Biomimetic Synthesis of Bipleiophylline

Dear Readers,

Here we go again with another December issue, another year is gone and Christmas is already looming. I can’t even remember when I had the last white Christmas, perhaps it was in 2010. Sadly, snow has become an incredibly rare event in many places in Europe. What everybody – children or grown-ups makes no difference – expects and craves is a peaceful Christmas day with relatives and friends, sitting for hours all together, chatting and eating awfully large amounts of food, with the snow falling outside the window. Nobody wants a sunny and dry Christmas day with mild temperatures, unless you are on holiday in a tropical place! What kind of Christmas is that!!! But that’s what we have been experiencing more and more frequently during the last couple of decades. And someone is still convinced that climate change is not real... Hopefully – regardless of the snow – this was a good year for most – if not all – of you. Certainly it has been a year packed full with plenty of exciting new chemistry, and this December 2017 issue of SYNFORM is a further demonstration of that! The issue starts with an Editorial Board Focus interview with the new Science of Synthesis editorial board member Margaret Faul (USA). The scientific kick-off is given by a team effort led by G. Vincent (France) presenting the biomimetic synthesis of bipleiophylline. The third article is a contribution from the group of S. Lin (USA) and their Science paper on the electrochemical diazidation of alkenes. It is followed by a Young Career Focus interview with M. Juríček (Switzerland) who tells us about his work and experience in research so far. And the very last article of this issue and of the entire year of SYNFORM is a very entertaining and insightful Name Reaction Biography on the Wolff–Kishner reduction written by the guest author David Lewis.

Wishing a happy and peaceful Christmas to all of you and – as always – enjoy your reading!

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

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Editorial Board Focus: Dr. Margaret Faul (Amgen, USA)

**Background and Purpose.** From time to time, SYNFORM portraits Thieme Chemistry Editorial Board or Editorial Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. This Editorial Board Focus presents Dr. Margaret Faul (Amgen, USA) who recently joined the Editorial Board of Science of Synthesis as a new member.

**Biographical Sketch**

**Margaret Faul** received her B.Sc. and M.Sc. degrees from University College Dublin (Ireland). She then moved to the USA where she received her Ph.D. degree in Synthetic Organic Chemistry from Harvard University (USA) with Professor David A. Evans. In 1993 Margaret joined the Chemical Process group at Eli Lilly and Company (USA) and in 2003 she moved to Amgen (USA) where she is currently the Executive Director in the Process Development organization. At Amgen, Margaret is responsible for the Commercial Process Development and Process Characterization of all molecules in both the Synthetic and Biologic Amgen Portfolio.

During her 25-year career, Margaret has leveraged her technical experience to support programs across all stages of development from preclinical to commercialization. She has supported the process development and supply of drug substance for clinical trials and commercial products and has significant experience in scale-up and GMP concepts. Margaret has experience working with Commercial Manufacturing Organizations worldwide and an ability to work with partners during licensing activities to ensure seamless integration and development of programs with the partner company. Margaret has a strong knowledge of regulatory and compliance issues as they relate to the development of pharmaceutical products. For her achievements in chemical research management Margaret was recognized as the recipient of the 2018 Earle Barnes recipient for Leadership in Chemical Research Management from the American Chemical Society.

Throughout her industrial career at Amgen, Margaret has invested significant effort in evolving a green chemistry culture focused on implementation of greener and more sustainable chemical processes towards the development of novel drug substances. These efforts resulted in Amgen being awarded the Presidential Green Chemistry Challenge Award in 2017 in recognition of their work to promote the environmental and economic benefits of novel green chemistry.

Margaret has achieved a strong scientific reputation and has invested significantly in supporting the external scientific efforts. She is a member of the Board of Directors of the International Consortium for Innovation and Quality in the Pharmaceutical Industry and Chair of the Enabling Technologies Consortium. Margaret also has a strong publication record as an author/co-author of more than 150 peer-reviewed publications, presentations and patents. Margaret has served as a symposium organizer and session chair for several major process chemistry events and is has been a member of the Editorial Boards for *Organic Syntheses*, Journal of Organic Chemistry and Organic and Biomedical Chemistry.

**INTERVIEW**

**SYNFORM** Please could you comment on your new role as a member of the Editorial Board of Science of Synthesis?

**Dr. M. Faul** I am very excited to join the Editorial Board of Science of Synthesis. This reference work provides valuable information to organic chemists by providing full-text descriptions of organic transformations in the form of critical reviews and, at the same time, experimental procedures. Having recently completed an eight-year term on the Editorial Board of Organic Syntheses, I feel this is a good transition for me where I can continue giving back value to the organic synthesis community by providing feedback on the value of the procedures based upon their application in an industrial setting.
SYNFORM What do you think about the modern role and prospects of synthetic chemistry, in particular its importance in and for the pharmaceutical industry?

Dr. M. Faul Organic synthesis continues to play a critical role in the pharmaceutical industry and is the basis on which we develop the commercial processes for our new chemical entities (NCEs). Continued learning across industry and academia is key to developing a deep understanding of our chemical processes ensuring that they can be safely applied in a manufacturing setting.

SYNFORM You are a leading researcher with regard to green chemistry. Could you tell us more about how important you perceive this particular topic to be?

Dr. M. Faul The pharmaceutical industry is invested in advancing sustainability through the application of green chemistry principles. As demands on our industry for ‘right first time’ and ‘reduced cost and time to market’ become ever more critical, my role as a leader in process development is to ensure that we can provide medicines to patients using cost-competitive manufacturing processes that minimize environmental impact.
Biomimetic Synthesis of Bipleiophylline

Nat. Chem. 2017, 9, 793

With over 2500 described structures, monoterpene indole alkaloids constitute a class of natural substances all derived from a single common precursor (strictosidine). These compounds are fascinating both in terms of complexity and diversity and are, needless to recall in detail, of great biological value, especially in the field of pharmacology. The synthesis of such molecules represents a challenging task for organic chemists, as well as an opportunity for developing innovative synthetic methods and strategies towards the assembling of these molecular scaffolds. Indeed, several research teams worldwide still consider monoterpene indole alkaloids as stimulating targets of choice in total synthesis. Even more challenging is the access to bis-indole alkaloids of this family. Among them, bipleiophylline, isolated from the bark of Alstonia angustifolia in Malaysia, has attracted attention since its discovery in 2008 due to its extreme complexity (Org. Lett. 2008, 10, 3749).

"For instance, it was recently pictured on top of a mountain ‘to climb’ on the front cover of an authoritative book dealing with the design of synthetic strategies by Hanessian, Giroux and Merner (Design and strategy in organic synthesis: from the chiron approach to catalysis, Wiley-VCH, 2013).” confirmed Dr. Guillaume Vincent of the ICMMO, Université Paris-Sud, Faculty of Sciences (France). Pleiocarpamine, a known monoterpene indole alkaloid, emerges as a constitutive key sub-structure of bipleiophylline. Two units of this monomer are anchored to pyrochatechuic acid via a benzofuroindoline and an isochromenoindoline as heterocyclic linkers.

To tackle the challenge of synthesizing bipleiophylline, Dr. Vincent’s group joined forces and knowledge with the team of Professor Erwan Poupon and Dr. Laurent Evanno (BioCIS, Université Paris-Sud, Faculty of Pharmacy, France) within the framework of a grant from the French National Research Agency (ANR).

"Importantly, our group holds expertise in synthetic methodology dealing with the indole nucleus, and has developed several methods to access the benzofuroindoline frameworks that can be found in bipleiophylline (Angew. Chem. Int. Ed. 2012, 51, 12546; Angew. Chem. Int. Ed. 2014, 53, 11881; Org. Lett. 2014, 16, 5752), and also benefits from the experience of Professor Cyrille Kouklovsky in all aspects of synthetic organic chemistry,” said Dr. Vincent, who continued: “Furthermore, the group of Erwan Poupon and Laurent Evanno specialize in natural product chemistry and has recently reported the biomimetic transformation of indole natural products (Angew. Chem. Int. Ed. 2014, 53, 6419; Eur. J. Org. Chem. 2015, 1894; Eur. J. Org. Chem. 2016, 1494).”

The first task was to develop a synthetic method to access selectively both the benzofuroindoline and isochromenoindoline motifs from simple indole starting materials. “The previous methods published by our group proved to be unsuitable in the context of bipleiophylline and we decided to take advantage of the knowledge in biomimicry of our partners in the Poupon/Evanno group to adopt a bioinspired approach,” said Dr. Vincent. Therefore, PhD student Natacha Denizot (ICMMO) generated a transient ortho-quinone with silver oxide from pyrocatechuic methyl ester on which a 2,3-disubstituted indole could undergo a 1,6-conjugate addition to deliver the benzofuroindoline part which corresponds to the first objective of the methodology.

“We were surprised and thrilled to note that the isochromenoindoline part, our second objective, was obtained via a 1,4-conjugate addition, simply by starting from the free benzoic acid instead of its methyl ester,” said Dr. Vincent, continuing: “The great potential of our method was demonstrated when we built, simultaneously, both the benzofuroindoline and the isochromenoindoline heterocyclic systems on the aromatic spacer when using an excess of the indole partner.”

“The efficiency of this method had then to be evaluated on complex indole alkaloids,” said Dr. Evanno and Professor Poupon. They revealed that postdoctoral researcher David Lachkar (BioCIS) first isolated tiny amounts of pleiocarpamine from Pleiocarpa mutica and Alstonia undulata (provided by Dr. Marc Litaudon and Dr. Vincent Dumontet, Institut de Chimie des Substances Naturelles, France) with the help of Dr. Mehdi Beniddir (BioCIS) and his students in the team. He then meticulously, and successfully, submitted this natural starting material to the oxidative coupling conditions with pyrochatechuic acid and silver oxide. The spectral data of the mono-coupling product corresponded to natural product voacalgine A (Tetrahedron 2013, 69, 10869). The originally assigned structure of the latter was thought to contain a benzofuroindoline unit. "Based on the selectivity obtained during the method development, we decided to reinvestigate the structure of voacalgine A by 2D NMR including HMBC. Indeed, we reassigned its structure which proved to contain an isochromenoindoline," said Dr. Evanno and Professor Poupon. Finally, voacalgine A, the postulated biosynthetic precursor of bipleiophylline, was subjected to a second oxidative coupling..."
A. Methodology

Scheme 1

B. Biomimetic synthesis of bipleiphylline

C. Molecular diversity
in the presence of pleiocarpamine which allowed the ‘climbing partners’ to reach their summit, since bipleiophylline was obtained in two steps and 3% yield from pleiocarpamine.

Dr. Vincent concluded: “To further demonstrate its synthetic potential, robustness and to access molecular diversity, the synthetic method was applied to a few indole alkaloids such as geissoschizine, yohimbine, and ajmalicine. Several isochromenoidoline natural-product-like derivatives were thus obtained.”

About the authors

Natacha Denizot was born in 1988 in Vienne (France). She obtained her Bachelor’s degree in chemistry from the Université d’Avignon et Pays du Vaucluse (France) in 2009. She then was awarded her MSc degree from the Université Joseph Fourier, Grenoble (France) in 2012 with an internship at Givaudan (Switzerland) with Dr. Philip Kraft. In November 2015, she obtained her PhD under the direction of Dr. Guillaume Vincent on the synthesis of benzofuroindoline-containing natural products with a fellowship from the ‘Fondation pour le développement de la chimie des substances naturelles et de ses applications sous l’égide de l’Académie des Sciences.’

David Lachkar received his MSc in organic chemistry from the Université Paris-Sud, Orsay (France) in 2011. He obtained a PhD degree working on polyoxometalate catalysis and supramolecular synthesis supervised by Dr. Emmanuel Lacôte at the Institut de Chimie des Substances Naturelles (ICSN-CNRS, France). Then he undertook postdoctoral research with Professor Erwan Poupon and Dr. Laurent Evanno, where he worked on extraction of marine natural indole alkaloids.

Cyrille Kouklovsky was born in Paris (France) and educated at the Université Paris-Sud (France). He defended his PhD in 1989 under the supervision of Professor Yves Langlois (CNRS, Gif-Sur-Yvette, France), working on the cationic asymmetric Diels–Alder reaction. Then he moved to a postdoctoral position in Professor Steven V. Ley’s research group (University of Cambridge, UK), working on the total synthesis of rapamycin. In 1995, he was appointed as a ‘Chargé de Recherche’ CNRS at Université Paris-Sud (France), working on asymmetric dipolar cycloaddition reactions and their synthetic applications. He was promoted to Professor of Chemistry in 2003. His research interests are in the fields of synthetic methodology, asymmetric synthesis, and peptide synthesis. He is currently the President of the Organic Division of the French Chemical Society (SCF).

Laurent Evanno received his PhD degree in 2007 from the Université Pierre et Marie Curie - Paris 6 (France), working on total synthesis under the supervision of Dr. Bastien Nay at the ‘Muséum National d’Histoire Naturelle’ (France). He then undertook postdoctoral research with Professor Petri Pihko at Helsinki University of Technology – TKK (Finland) in 2008 and with Professor Janine Cossey at ESPCI–Paris Tech (France) in 2009. Since 2010, he has been assistant professor at the Université Paris-Sud (France). His research interests encompass biomimetic synthesis and isolation of natural substances.

About the authors

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Prof. C. Kouklovsky

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Erwan Poupon is full professor of pharmacognosy and natural product chemistry at the Université Paris-Sud (France), now part of the Université Paris-Saclay. He obtained his PharmD from the Université de Rennes (France) in 1996 and his PhD from the Université Paris Descartes (France) in 2000 under the guidance of Professor Henri-Philippe Husson. After a postdoctoral period in the group of Emmanuel Theodorakis (University of California in San Diego, USA), he joined the faculty at the Université Paris-Sud. His scientific interests include all aspects of natural product chemistry from their origin and evolution to their total synthesis.

Guillaume Vincent was born in 1978 in Lyon (France). He graduated in 2002 from the Ecole Supérieure de Chimie Physique et Electronique de Lyon (CPE Lyon, France). During this period, he spent one year at the Dupont Pharmaceuticals Company in Wilmington (USA) working with Dr. Patrick Y. S. Lam. In 2002, he also obtained his MSc degree from the Université Lyon 1 (France), having worked in the group of Professor Marco A. Ciufolini. He completed his PhD in 2005 under the supervision of Professor Ciufolini. He then joined Professor Robert M. Williams at Colorado State University (USA) as a postdoctoral associate. At the beginning of 2007 he returned to France to the group of Professors Max Malacria and Louis Fensterbank at the Université Pierre et Marie Curie - Paris 6 (France). Finally, at the end of 2007 he was appointed ‘Chargé de Recherche’ by the CNRS at the Institut de Chimie Moléculaire et des Matériaux d’Orsay at the Université Paris-Sud working with Professor Cyril Kouklovy on nitroso-Diels–Alder cycloaddition and total synthesis of natural products. In 2011, he launched an independent research program towards synthetic applications and understanding of unusual reactivity of the indole nucleus.
Metal-Catalyzed Electrochemical Diazidation of Alkenes

*Science 2017, 357, 575–579*

Electrochemistry offers an efficient and sustainable alternative to conventional chemical approaches for organic synthesis. The group of Professor Song Lin at Cornell University (USA) has been developing novel efficient and sustainable synthetic processes in recent years. Professor Lin said: “Our research was built on tremendous pioneering work in the area of electro-organic synthesis, but also gained inspiration from creative research on small-molecule activation using electrocatalysis.”

Professor Lin continued: “Our main contribution to the area through this work we published in *Science* is the integration of electrochemistry and catalysis, which synergistically controls the direct generation of highly reactive radical intermediates and the selective downstream reactivity of these open-shell species.”

The group’s strategy culminated in a reaction involving radical intermediates under very mild conditions, which...
resulted in a broad substrate scope and exceptionally high functional group compatibility compared to existing protocols for alkene diamination. “This reaction protocol thus serves as a general approach to accessing vicinal diamines, structural motifs highly prevalent in bioactive compounds and privileged molecular catalysts,” said Professor Lin.

He explained: “Our new mode of redox catalysis, where different anodic catalytic events are joined to complete the full transformation, is reminiscent of but complimentary to photoredox catalysis where an oxidative and a reductive event are combined.”

Concerning the future directions of this work, the group intends to continue exploring the tremendous potential of electrocatalysis in innovating chemical synthesis. “In the near future, we are looking to understand the reaction mechanism of the electrocatalytic diazidation of alkenes and use these mechanistic insights to guide future design of a variety of new alkene functionalization reactions,” said Professor Lin. He continued: “In collaboration with industrial partners, we also hope to apply our new methods to streamline the synthesis of key intermediates en route to medicinally relevant products. We hope that, in the long term, our efforts can contribute to improving the cost efficiency and sustainability of pharmaceutical production.”

The Lin lab is very young as it was established in the summer of 2016. The authors of this paper include a postdoctoral associate (Niankai Fu), who obtained his PhD in organic chemistry, a then-first-year graduate student (Greg Sauer), and two undergraduate researchers. Although Professor Lin conducted postdoctoral research in electrocatalytic CO₂ reduction, none of the group members had extensive experience in synthetic electrochemistry. “With the help of colleagues and friends, we learned the theory and experimental techniques as a group,” said Professor Lin. He concluded: “After a year of learning and exploration, now I can proudly say that we have become experts in synthetic electrochemistry.”

Scheme 2 Proposed mechanism for the electrocatalytic diazidation of alkenes
About the authors

Niankai Fu was born in Hubei Province (P. R. of China). He obtained his B.S. at Hubei University in 2009 and Ph.D. in organic chemistry under the guidance of Professor Sanzhong Luo at the Institute of Chemistry, Chinese Academy of Sciences (P. R. of China) in 2014. In July 2016, he began his postdoctoral appointment with Professor Song Lin at Cornell University (USA) where his research is focused on the development of electrocatalytic methods for organic synthesis.

Greg Sauer was born and raised in Pittsburgh, PA (USA). He completed his B.S. at Binghamton University (USA) where he conducted his undergraduate research under Dr. Zhitao Li in carbohydrate synthesis and post-baccalaureate research under Dr. Mathew Vetticatt studying organocatalytic mechanisms.

In October 2016, he joined Professor Song Lin’s lab at Cornell University (USA) as an NSF graduate research fellow and his research is focused on studying the mechanism of electrocatalytic alkene functionalization.

Ambarneil Saha was born in Starkville, MI, and grew up in Cupertino, CA (USA). He joined Professor Song Lin’s lab in 2016 as a junior and will graduate with an A.B. in the spring of 2018. His current research is focused on electrochemical synthesis.

Aaron Loo grew up in New York City (USA) and moved to Ithaca for college in 2015. He joined Professor Song Lin’s lab in 2017 as a sophomore. His research interest lies in the application of electrochemistry to sustainable organic synthesis.

Song Lin was born and raised in Tianjin (P. R. of China). After earning his B.S. from Peking University (P. R. of China) in 2008, he pursued graduate studies at Harvard University (USA) working under the direction of Professor Eric Jacobsen. His doctoral research was focused on the development and mechanistic understanding of enantioselective organocatalysis. He then carried out postdoctoral studies with Professor Chris Chang at UC Berkeley (USA) on electrocatalytic reduction of CO₂ using covalent organic frameworks. In the summer of 2016, Professor Song Lin joined the faculty at Cornell University (USA). His research focuses on the discovery of new catalytic strategies for organic synthesis.

From left: Dr. N Fu, Prof. S. Lin, G. Sauer (Photo: Cornell University)
Young Career Focus: Professor Dr. Michal Juríček  
(University of Zurich, Switzerland)

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 Dr. Michal Juríček (University of Zurich, Switzerland).

Biographical Sketch

Michal Juríček was born in Bojnice and raised in Prievidza, two small cities in Slovakia. He received his Master’s degree in organic chemistry in 2005 from the Comenius University in Bratislava (Slovakia), where he explored the stereochemistry of binaphthyls under the supervision of Professor Martin Putala. He then moved to The Netherlands to pursue his PhD at the Radboud University Nijmegen mentored by Professor Alan Rowan. His dissertation work revolved around the chemistry of triazoles, which he employed in the design and synthesis of functional materials. In 2011, he received Dutch fellowship Rubicon and went on to spend two years at Northwestern University in Evanston (USA). There, as a postdoctoral scholar in the group of Professor Sir Fraser Stoddart, he extended the size of tetraactylcyclophanes to sequester hydrocarbon pollutants, mimic enzyme catalysis, and make molecular switches. In 2013, he returned to Europe and started his independent research career in Switzerland: first at the University of Basel as an Ambizione fellow of the Swiss National Science Foundation (SNSF) hosted in the group of Professor Marcel Mayor and, as of April this year, as an Assistant Professor at the University of Zurich, where his research is supported by the European Research Council and SNSF. His group designs, synthesizes, and investigates functional organic molecules with delocalized spin densities. Michal is a 2017 recipient of the Thieme Chemistry Journals Award.

INTERVIEW

SYNFORM What is the focus of your current research activity?

Prof. Dr. M. Juríček Our group develops functional materials based on organic molecules that contain one or more unpaired electrons for applications in spin electronics or simply ‘spintronics’. The research in our group lies at the interface between organic synthesis, physical organic chemistry, materials science and supramolecular chemistry, and revolves around spin-delocalized open-shell systems. Our biggest excitement is to design and make molecules, where new functionality arises from the presence of unpaired electrons and spin interactions between them.

SYNFORM When did you get interested in synthesis?

Prof. Dr. M. Juríček During my high-school years, for which I am indebted to my chemistry teacher Miroslav Kozák, who motivated me to participate in Chemistry Olympiads. Organic chemistry fast became my favorite topic and in the third and the fourth year of my high-school studies, I had my first experience with organic synthesis. Later during my undergraduate studies in Bratislava, my interest in making and studying new molecules deepened and ever since it has remained my passion. One of the reactions that I enjoyed performing the most is one step in the synthesis of hexacene reported1 by Chow. This step was mediated by 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine, a bright magenta solid, and involved a double sequence of Diels–Alder and retro-Diels–Alder reactions and release of two molecules of dinitrogen per one molecule of product. It was fascinating to see how the beautiful magenta color turned black while heaps of gas formed. After the work-up, the product was isolated as a white solid.
**SYNFORM** What do you think about the modern role and prospects of organic synthesis?

Prof. Dr. M. Juriček Our group does not develop new reactions or methods, unless it happens by serendipity. But we do use reactions to synthesize our targets and rely on efficient methodologies that are available. Often, it is the latest synthetic advancement that makes it possible for us to reach the molecules of our interest. I therefore believe that the development of new organic reactions and methods – whether they are catalyzed, sustainable, or not – plays a central role in accessing structural motifs that are not within reach by current synthetic means. This is equally important for materials science as it is for natural product synthesis and other fields.

**SYNFORM** Your research group is active in the areas of organic chemistry and materials science. Could you tell us more about your research and its aims?

Prof. Dr. M. Juriček Our aim is to learn how to introduce and control multiple functionalities in a bulk material assembled from molecules that contain unpaired electrons through manipulation of spin interactions within and between the molecules. One type of molecule that we investigate is π-conjugated Kekulé hydrocarbons with a biradicaloid singlet ground state and a low-lying triplet excited state that can be populated thermally (Figure 1c). One of the strategies that we use to control the spin interactions is that we ‘embed’ unpaired electrons within a helical π-conjugated backbone reminiscent of a helical staircase (Figure 1a). Last year, we reported the first molecule of this kind, namely, a helically twisted ‘C’-shaped cethrene (Figure 1d), an isomer of a planar ‘Z’-shaped heptazethrene (Figure 1b). We showed that in cethrene, the singlet–triplet energy gap is markedly lower (5.6 kcal mol⁻¹) than that of its isomer heptazethrene (8.9 kcal mol⁻¹), on account of through-space interactions that arise within the frontier molecular orbitals because of the helical twist (Figure 1e). The next step is to explore the effect of other parameters, so that we can alter the size of this gap even further. This would allow us to fine-tune the properties on a molecular level and systematically investigate how they impact the properties in the bulk.

**Figure 1** (a) Prof. Dr. M. Juriček on the left-handed helical staircase at the University of Zurich and (d) molecular helix cethrene made in the Juriček group. The singlet–triplet gap ($\Delta E_{ST}$) of cethrene is lower than that of (b) its planar isomer heptazethrene on account of (e) through-space interactions within HOMO (ab = antibonding) and LUMO (b = bonding). (c) Both compounds have biradicaloid singlet ground state and low-lying triplet excited state.
SYNFORM  What is your most important scientific achievement to date and why?

Prof. Dr. M. Juriček  For me, the most important and exciting achievements are always the latest findings from our group, which are at the time still in the process of being fully understood. Then there is the thrill of not-knowing-but-trying-to-find the right answer. Currently, we are completing one study, dealing with unusual reactivity of cethrene, which we are very excited about.

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   *Synlett* 2016, 27, 1613.
Independent Discoveries: The Wolff–Kishner Reduction

This year is the 150th anniversary of the birth of Russian chemist Nikolai Matveevich Kizhner (1867–1935), and the 160th anniversary of the birth of German chemist Ludwig Wolff (1857–1919). These two chemists carried out seminal studies in the reactions of compounds with N–N bonds, leading to three eponymous reactions: the Wolff–Kishner deoxygenation of aldehydes and ketones, the Wolff rearrangement of α-diazoketones, and the Kishner cyclopropane synthesis. Here we concentrate on the first.

Kizhner graduated from the First Moscow Gymnasium and entered Moscow University in 1886 as a student in the Natural Science Division of the Physics-Mathematics Faculty. Here, two years later, he came under the influence of the mercurial Vladimir Vasil’evich Markovnikov (1838–1904) and his colleague, the physical chemist and thermodynamicist Vladimir Fyodorovich Luginin (1834–1911). These two men led Kizhner to choose organic chemistry for his career.

Following his graduation (Diplom) in 1890, Kizhner was appointed to a supernumerary position as a laboratory assistant teaching qualitative and quantitative analysis while he pursued the M. Khim. degree. In 1894, he was elected Privat-Docent, and was permitted to deliver lectures. At the same time, he also taught chemistry and electrical engineering at the Alexander Military School. During his M. Khim. period, Kizhner published a paper explaining the unexpected physical and chemical properties of ‘hexahydrobenzene’ obtained by the reduction of benzene with hydrogen iodide by identifying it as methycyclopentane rather than cyclohexane or n-hexane.

Kizhner graduated with the M. Khim. degree in 1895. His dissertation ‘Amines and hydrazines of the polymethylene series, methods of their formation and transformation’ reported his work in the chemistry of N-bromoamines and his first work with hydrazines and hydrazones (Scheme 1).

In 1900, Kizhner graduated with the Dr. Khim. degree, the minimum qualification for appointment as Ordinary Professor in Russian universities. In 1901, at the urging of Mendeleev, Kizhner was offered the position of inaugural Professor of Organic Chemistry at the new Tomsk Technological Institute (now Tomsk Polytechnic University) in Siberia. Here, Kizhner built the Department of Chemistry, and he used each of his frequent trips to the West to accumulate books, journals, and apparatus for his department. His early work here continued his investigations of bromoamines as well as the synthesis and reactions of small-ring compounds.

In 1902, Kizhner was diagnosed with ‘gangrene of the limbs,’ a painful and even life-threatening malady that led to the amputation of his left foot above the ankle in 1904. In 1910, he lost the other foot to the same disease. After his first amputation, Kizhner continued his teaching, but he relinquished his research laboratory to a colleague. What is amazing is that, confined to a wheelchair after his second amputation, which made his teaching extremely difficult, he returned to the research laboratory with a vengeance. It was a year after this second amputation that he first described his hydrazine decomposition.

Kizhner was a political progressive. During the Revolution of 1905, the students at Tomsk went on strike, asking autonomy for the universities from the Ministry of Education, and Kizhner was supportive of their actions, helped to organize similar activities by the faculty, and refused to impose sanctions on striking students. This earned him the enmity of the powerful Trustee of the Educational District, Leonid Ivanovich Lavrent’ev (d. 1914). In 1906, he was branded a ‘free thinker’ and exiled from Siberia, along with several colleagues. The intervention of the influential member of court, Count Witte,
earned his reinstatement in 1907. His political enemies were not appeased, however, and the continued machinations and veiled threats against his family by right-wing extremists resulted in Kizhner being forced from his professorship in 1912, and him leaving Tomsk permanently in 1914. Kizhner felt a very special bond to the Department that he had built, to his students, and to his uncompleted research there; leaving was very hard for him.

Still, Kizhner got the last laugh. Instead of resigning from his professorship, he retired on medical grounds, which provided him with a full pension! He moved to Moscow, where his pension allowed him to work, although he never again achieved the level of productivity he had in Tomsk. With the help of Aleksei Yevgen’evich Chichibabin (1871–1945), another Markovnikov student, he obtained an appointment to the Shanyavskii People’s University, an informal institution set up by the professors who had resigned from Moscow University in protest of the actions of the reactionary Minister of Education, Lev Aristidovich Kasso (1865–1914). Although it was not authorized to grant degrees, its standards were so high that even members of the faculty of Moscow University itself attended their lectures.

Following the October Revolution, Kizhner became the guiding force of the Soviet dye industry, and he was elected a Corresponding Member of the USSR Academy of Sciences in 1929, and an Honorary Member in 1934. It is worth noting that in all of Kizhner’s papers, he carried out the experimental work himself, in spite of his disabilities, and he also insisted on an equal level of care in the work of his students. It is fully in keeping with his character that he died just hours after returning home after a typically long day in the laboratory.

In contrast to the wealth of information about Kizhner, biographies of Wolff are few, and usually devoid of much detail. Wolff was born in Neustadt an der Haardt in 1857 and graduated from the Gymnasium at Speyer in 1876. Typical of young German chemists of this time, Wolff studied at several universities before taking his doctorate. From 1876–1881, he studied first at the University of Würzburg and the Technical University of Munich, and then at the University of Strasbourg, where Rudolf Fittig (1835–1919) and Adolf von Baeyer (1835–1917) were professors. He passed the Diplom examinations in 1880 and the State examinations for admission as a student in the higher schools of Bavaria in 1881. He held the position of Assistant in the Chemical Institute at Strasbourg from 1882–1891. As a graduate student, Wolff chose to study with Fittig. His research focused on δ-lactones and their derivatives and on levulinic acid and its derivatives. His work with δ-lactones led to his doctoral dissertation entitled ‘Über eine einfache Darstellungsweise und die Constitution des Valerolactons und über das chemische Verhalten der δ-Oxycapronsäure.’ He qualified for faculty status by earning his Habilitation at Strasbourg in 1885 for his treatise ‘Über einige Abkömmlinge der Lävulinsäure.’ In 1891, he joined the faculty at Jena, where he remained for the rest of his career. At Jena, Wolff became a colleague of Ludwig Knorr (1859–1921), who was Director of the Laboratory. It was Knorr who called Wolff to Jena to teach analytical chemistry, but it is also reported that Wolff, known as an organic chemist, was not subjected to questioning about analytical chemistry before he was hired! Nevertheless, he did teach analytical chemistry so well that he became the Head of the new Division of Analytical and Inorganic Chemistry. In his obituary of his colleague, Ludwig Knorr described Wolff as a quiet man who did not court publicity, and who found his greatest satisfaction in carrying out his duties well. Knorr describes him as an excellent and dedicated teacher, and reports that, even in the final throes of his illness, he maintained his office and its duties with his characteristic efficiency – in spite of the pain. Wolff died of a painful internal disease (possibly cancer) at the relatively young age of 61.
In contrast to his teaching, Wolff’s research at Jena was exclusively in organic chemistry. He closely followed the careers of his students, advancing their interests wherever possible. In his early independent work, he continued his studies of the chemistry of brominated levulinic acids and extended this work to the synthesis of heterocycles (Scheme 2).7

The deoxygenation of the hydrazones of aldehydes and ketones by base is now over a century old, discovered by Kizhner in 1911.8 Because Kizhner had published his results only in Russian, they were not widely known in Western Europe. Consequently, the reaction was discovered independently, in the form of the decomposition of semicarbazones by base, by Wolff in 1912.9 Initially, the reaction was known as the Wolff reduction, but in 1913 Wolff wrote to Kizhner to acknowledge his priority for the discovery. Since that time, the reduction has borne the names of both chemists, and it holds a central position in the organic chemist’s arsenal of carbonyl reductions.10

In the first of his two papers in 1911, Kizhner described the reduction of a series of saturated ketones by heating their hydrazones with solid potassium hydroxide (Scheme 3). In the second paper, he extended the reaction to unsaturated ketones, including conjugated cyclic ketones.

In 1912, Wolff independently described the base-promoted decomposition of the monohydrazone of a p-benzoquinone derivative. The product of the reaction was a phenol, clearly obtained by tautomerization of the 2,5-cyclohexadiene (Scheme 4).

Since 1911, the reaction has been modified many times11 in an effort to improve yields and lower the reaction temperature (Scheme 5).

Scheme 3

Scheme 4
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(1) Kizhner's name has been variously transliterated as Kijner, Kižner, Kishner, or Kizhner; the last option is based on the BGN/PCGN Romanization system for Russian, and is used here as the most intuitive for English speakers.


(3) Biographies in German: (a) L. Knorr In Hofmann, K. A. Ber. Dtsch. Chem. Ges. 1919, 52, A67–68; (b) P. Hallpap Chemiehistorische Notiz 3/2012, am 17.01.2012, am Institut für Organische Chemie und Makromolekulare Chemie (Humboldtstr. 10).


(5) N. M. Kizhner Aminy i gidraniny polymetilenobogo ryada, metody ikh obrazovaniq i prevrashcheniya [Amines and hydrazines of the polymethylene series, methods of their formation and transformation], M. Khim. Diss., St. Petersburg University, 1895.

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(f) L. Caglioti, M. Magi Tetrahedron 1963, 19, 1127–1131;
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