with the November blues!

Enjoy your reading!



In this issue

Young Career Focus

Young Career Focus: Professor Shanta Dhar (University of Miami, USA) A162

Literature Coverage

Library of Cationic Organic Dyes for Visible-Light-Driven Photoredox Transformations A166

Literature Coverage

Total Synthesis of Aurantoside G, an *N*- β -Glycosylated 3-Oligoenoyltetramic Acid from *Theonella swinhoei* A168

Literature Coverage

Triiodide-Mediated δ -Amination of Secondary C–H Bonds A171

Coming soon A174

Contact

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

Young Career Focus: Professor Shanta Dhar (Miller School of Medicine, University of Miami, USA)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Shanta Dhar (Miller School of Medicine, University of Miami, USA).

Biographical Sketch



Prof. S. Dhar

Shanta Dhar is originally from West Bengal, India. She obtained her Bachelor of Science degree with honors in chemistry from the University of North Bengal and she was a silver medalist. She then received her Masters in Science with inorganic chemistry specialization and she was a gold medalist. She pursued her PhD at one of India's finest institutions of higher education – the Indian Institute of Science, Bangalore – under the supervision of Professor Akhil R. Chakravarty. Her thesis work in the area of Metals in Medicine received a “Best Thesis” award for chemical sciences. In 2006, she went to the other side of the globe and joined Johns Hopkins University (USA) as a postdoctoral fellow, where she worked in the area of bioorganic chemistry with Professor Marc M. Greenberg, developing fluorescent sensors for detection of DNA lesions. In 2007, she began her postdoctoral work in the group of Professor Stephen J. Lippard at the Massachusetts Institute of Technology (MIT, USA). Her postdoctoral studies as an Anna Fuller Postdoctoral Fellow of molecular oncology were focused on nanocarrier-mediated delivery of platinum-based compounds for potential applications in cancer. In 2010, she joined the Department of Chemistry at the University of Georgia (USA). In June 2016, she moved to the Department of Biochemistry and Molecular Biology, University of Miami Miller School of Medicine (USA) as an Associate Professor. She also serves as an Assistant Director of Technology and Innovation at Sylvester Comprehensive Cancer Center at Miller School of Medicine. She received the Prostate Cancer Idea Development Award from the Department of Defense, the National Scientist Development Award from the American Heart Association, the Ralph E. Powe Junior

Faculty Development Award from Oak Ridge Associated Universities, the best scientific contribution by the International Society of antioxidants in nutrition and health and the targeting mitochondria conference in 2012, one of “Georgia’s top medical researchers” by Atlanta Business Chronicle in 2014, one of Georgia’s 40 under 40 by the Georgia Trend in 2014, and the Thieme Chemistry Journals Award 2015. She also co-founded a start-up biotechnology company, Partikula LLC, and currently serves as the chair of the Scientific Advisory Board of this company.

INTERVIEW

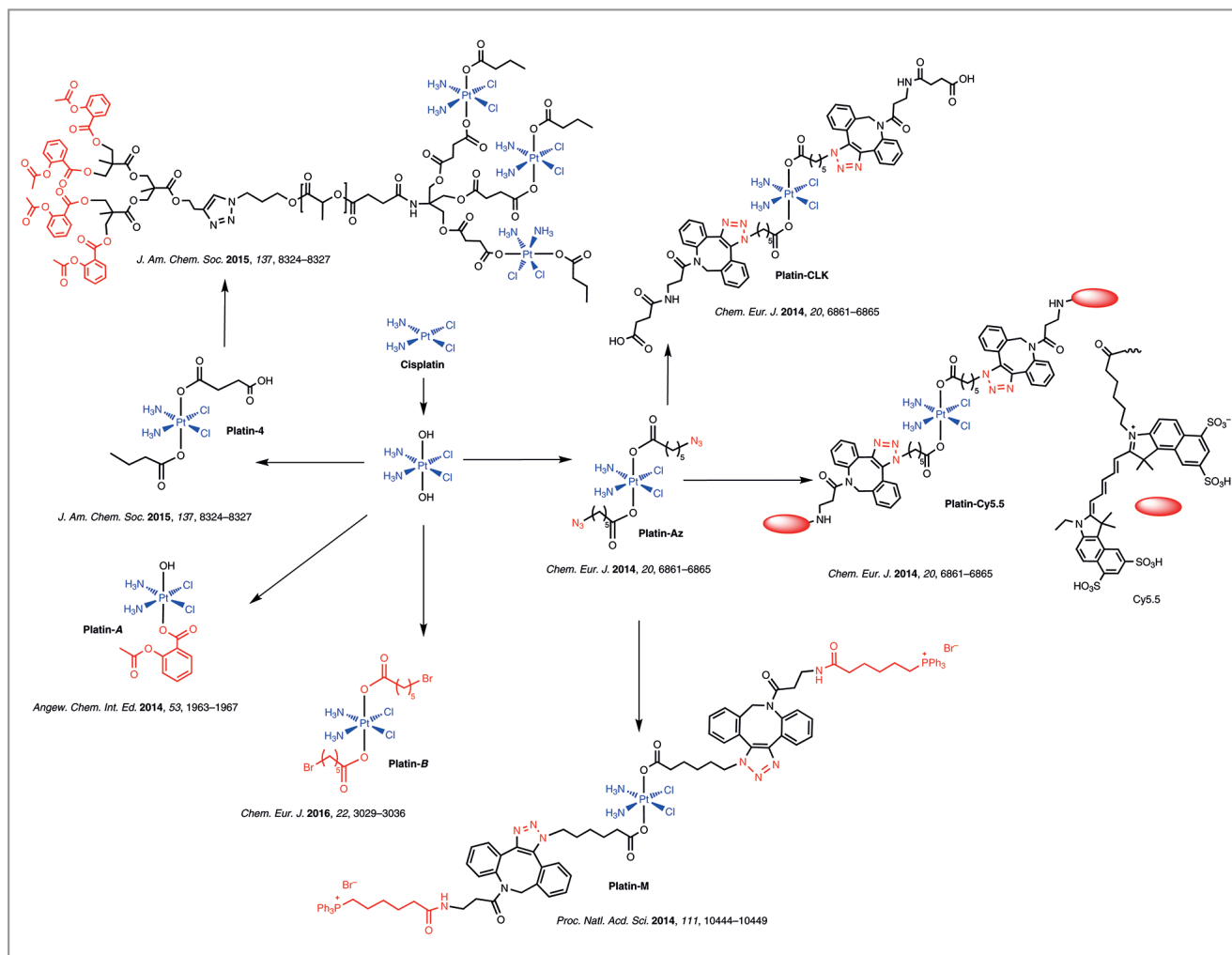
SYNFORM What is the focus of your current research activity?

Prof. S. Dhar I came across an article in *Science Illustrated* about “The top 10 challenges for the coming decade” in human health (*Science Illustrated* **2011**, page 54, Jan/Feb issue). This list included mapping the metabolic system, aging, targeted cancer therapy, obesity, malaria, etc. When I started my independent research program, this article made me think what a chemist with keen interest in solving biomedical problems can do. I looked for common connecting points for these problems to apply my expertise in chemistry, biology, and nanotechnology. I realized if I can focus at the basic level, for example, to mitochondria, which are common connecting points in all these problems, and apply my knowledge, we might have a platform technology. Mitochondrial dysfunctions are involved in most of these diseases. However, most available mitochondria-acting therapeutics face tremendous challenges in reaching the mitochondrial lumen where the therapeutic targets are located. A major focus of my research group is the study and development of nanocarriers for tar-

geted delivery of therapeutics, contrast agents, and other payloads at tunable and/or controlled rates in the mitochondrial lumen. Our work is focused in the following areas: providing new targets for platinum-based compounds using a unique combination of chemistry and nanoengineering, developing sensors and therapeutics for cardiovascular diseases, construction of cell-specific mitochondria-targeted delivery systems with the ability of multiple drug release, creation of nanovaccines, nanoparticle-based therapeutic options for brain trauma, and small-molecule-based prodrugs for cancer and inflammatory diseases.

SYNFORM When did you get interested in synthesis?

Prof. S. Dhar My love for organic synthesis started in college. I remember even trying to teach my little brother, 10 years younger than me, some organic synthesis during my college days when he was in elementary school. During my college days, one of my teachers would challenge me with organic mechanisms and organic transformations. I specialized in inorganic chemistry during my masters training and conducted my PhD in bioinorganic chemistry, and I always enjoyed organic and inorganic synthesis. In my PhD, I was synthesizing copper(II) ternary complexes, which were interpreted as difficult to synthesize. I ended up synthesizing numerous ternary complexes and was even able to get 18 such



Scheme 1 Synthesis of numerous platinum-based compounds/conjugated polymers with anti-tumor properties that were synthesized from a single FDA approved drug cisplatin as a precursor

complexes characterized by single-molecule X-ray crystallography. I love doing synthesis. I then had a one-year bootcamp organic synthesis training in Professor Greenberg's lab and I really got interested in doing organic synthesis and the new molecules one can construct using organic reactions. This training helped me to integrate organic and inorganic synthetic strategies together to create small and macromolecules. At MIT, I fell in love with synthetic aspects dealing with platinum complexes by taking advantage of different oxidation states and geometries that this precious metal offers.

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

Prof. S. Dhar Being a chemist who aims to use synthetic chemistry to develop organic and inorganic molecules, nanodelivery vehicles, and combination therapeutic approaches for medical/biological applications, I would like to express my view of the role and prospects of organic synthesis by quoting the exciting comment of German chemist Friedrich Wöhler after he synthesized urea and wrote to his mentor "...I cannot, so to say, hold my chemical water, and must tell you that I can make urea, without thereby needing to have kidneys, or anyhow, an animal, be it human or dog..." Organic synthesis provides a valuable tool towards recreating biologically relevant compounds for a multitude of different purposes. In addition to traditional medicinal chemistry, organic synthesis has the power to truly transform the field of nanomedicine and bioinorganic chemistry. One of the major challenges we often observe in nanomedicine is to reproducibly construct drug-loaded materials when we consider advancing these unique technologies to the clinic. Organic synthesis has the potential to provide solutions to these problems; one can use unique organic synthetic strategies to reproducibly make these materials. Platinum complexes with anti-tumor properties are the most conspicuous representatives in medicinal inorganic chemistry and organic synthesis provided tools to modify the completely inorganic parent compound cisplatin, resulting in the platin-based subfield of bioinorganic chemistry. The impact of organic synthesis in medicine in the last two centuries has been extraordinary and this will continue to happen as organic synthetic chemists find sophisticated synthetic strategies. Organic synthesis will continue to influence the growth of nanomedicine, metal-based medicine, and other relevant fields in medicine.

SYNFORM *Your research group is active in the areas of organic synthesis, nanotechnology and biomedicine. Could you tell us more about your research and its aims?*

Prof. S. Dhar Mitochondria are not only the energy factories of cells but these dynamic organelles participate in the overall process of cellular mortality; thus, their dysfunctions lead to various diseases such as cancer, atherosclerosis, and neurodegenerative diseases in addition to conventional mitochondrial dysfunction-related diseases. To tackle these diseases, one needs to access the targets, which are located in mitochondrial lumen. Targeting mitochondria has been notoriously challenging due to their complex and dynamic nature. My lab is actively involved in generating biodegradable, tunable nanodelivery vehicles for efficacious mitochondrial delivery of therapeutics for cancer, neurodegenerative diseases, and cardiovascular diseases. As we move forward, we plan to expand the application of such nanoparticle (NP)-based platforms to other diseases where mitochondria and their abnormalities play integral roles. We also discovered that suitably optimized mitochondria-targeted NPs could distribute in the brain and we are working on the potential of mitochondria-targeted lipophilic biodegradable NPs with the ability of traversing the blood-brain barrier in neurodegenerative diseases and brain cancers.

Coronary events continue to be the leading cause of death in the United States. We are active in applying our synthetic chemistry to construct synthetic, biodegradable, mitochondria-targeted NP platforms with the ability to participate in extra- and intra-cellular lipid reduction pathways for cardiovascular diseases.

We have several programs developing alternative therapeutic platforms for cancer. One of the effective methods to tackle metastatic cancers will be to engage our immune system. We use a unique combination of mitochondrial stimulation of cancer cells using targeted NPs and light to activate the immune system. Targeting mitochondrial DNA (mtDNA) can be important for cisplatin-based chemotherapy. Cisplatin is a widely used and FDA-approved chemotherapeutic agent which is highly effective against several cancers. Therapeutic action of cisplatin relies on its ability to form interstrand and intrastrand nuclear DNA (nDNA) cross-links. Resistance to cisplatin-based chemotherapy arises from different cellular processes, one of which is accelerated DNA repair by nucleotide excision repair machinery. The absence of such repair machinery in the mitochondria and enhanced mtDNA mutation in aggressive cancers motivated us to reroute cisplatin to attack mtDNA. We are developing such technologies for nanoparticle-mediated cisplatin delivery in the form of activable prodrugs to the mitochondria of different cancer cells to attack mitochondrial genome for chemo-resistant cancers.

In the search for a successful treatment, it is evident that a single magic bullet is not enough for metastatic cancers. However, systemic administering of bolus doses of multiple therapeutics often results in intense side effects. We are engineering polymers with biodegradable dendrons at the termini through direct conjugation to incorporate anti-inflammatory drugs, chemotherapeutics along with cancer cell targeting moieties to provide an all-in-one therapeutic NP platform for metastatic cancers.

Cancer-related mitochondrial alterations such as defective oxidative phosphorylation, mitochondrial biogenesis, down-regulation of ATP synthase, and mitochondrial-reactive oxygen species provide unique targets for selective treatment modalities. Thus, engineering of small molecules known to work at different targets inside the mitochondria or developments of such molecular payloads containing mitochondria-targeted NPs have the potential to provide tumor-specific anticancer agents. We are involved in the development of mitochondria-targeted prodrugs that can be locally activated at the target sites: some examples are dichloroacetic acid, 3-bromopyruvate, Bcl-2 inhibitors.

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

Prof. S. Dhar My most significant research accomplishment to date is the development of a biodegradable nanoparticle platform from Food and Drug Administration approved components for mitochondrial dysfunction-related diseases. This technology can be useful to study a wide range of human diseases where mitochondrial dysfunction is a major player. This platform technology has resulted in several other important contributions, including the first synthetic mitochondria-targeted nanoparticle that can mimic the functional behaviors of high-density lipoprotein for potential applications in coronary artery disease, the ability to generate functional immune cells in vitro for cancer vaccines, providing an alternative target to platinum-based drugs for overcoming resistance, the development of biodegradable dendron-functionalized polymeric nanoparticles for combination therapy, mitochondria-targeted metabolic reprogramming of cancer cells, and the evaluation of nanoparticle-based neuroprotection therapy for brain injury.



Library of Cationic Organic Dyes for Visible-Light-Driven Photoredox Transformations

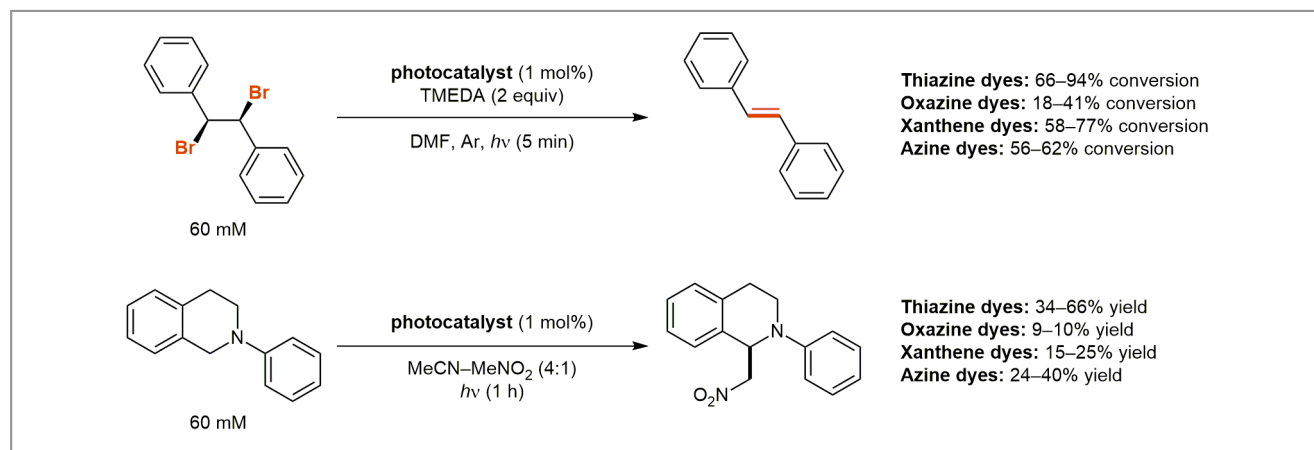
ACS Omega 2016, 1, 66–76

The field of photoredox catalysis has grown exponentially in the last decade because it provides synthetic chemists with a means to perform free-radical reactions under mild conditions and irradiation from simple, household light sources. In a vast majority of the contributions, these transformations have been mediated by transition-metal catalysts, in particular polypyridyl ruthenium and iridium complexes, decreasing the economic benefit of these reactions. However, the possibility of using metal-free catalysts, such as organic dyes, for achieving efficient light-mediated photoredox reactions is an attractive option, as they offer a variety of environmental and economic benefits. Recently, the group of Professor Juan C. (Tito) Scaiano from the University of Ottawa (Canada) has reported a systematic study of the efficiency of cationic organic dyes as catalysts for photoredox transformations. In this work, the ability of four different classes of organic dyes to mediate photoredox transformations was examined using two model reactions, the debromination of *meso*-1,2-dibromo-1,2-diphenylethane, and the nitromethylation of a tertiary amine at the α -amino position, also known as the light-mediated aza-Henry reaction (Scheme 1). The authors were able to correlate the observed activity of the organic dye with the rate constants of mechanistically key steps, demonstrating the importance of proper kinetic analysis for understanding the underlying mechanism of photoredox systems. However, the

goal of this contribution by Scaiano and co-workers was not only to demonstrate that these dyes can mediate photoredox reactions, but also to increase their popularity among practitioners of photoredox by carefully analyzing all of the relevant photophysical and electrochemical properties of these dyes, and to compile this information in a single, open-access contribution that would allow practitioners of photoredox easy access to the data.

“The popularity of transition-metal catalysts, in particular $\text{Ru}(\text{bpy})_3\text{Cl}_2$, in photoredox transformations stems from the fact that these complexes are well characterized in the literature. In fact, much of this data has been available since the 1970s for many of these complexes, including countless reviews on the photophysics of $\text{Ru}(\text{bpy})_3\text{Cl}_2$,” said Professor Scaiano. “On the other hand, organic dyes, which we have shown can be excellent metal-free alternatives for photoredox transformations, do not have the same collection of data available. Therefore, chemists who practice photoredox catalysis tend to stick with catalysts where the electrochemistry and photophysics are already known, instead of using organic dyes where the same data is either unknown or difficult to find,” he added.

Professor Scaiano explained: “We hand-picked 13 different organic dyes, as well as three popular photoredox catalysts in $\text{Ru}(\text{bpy})_3\text{Cl}_2$, $\text{Ir}(\text{ppy})_3$, and 9-mesityl-10-methylacridinium



Scheme 1 The model photoredox reactions used to evaluate the photocatalytic efficiency of the organic dyes examined in this work

perchlorate, and fully characterized both their photophysical and electrochemical properties. We compiled these data, and included them as an Appendix section in our recent contribution in *ACS Omega*.¹ The Appendix, located in the later pages of the manuscript, provides ‘cards’ with detailed descriptions of all the relevant photophysical and electrochemical data chemists who practice photoredox would require to design a photocatalytic system. An example of information the Appendix provides is demonstrated in Figure 1, which shows the Appendix ‘card’ for the thiazine dye Methylene Blue.

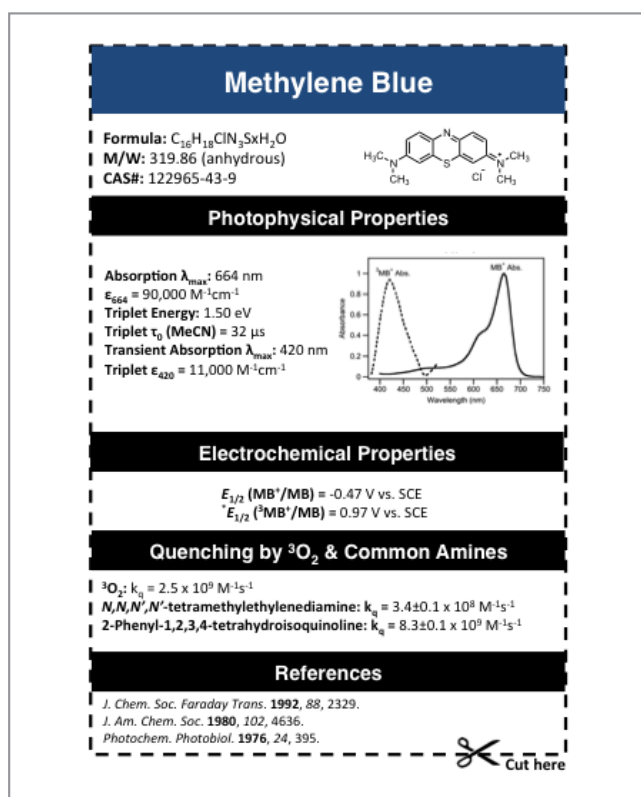
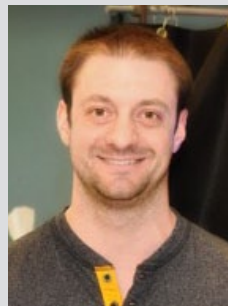


Figure 1 Appendix card for Methylene Blue as published in *ACS Omega* (image reused with permission from: Pitre, S. P.; McTiernan, C. D.; Scaiano, J. C., “Library of Cationic Organic Dyes for Visible-Light-Driven Photoredox Transformations”, *ACS Omega* **2016**, 1, 66–76)

To conclude, Professor Scaiano stated: “We envision that this collection of data will help popularize organic dyes as photoredox catalysts, as for the first time all the pertinent information for these dyes will be easily accessible in a single document.”

Matthew Farnish

About the authors



S. P. Pitre

Spencer P. Pitre received his B.Sc. in chemistry in 2012 from the University of Prince Edward Island (Canada) before joining the Scaiano group at the University of Ottawa (Canada) in autumn 2012 as a Ph.D. candidate. His current research interests involve the development of both precious-metal-free and heterogeneous alternatives for photoredox catalysis.



C. D. McTiernan

Christopher D. McTiernan received his B.Sc. in biochemistry (2008) and M.Sc. in chemical sciences (2010) from Laurentian University (Canada) before joining the Scaiano group at the University of Ottawa (Canada) in autumn 2011 as a Ph.D. candidate. His current research interests involve the study of photoredox reaction mechanisms and the development of heterogeneous systems for photocatalysis.



Prof. J. C. (Tito) Scaiano

Juan C. (Tito) Scaiano came to the National Research Council (NRC) in Ottawa (Canada) from Argentina in 1975 to join the Ingold group. After holding a position at the University of Notre Dame (USA, 1976–1979), he returned to the NRC in 1979, where he studied organic reaction intermediates using laser techniques. In 1991, he joined the University of Ottawa, where he is currently a Distinguished University Professor and holds the Canada Research Chair in Applied Photochemistry. His current interests include the study of organic photochemistry and reaction mechanisms, the application of nanomaterials to organic chemistry, single-molecule catalysis, and biomaterials.

Total Synthesis of Aurantoside G, an *N*- β -Glycosylated 3-Oligoenoyltetramic Acid from *Theonella swinhoei*

Angew. Chem. Int. Ed. 2016, 55, 10122–10125

3-Acyltetramic acids are metabolites of a variety of marine and terrestrial species such as sponges, bacteria, fungi, and lichens with an impressive range of biological and pharmacological activities. “This, and the scurrility that compounds with such deceptively ‘simple’ looking structures can turn out to be a nightmare when it comes to purification or spectral interpretation, has attracted the interest of synthetic organic chemists,” said Professor Rainer Schobert from the University of Bayreuth (Germany). “Our group got involved with these compounds some twenty years ago when we serendipitously found a new Wittig-based access to their pyrrolidine-2,4-dione core. Since then we have learned the hard way that each structural subclass of 3-acyltetramic acids requires its own synthetic approach.”

Professor Schobert explained: “When we focus on derivatives of marine origin there are, for example, the chemically robust melophlins, metabolites of bacteria that dwell on the sponge *Melophlus sarassinorum*, which can be readily synthesized by an acylation of the parent pyrrolidine-2,4-dione with the respective carboxylic acid chloride in the presence of an excess of $\text{BF}_3 \cdot \text{OEt}_2$ according to a method by Raymond Jones.”¹ He continued: “In contrast, epicoccamide D, which is produced by the fungus *Epicoccum purpurascens* associated with the jellyfish *Aurelia aurita*, and which is comprised not only of polyketide and amino acid as all 3-acyltetramic acids, but also of a mannose, would not stand being steeped in Lewis acid. Its side chain had to be installed by other means prior to

ring closure via a Dieckmann condensation as the final step (Figure 1).²”

The genuine sponge metabolite aurantoside G posed even more intricate problems. “It is a deep-red solid which confers this color to the sponge (Figure 2, right, shows a protected derivative of the same color) and it is moderately active against *Candida albicans*.³ This antifungal activity depends on the β -linkage between tetramic acid and sugar,” explained Professor Schobert, continuing: “Given that aurantoside G is a natural product it is amazingly sensitive, and so are its components. Its chlorinated, highly unsaturated side chain is sensitive to light and prone to decomposition. Figure 2 shows a flask with its golden thioester which was built up by consecutive Wittig and HWE olefinations as planned by Sebastian Loscher and Markus Petermichl as early as in 2014.”

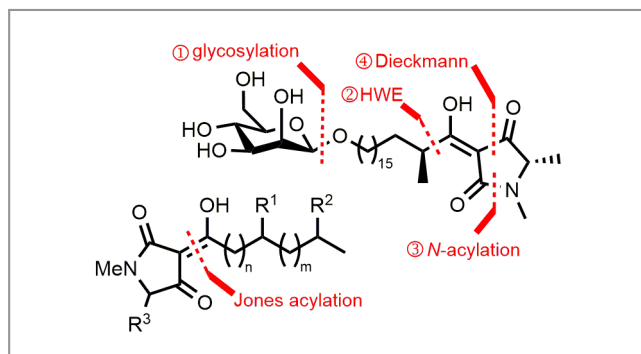


Figure 1 Synthetic access to melophlins (bottom/left) and epicoccamide D (top/right)

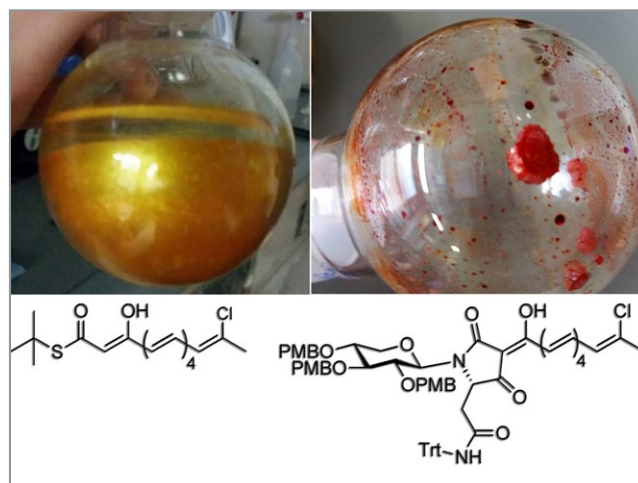


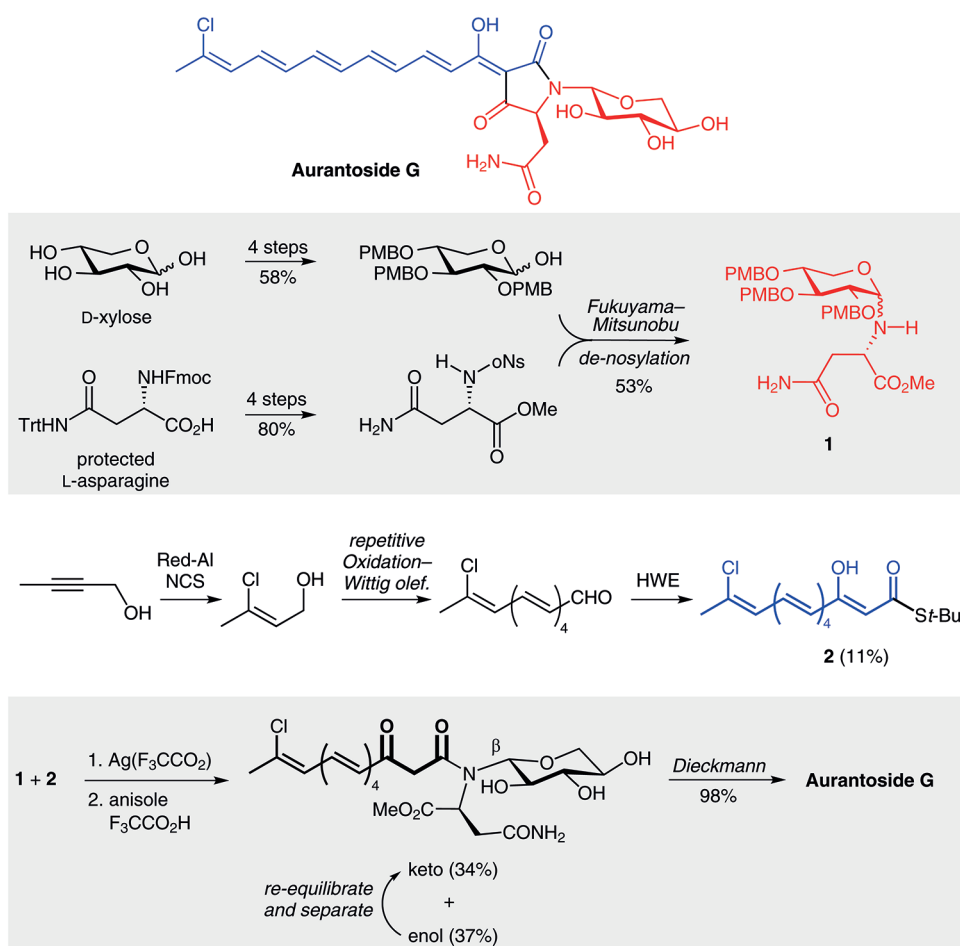
Figure 2 Flamboyant chemistry: the side-chain thioester (left) and a protected aurantoside G (right)

Professor Schobert recalls that Sebastian Loscher, who was then nearing the end of his PhD project, and Markus Petermichl, at that time embarking on his MSc project, also explored ways to attach a sugar to the nitrogen of a model 3-acyltetramic acid, but found it was not practicable. More successful were attempts to attach a protected xylose to an *N*-nosylated alanine ester via a Fukuyama–Mitsunobu reaction.

Professor Schobert said: “In the end, it took Markus a year and a half in the lab to synthesize aurantioside G by starting out on the basis of these exploratory experiments and circumventing a host of unforeseeable problems cropping up at almost every step.”

Scheme 1 outlines the synthetic route that was eventually worked out. “Markus first attached the D-xylose to the asparagine by a Fukuyama–Mitsunobu reaction, which requires the nitrogen to be nosylated in order to render its hydrogen atom acidic enough,” said Professor Schobert. “The actual glycosylation of this relatively electron-poor nitrogen atom was then possible only with electron-releasing *p*-methoxybenzyl (PMB) protecting groups on the sugar, as Markus and Sebastian had found out during their exploratory studies with alanine esters.”

The resulting *N*-nosyl-*N*-xylosylasparagine was de-nosylated to give building block **1** (red). This had to be *N*-acylated with the thioester **2** shown in Figure 2. “This thioester was synthesized in 11% yield over nine steps starting from (*Z*)-3-chlorobut-2-en-1-ol, which was prepared by reaction of but-2-yn-1-ol with Red-Al and *N*-chlorosuccinimide (NCS),” said Professor Schobert, who continued: “The stepwise chain elongation of this alcohol, by employing three cycles of domino oxidation–Wittig olefination using MnO_2 and $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ followed by reduction of the product esters with DIBAL-H, afforded a pentenal. Due to its instability, it was immediately subjected to a HWE reaction with Steve Ley’s *S*-*tert*-butyl 4-(diethylphosphono)-3-oxobutanethioate⁴ to give the desired thioester **2**.”



Scheme 1 Synthetic route to aurantioside G

The aminolysis of thioester **2** with a mixture of anomers of methyl *N*-D-xylosylasparaginate **1** and silver trifluoroacetate according to Ley's general protocol⁵ afforded the corresponding β -keto amide (not shown in Scheme 1) as a pure β -isomer in 49% yield with respect to recovered, unreacted **1**. "Apparently, only the β -anomer of **1** enters into a reaction with **2**, due to the directing effects of the PMB groups. The recovered α -anomer was re-epimerized during workup," said Professor Schobert, who revealed that it took several cycles to convert the entire **1** into the β -keto amide. Cleavage of its PMB groups with anisole gave the unprotected β -keto amide as a separable 1:1 mixture of keto (shown in Scheme 1) and enol tautomers. "Only the keto tautomer could be cyclized with NaOMe by a Dieckmann condensation to afford pure aurantoside G in quantitative yield (3.7% overall yield). The enol tautomer needed to be re-equilibrated with acid to give the initial mixture of tautomers," said Professor Schobert, adding: "There are several lessons we have learned from this synthesis: the PMB groups were crucial for its success by enabling the Fukuyama-Mitsunobu reaction *electronically* (electron-releasing effect) and by controlling the β -selective *N*-acylation *sterically*. The Dieckmann cyclization may be used for the synthesis of even delicate tetramic acids. It does not give rise to partial racemization at the C-5 of the heterocycle, nor does it interfere with highly unsaturated fragments or unprotected sugars. So, this synthetic route should be applicable also to other, more complex *N*- β -glycosylated congeners of aurantoside G."

Professor Schobert concluded: "The mind-boggling sensitivity of aurantoside G – after all a natural product! – is not without precedence. Kalesse and Hartmann had a similar experience with the related lipomycins.⁶ What might stabilize such compounds within the producing organism is an interesting question to muse on."

Matthew Fenske

REFERENCES

- (1) R. Schobert, C. Jagusch *Tetrahedron* **2005**, *61*, 2301.
- (2) S. Loscher, R. Schobert *Chem. Eur. J.* **2013**, *19*, 10619.
- (3) A. S. Ratnayake, R. A. Davis, M. K. Harper, C. A. Veltri, C. D. Andjelic, L. R. Barrows, C. M. Ireland *J. Nat. Prod.* **2005**, *68*, 104.
- (4) S. V. Ley, P. R. Woodward *Tetrahedron Lett.* **1987**, *28*, 345.
- (5) L. T. Burke, D. J. Dixon, S. V. Ley, F. Rodríguez *Org. Biomol. Chem.* **2005**, *3*, 274.
- (6) O. Hartmann, M. Kalesse *Angew. Chem. Int. Ed.* **2014**, *53*, 7335.

About the authors



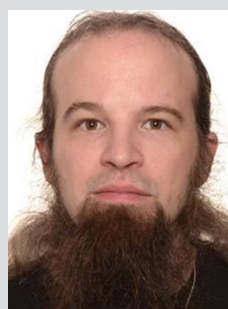
Prof. R. Schobert

Rainer Schobert received his doctoral degree in 1985 for synthetic work on macrolide antibiotics in the group of Hans-Jürgen Bestmann at the University of Erlangen (Germany). After a postdoctoral project on organoiron chemistry with Steven Ley at the Imperial College in London (UK) he went back to Erlangen to finish his habilitation on early transition metallocenes in 1993. Between 1999 and 2001 he was a senior lecturer at The Queen's University Belfast (UK). He currently holds the Chair of Organic Chemistry at the University of Bayreuth (Germany). His research interests span a wide range including bioactive lactones and lactams, siderophore-penam conjugates, and anticancer metallodrugs.



M. Petermichl

Markus Petermichl obtained his B.Sc. (2012) and his M.Sc. (2015) degrees in chemistry for his synthetic studies of the chemistry of complex acyltetramic acids in the group of Professor R. Schobert at the University of Bayreuth (Germany). He stayed in the group for a Ph.D. project and is currently pursuing total syntheses of further glycosylated tetramic acids and of other natural heterocycles with biological activity.



Dr. S. Loscher

Sebastian Loscher studied chemistry at the University of Stuttgart (Germany). After research internships with Professor K. Kern at the Max Planck Institute for Solid State Research (Germany) in 2005 and with Professor P. H. Seeberger at the ETH Zürich (Switzerland) in 2008, he undertook a diploma project in 2009 on α -glucosidase inhibitors with Dr. T. D. Butters at the Oxford Glycobiology Institute (UK). In 2010, he joined the group of Professor R. Schobert to work on the total synthesis of glycosylated tetramic acids until his graduation in summer 2015. Since September 2015 he has been a postdoctoral fellow in the group of Professor Dr. M. Bogoy in the Department of Pathology at Stanford University (USA).

Triiodide-Mediated δ -Amination of Secondary C–H Bonds

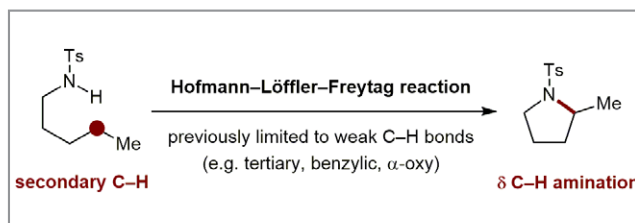
Angew. Chem. Int. Ed. **2016**, *55*, 9974–9978

A recent article published by the group of Professor David Nagib from The Ohio State University (USA) describes a highly innovative chemical method that enables the δ -amination of secondary C–H bonds within a large range of unactivated amines bearing biologically relevant functionalities (Scheme 1).

Professor Nagib explained: “This work is the first discovery from our lab that we expect will serve as the cornerstone of our entire program focused on remote C–H functionalization. As we set out to begin our research on selective C–H functionalization, we quickly realized that a general strategy for the δ -amination of secondary C–H bonds remains an unsolved problem.” In fact – as explained by Professor Nagib – although the century-old Hofmann–Löffler–Freitag (HLF) reaction (Scheme 2) has been developed to solve this challenge in the context of biased amines containing weak C–H bonds (e.g. tertiary, benzylic, α -oxy), a solution does not yet exist for applying this approach to the δ -selective amination of secondary C–H bonds.

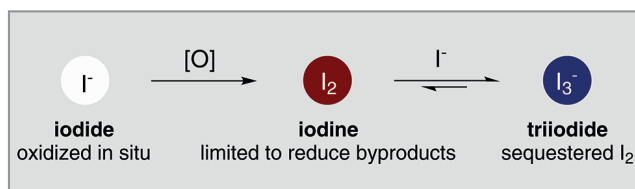
“It is understood that the requisite use of I_2 in the modified Suarez–HLF reaction limits synthetic scope and utility due to competitive byproducts associated with I_2 decomposition,” said Professor Nagib. “Others have attempted to address this I_2 problem through portion-wise or sub-stoichiometric addition of I_2 ; however, neither approach has been able to solve the long-standing challenge for δ -amination of unbiased, secondary C–H bonds, due to the either insufficient or excessive reactivity of those methods.”

Professor Nagib continued: “In this manuscript, we presented a new strategy in which I_2 is prepared in situ from NaI and rapidly trapped as a triiodide (I_3^-) species (Scheme 3). By sequestering the necessary, albeit prone to forming



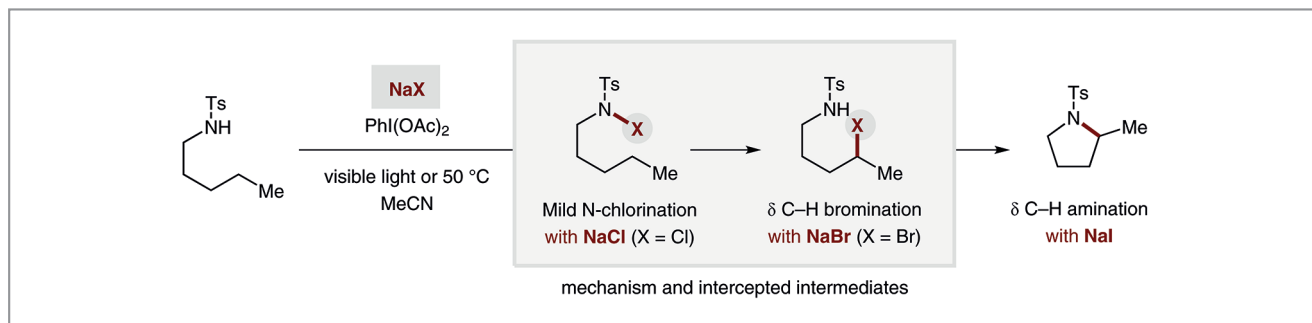
Scheme 2 The Hofmann–Löffler–Freitag (HLF) reaction

by-products, I_2 as I_3^- , we have demonstrated that this new triiodide strategy can solve the ongoing synthetic challenge of δ -amination of unactivated, secondary C–H bonds.”



Scheme 3 The triiodide strategy enables amination of unbiased C–H bonds by sequestering I_2 as I_3^-

“At first, we had been trying to catalyze this reaction also with CuI,” explained Professor Nagib. He added: “Yet, we were amused that as we added less and less catalyst (while adding more NaI salt), we still observed the same (or better) efficiency. We ultimately decided that the only thing better than 1–2% catalyst loading is 0%. And replacing it with salt, which is nearly free, is great too!”



Scheme 1 The new δ -amination methodology

During his undergraduate studies, Ethan Wappes' research was in the field of organic electrochemistry. "The moment Ethan realized that triiodide – a common electron mediator in batteries – was the key to solving this synthetic method, it was a very fortunate déjà vu experience!" said Professor Nagib.

The broad impact, significance, and synthetic utility of this triiodide strategy have been demonstrated in the δ -amination of a wide range of amines containing unbiased, secondary C–H bonds (Scheme 4). "Notably, many of the pyrrolidine products that we efficiently generate through this approach have been previously inaccessible due to the limitations of the I_2 -based methods," said Professor Nagib. "Furthermore, the broad tolerance of this transiently trapped I_3^- approach to biologically relevant functionality (e.g. ethers, esters, ketones, arenes, and organofluorines) suggests that this strategy will have broad applicability across many research areas at the frontiers of organic synthesis."

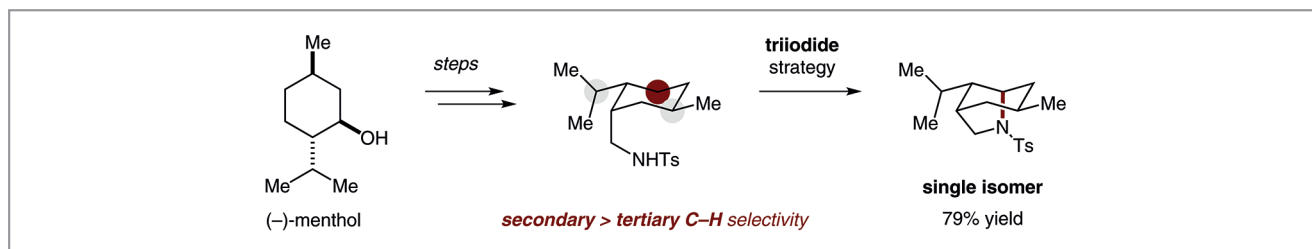
"Importantly, this manuscript includes significant mechanistic evidence to support the role, presence, and utility of triiodide in our hypothesized strategy," remarked Professor Nagib. "For example, UV-Vis spectroscopic evidence of this reaction confirms the presence of increasing triiodide absorp-

tion that correlates with increasing (and unprecedented) reaction efficiency in the presence of added NaI. Furthermore, sequestration of I_2 as I_3^- , which we proposed would lead to efficient product formation, is corroborated by significantly cleaner crude 1H NMR spectral data that indicate a termination of the major byproduct formation pathways (Figure 1)."

He continued: "Perhaps most importantly, we have intercepted and characterized a pair of proposed intermediates by replacing the NaI starting material for NaCl or NaBr salts. These examples of interrupted mechanisms point to the mildness of this new reaction method as well as the opportunity to extend this strategy to avoiding unwanted byproducts in other polyhalide-mediated reactivity."

Professor Nagib revealed that in a private communication, Professor Richmond Sarpong of UC Berkeley (USA) has called this work a "Nice solution to an age-old problem!" Additionally, he has expressed interest "in using robust ways (like yours) in alkaloid synthesis" and even stating: "There is a total synthesis we are working on where this could come in handy."

Professor Nagib concluded: "We anticipate that due to the prevalence of pyrrolidines in pharmaceuticals (fifth most common heterocycle in US FDA approved drugs) this chemistry



Scheme 4 One of the synthetic applications of the new method

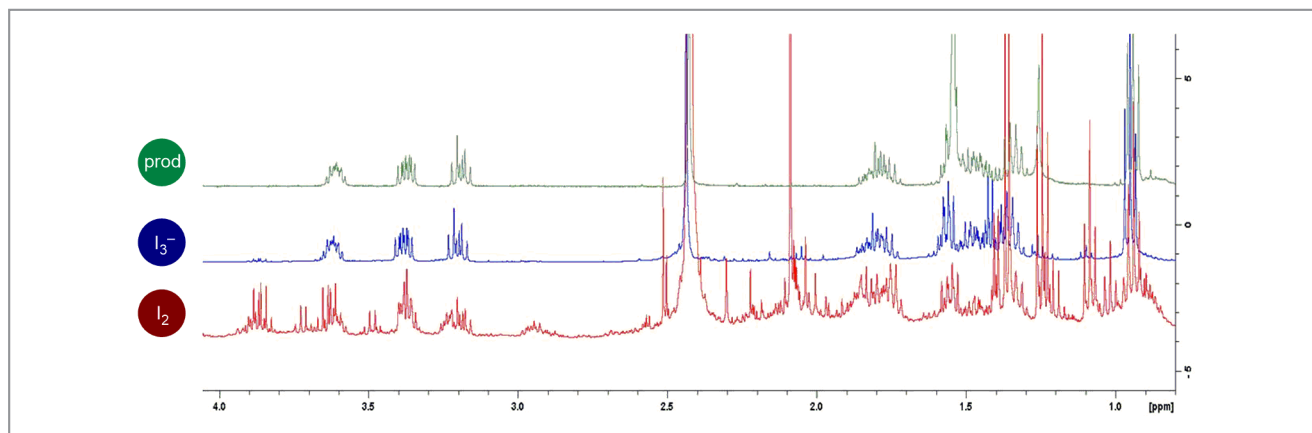


Figure 1 1H NMR analysis of new I_3^- strategy vs I_2 reaction applied to the synthesis of *N*-tosyl-2-*n*-propyl-pyrrolidine

will be particularly valuable for chemists in both industrial sectors (e.g. medicinal chemistry) as well as in the academic community (especially in the field of C–H functionalization). We hope that many people will use our simple, new method for derivatizing their secondary C–H bonds.”

Mattos Fenske

About the authors



From left: S. Fosu, Prof. D. Nagib, E. Wappes

Ethan Wappes (Fort Wayne, IN, USA) earned a B.Sc. with honors at Indiana University (USA) in 2014, where he studied electrochemical ring-expansions with Professor Dennis Peters. At Ohio State University (OSU, USA), he has been awarded a Charles Waring fellowship (OSU) and honorable mention by the National Science Foundation (NSF) Graduate Research Fellowship program.

Stacy Fosu (Macomb, IL, USA) earned a B.Sc. at the University of Illinois at Urbana-Champaign (USA) in 2011 and her M.Sc. from Illinois State University (USA) in 2014, where she synthesized novel benziporphyrins with Professor Timothy Lash. At OSU (USA), she has been awarded a Chemistry-Biology Interface Program fellowship and is a Howard Hughes Medical Institute (HHMI) Gilliam Fellow.

Trevor Chopko (Akron, OH, USA) earned a B.Sc. with honors at The Ohio State University (USA) in 2016, where he developed radical-mediated C–H functionalizations with Professor David Nagib and was a fellow of the OSU Honors & Scholars Center. He is currently an intern in the Translational Imaging division of Merck & Co.

David Nagib (Philadelphia, PA, USA) earned a B.Sc. with honors at Boston College (USA) (Scholar of the College, 2006), while desymmetrizing alcohols via de novo peptide catalysts with Professor Scott Miller. At Princeton University (USA) (Ph.D., 2011), he developed new trifluoromethylation reactions via photoredox catalysis with Professor David MacMillan. As an NIH Postdoctoral Scholar at the University of California, Berkeley (USA, 2014), David studied C–H activation via oxidative gold mechanisms with Professor F. Dean Toste, and catalysis in post-synthetically modified metal-organic framework materials with Professor Omar Yaghi. David is an Assistant Professor in the Department of Chemistry and Biochemistry at The Ohio State University (USA), where his team’s research on radical-mediated C–H functionalization has been recognized with a 2015 Doctoral New Investigator Award by the American Chemical Society Petroleum Research Foundation (ACS PRF) and a 2016 Outstanding Investigator Award by the National Institutes of Health (NIH MIRA).

When not working alongside their awesome labmates, Ethan, Stacy, Trevor, and David enjoy running, reading, baking, building miniature pyramids, and exploring Columbus’ great food, art, and music scenes.

Coming soon

■ Literature Coverage

Palladium-Catalyzed Regioselective B–C(sp) Coupling via Direct Cage B–H Activation: Synthesis of B(4)-Alkynylated o-Carboranes

■ Literature Coverage

Charge-Transfer-Directed Radical Substitution Enables *para*-Selective C–H Functionalization

■ Literature Coverage

Exploiting the Distal Reactivity of Indolyl-methylenemalononitriles: An Asymmetric Organocatalyzed [4+2] Cycloaddition with Enals Enables the Assembly of Elusive Dihydrocarbazoles

Further highlights

Synthesis Review: Direct (Hetero)arylation Reactions of (Hetero)arenes as Tools for the Step- and Atom-Economical Synthesis of Biologically Active Unnatural Compounds Including Pharmaceutical Targets

(by R. Rossi, F. Bellina and co-workers)

Synlett Account: Photocatalytic E → Z Isomerization of Alkenes

(by R. Gilmour and J. B. Metternich)

Synfacts Synfact of the Month in category “Synthesis of Materials and Unnatural Products”: Nanohoop through Anthracene Photodimerization–Cycloreversion

For current SYNFORM articles, please visit www.thieme-chemistry.com
 SYNFORM issue 2016/12 is available from November 17, 2016
 at www.thieme-connect.com/ejournals

Impressum

Editor

Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, 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 Editor: Michael Binanzer,
michael.binanzer@thieme.de, phone: +49 711 8931 768
 ■ Scientific Editor: Selena Boothroyd,
selena.boothroyd@thieme.de
 ■ Assistant Scientific Editor: Kathrin Ulbrich,
kathrin.ulbrich@thieme.de, phone: +49 711 8931 785
 ■ Senior Production Editor: Thomas Loop,
thomas.loop@thieme.de, phone: +49 711 8931 778
 ■ Production Editor: Helene Ott,
helene.ott@thieme.de, phone: +49 711 8931 929
 ■ Production Editor: Thorsten Schön,
thorsten.schoen@thieme.de, phone: +49 711 8931 781
 ■ Editorial Assistant: Sabine Heller,
sabine.heller@thieme.de, phone: +49 711 8931 744
 ■ Senior Marketing Manager: Julia Stötzner,
julia.stoetznier@thieme.de, phone: +49 711 8931 771
 ■ Postal Address: Synthesis/Synlett/Synfacts, Editorial Office, Georg Thieme Verlag KG,
 Rüdigerstraße 14, 70469 Stuttgart, Germany,
 ■ Homepage: www.thieme-chemistry.com

Publication Information

Synform will be published 12 times in 2016 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

Publication Policy

Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to Synthesis, Synlett and Synfacts

The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
 Via e-mail: customerservice@thieme.com
 Via website: www.thieme-chemistry.com
 Phone: +1 212 760 0888; Fax: +1 212 947 1112
 Order toll-free within the USA: +1 800 782 3488
 Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.
 Via e-mail: customerservice@thieme.de
 Via website: www.thieme-chemistry.com
 Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through www.thieme-chemistry.com.

Online Access

The online versions of Synform as well Synthesis, Synlett and Synfacts are available through www.thiemeconnect.com/products/ejournals/journals where it is also possible to register for a free trial account. For information on multi-site licenses and pricing for corporate customers as well as backfiles, please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695
 Europe, Africa, Asia, and Australia: eproducts@thieme.de, phone: +49 711 8931 407
 India: eproducts@thieme.in, phone: +91 120 45 56 600
 Japan: brhosoya@poplar.ocn.ne.jp, phone: +81 3 3358 0692

Manuscript Submission to Synthesis and Synlett

Manuscript submissions will be processed exclusively online via <http://mc.manuscriptcentral.com/synthesis> and <http://mc.manuscriptcentral.com/synlett>, respectively. Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com.

Copyright

This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies to translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart · New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US\$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.