SYNTHESIS Best Paper Award 2015: Harnessing the Intrinsic Reactivity within the Aplysinopsin Series for the Synthesis of Intricate Dimers: Natural from Start to Finish

Highlighted article by A. Skiredj, M. A. Beniddir, D. Joseph, G. Bernadat, L. Evanno, E. Poupon
Dear Readers,

This September 2016 issue of SYNFORM opens with an interview to Professor Erwan Poupon and Dr. Laurent Evanno (France) who are the winners of the first SYNTHESIS Best Paper Award (2015). You may remember that the May 2016 issue opened with an interview to Professor Frank Glorius (Germany) who was the winner of the first SYNLETT Best Paper Award, so this completes the 2015 Awards. The winners received € 3000 and a framed certificate, together with the great honor of being featured in SYNFORM! Quoting the SYNTHESIS Editor-in-Chief – Professor Paul Knochel – Laurent Evanno and Erwan Poupon described "in an elegant way how the consideration of biosynthetic aspects has led to the first total synthesis of dictazole B and its cyclobutane analogue. Their total synthesis of tubastrindole B has been achieved through a very original ring expansion starting from the dictazole precursor. In summary, a remarkable work clearly deserving the merits for best paper in 2015." Well done to both and their research team! And I suspect that the competition among the Thieme Chemistry authors will be even tougher this year to try to secure either the SYNLETT or the SYNTHESIS Best Paper Award 2016!

The second contribution is a report on the intriguing and clever method developed by B. Wang and G.-J. Boons (USA) for the sensitive detection of inorganic azide, which is odorless, tasteless and remarkably poisonous! The third article is a story describing the radical intramolecular cyclization of hydrazones recently published by J.-R. Chen (P. R. of China) in Nat. Commun. The issue is completed by a Young Career Focus having F. Beuerle (Germany) as the protagonist.

Enjoy your reading!

Matteo Zanda

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

© Georg Thieme Verlag Stuttgart • New York – Synform 2016/09, A127 • Published online: August 18, 2016 • DOI: 10.1055/s-0035-1562370
SYNTHESIS Best Paper Award 2015: Harnessing the Intrinsic Reactivity within the Aplysinopsin Series for the Synthesis of Intricate Dimers: Natural from Start to Finish

Synthesis 2015, 47, 2367–2376

**Background.** Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the ‘SYNTHESIS/SYNLETT Best Paper Awards’. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis. Erwan Poupon, Laurent Evanno and their co-workers from the Paris-Sud University (France) have won the inaugural SYNTHESIS Best Paper Award for the year 2015. The authors are recognized for their work on the synthesis of intricate dimers from alysinopsin-type compounds. Paul Knochel, Editor-in-Chief of SYNTHESIS, remarked that the authors describe “in an elegant way how the consideration of biosynthetic aspects has led to the first total synthesis of dictazole B and its cyclobutane analogue. Their total synthesis of tubastrindole B has been achieved through a very original ring expansion starting from the dictazole precursor. In summary, a remarkable work clearly deserving the merits for best paper in 2015.” SYNFORM talked to Erwan Poupon and Laurent Evanno who were happy to share some background information regarding the prize-winning paper as well as their current research activities.

**Biographical Sketches**

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

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

**Interview**

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INTERVIEW

SYNFORM Could you highlight the value of your award-winning paper with respect to the state-of-the-art, potential or actual applications, and explain the origin, motivations and strategy used for conducting the research?

Prof. E. Poupon/Dr. L. Evanno We started the ‘aplysinop-sin project’ in early 2013 and we quickly wanted to evaluate the possibility of total syntheses with a high degree of atom economy in a limited number of synthetic steps with a storyline deeply based on biosynthetic considerations. We naively tried to dimerize an aplysinopsin-type starting material: we made numerous unsuccessful and frustrating attempts at this. Mehdi Beniddir (who was a post-doc in the team) made a fortuitous observation that opened the way out of the maze. Indeed, a sample of our starting material left on the bench in front of a window for several months had a slightly different appearance when compared to a freshly prepared batch. A routine LC-MS analysis of the sample indicated the presence of a small, intriguing new peak that could be a new dimeric compound. To be able to isolate the dimer, a sample was crushed daily in a mortar and left directly under the sunlight for one month during August 2013. It was a great pleasure to isolate and characterize a dictazole-type adduct for the first time. The design of a photochemical reactor efficiently mimicking sunlight (just as in a coral reef environment?) was a pressing need. Adam Skiredj, the PhD student involved in the project, brought us the solution through his passion for tropical frogs. Indeed, UV-enriched lamps made for terrariums were used to create sorts of ‘artificial lagoons’ in the lab mimicking thereby an intense sunlight exposure. To realize the synthesis of dictazole B (a cyclobutane-centered molecule), to achieve a ring expansion toward tubastrindole B (a tetrahydrocarbazole) and to rationalize the ‘aplysinopsin cascade’, the hard work of optimization had to be done. The project permitted access to these unusual densely-functionalized scaffolds starting only from creatinine, iodomethane and formylindoles as the sole, costless starting materials. Ongoing prospects of the project include an asymmetric version of the sequence. The project excited the whole team for several months, making our nights quite short, and we now feel honored that SYNTHESIS selected our article for the Best Paper Award 2015.

Figure 1 Overview of the project (picture: copyright debitus/IRD)
SYNFORM What is the focus of your current research activity, both related to the award paper and in general?

Prof. E. Poupon/Dr. L. Evanno We are fascinated by natural substances, whatever their origin (plants, marine invertebrates, insects, micro-organisms...). We are currently engaged in multidisciplinary projects: discovering new molecules from nature, drug-design projects from natural product scaffolds, answering chemical ecology issues... One of our main sources for reflection (and sometimes philosophical meditation) is trying to understand how molecular complexity is generated in nature and has emerged during evolution. For that, biomimetic strategies in total synthesis of complex molecules appear to us as not only a way to reach our synthetic targets, but also an ideal tool to dissect intimate mechanisms of biosynthetic pathways. Our challenge is to find targets that may deploy impressive cascades of reactions from simple building blocks to afford complex skeletons: in that way the ‘aplysinopsin project’ was ideal. A lesson we have learned in the last few years is that the simplest conditions are often the best in biomimetic strategies (no protecting group, room temperature, sunlight, air...).

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

Prof. E. Poupon/Dr. L. Evanno Quite a difficult question to answer... let us put aside issues which are now consensual (environment-friendly chemistry, alternative carbon resources) and focus more specifically on natural product chemistry and biomimetic approaches. Facing the ‘big data area’, we wish to try to transfer the huge body of knowledge, techniques and ways of thinking acquired in recent decades in genomics, proteomics and metabolomics to the field of organic synthesis. For this, routine analysis of complex mixtures, chemistry in confined media, supramolecular bio-inspired catalysis and many other tools will undoubtedly be fully integrated in hyphenated projects in the coming years. Should our political and institutional leaders be conscious of the importance of fundamental and basic sciences, many discoveries, breakthroughs and surprises, as well as much fun, are waiting for curious and motivated students. Also, as professors, education is essential for us especially at a period of sometimes re-emerging scientific obscurantism.

The award-winning team, from left: A. Skiredj, Prof. E. Poupon, Prof. D. Joseph, Dr. M. Beniddir, Dr. L. Evanno, Dr. G. Bernadat
A Metal-Free Turn-On Fluorescent Probe for the Fast and Sensitive Detection of Inorganic Azide


Sodium azide is a colorless, tasteless, odorless and salt-like solid that has been widely used in agricultural, laboratory, and medical applications. For example, azide is used in automobile airbags, for pest control, as a preservative, and in chemical research.\(^1\)\(^2\) However, in addition to environmental concerns regarding this substance, it has also recently attracted attention for safety issues. In fact, due to its acute toxicity while being odorless and tasteless, several poisoning cases have been reported in the past 20 years.\(^3\)\(^–\)\(^5\) Despite the clear public health concerns related to sodium azide, there is no quick detection method available for environmental, medical, and forensic applications: in one case of deliberate azide poisoning, for example, it was reported that it took the FBI five months to determine that azide was the poison used.\(^5\)

Meanwhile, in the field of click chemistry, Huisgen 1,3-dipolar cycloaddition has been commonly used as a useful synthetic tool.\(^6\)\(^–\)\(^8\) Because of this reaction’s simple operation, fast reaction rate and biocompatibility, it has become an important step in intermediate synthesis in medicinal chemistry. However, a trace amount of sodium azide would affect the bioactivity and cytotoxicity of synthesized drug candidates. As a result, there is a real need for the development of a simple, rapid and accurate azide detection method. The groups of Professor Binghe Wang at Georgia State University (USA) and Professor Geert-Jan Boons at the University of Georgia (USA) have therefore been investigating a method of detecting inorganic azide, resulting in this paper.

“Current sodium azide detection methods include chromatography\(^9\)\(^–\)\(^11\) and electrochemical detection,\(^12\)\(^–\)\(^14\) which involves complicated procedures and specialized instruments,” said Professor Wang. He continued: “Fluorescence has emerged as a simple and rapid detection tool, and a few fluorescent probes for sodium azide have been reported.\(^15\)\(^–\)\(^17\) However, each one of them leaves something to be desired including the ability for quantitatively determining azide concentrations.\(^16\) In some cases, interference from other inorganic anions was an issue too.\(^17\) Therefore, we were interested in developing a method for the simple, sensitive, selective, and quantitative detection of sodium azide.”

In click chemistry, organic azido compounds (N\(_3\)-R) are known to react easily and selectively with terminal alkynes via copper(I)-catalyzed cycloaddition (CuAAC), and strained alkynes without Cu(I) catalysis via strain-promoted azide–alkyne cycloaddition (SPAAC).\(^18\) Unlike organic azido com-

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**Figure 1** A cartoon representation of the inorganic azide and Fi-DIBO reaction
pounds, inorganic azide does not readily undergo the same reaction in most cases. In 2011, the Wang lab reported a liquid chromatography–mass spectrometry (LC-MS) detection method for sodium azide based on the reaction between a strained alkyne, dibenzocycloocta-4a,6a-diene-5,11-diyne (DBA), and inorganic azide.\textsuperscript{19}

Over the past eight years, the Boons lab has developed many strained dibenzocycloalkyne (DIBO) probes in order to visualize complex glycans in living cells.\textsuperscript{20} Interested in modifying the physical properties of these molecules, they also developed a fully water-soluble sulfated analogue S-DIBO\textsuperscript{20} and recently a fluorogenic cyclooctyne (Fl-DIBO),\textsuperscript{21–23} which only generates fluorescence after a click reaction. Professor Wang said: “Such results triggered our interest in examining whether such a strained alkyne could be used to react with inorganic azide, leading to a fluorescent cycloaddition product for azide detection using fluorescence.”

Professor Wang continued: “To demonstrate the design, we used Fl-DIBO to react with sodium azide in a mixture of dioxane and H\textsubscript{2}O (1:1). Because of the nonpolar nature of DIBO, 50% of organic solvent was required to fully dissolve the probe. A highly fluorescent product was obtained and characterized (Figure 1). Other chemosensor properties were examined as well, leading to the conclusion that this strained alkyne compound was suitable as a fast, sensitive and selective probe for inorganic azide.”

To test the utility of this sodium azide probe in real life, tea samples were prepared with azide at various concentrations. This probe showed concentration-dependent fluorescence intensity changes upon addition of sodium azide. “The sensitivity of the detection method is in a pathologically relevant range,” said Professor Wang. As seen in Figure 2, the fluorescence emission can be easily observed by the naked eye ($\lambda_{\text{ex}} = 363$ nm). Professor Wang concluded: “This probe showed excellent potential to be applied in real samples for azide detection. We expect quick and accurate determination of the existence and concentration of inorganic azide in aqueous and organic solutions using this simple method.”

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.jpg}
\caption{Fluorescence responses of Fl-DIBO to sodium azide in a tea sample; Fl-DIBO 100 \textmu M, NaN\textsubscript{3} (1.12 mg/cup) in a mixture of tea solution and dioxane (1:1) at pH 7.4}
\end{figure}

About the authors

\textbf{Ke Wang} received her B.S. degree in chemistry from Lanzhou University (P. R. of China) in 2010, and then moved to Georgia State University (USA) to pursue her Ph.D. in medicinal chemistry with Dr. Binghe Wang. In 2015, she obtained her Ph.D. degree with research on boronic acid modified nucleotides for diagnostic applications and development of fluorescent chemoprobes for molecules of biological importance.

\textbf{Frédéric Friscourt} received his M.Sc. and chemical engineering diploma from the University of Clermont-Ferrand (France). After completing a Ph.D. in chemistry on asymmetric organometallic and organic catalysis with Professor Pavel Kočovský at the University of Glasgow (UK), he transitioned to the field of chemical biology during his postdoctoral fellowship (2009–2014) in the laboratory of Professor Geert-Jan Boons at the Complex Carbohydrate Research Center (GA, USA), where he developed novel chemical probes for imaging the glycome in living cells. In 2014, he obtained a Junior Chair position from the Excellence Initiative program (IdEx) at the University of Bordeaux (INCIA lab, CNRS UMR 5287, France) and was recently recruited as a group leader at the European Institute of Chemistry and Biology in Bordeaux. His research focuses on using organic chemistry to develop novel tools that can probe the influence of biomolecules in the brain, notably in healthy vs diseased states.

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Chaofeng Dai received his B.S. degree in organic chemistry from Lanzhou University (P. R. of China) in 1999, and his Ph.D. degree in organic chemistry from Xiamen University (P. R. of China) in 2007. Then he moved to the USA and joined Professor Binghe Wang’s research group first as a postdoctoral research associate and then as a research scientist. His research interests include organic synthesis, medicinal chemistry, bioconjugation chemistry, nucleic acids chemistry, and click chemistry.

Lifang Wang received her B.S. degree in organic chemistry from Lanzhou University (P.R. of China) in 2000, and her Ph.D. degree in 2007 from Institute of Chemistry, Chinese Academy of Sciences in Shanghai (P. R. of China). She moved to the USA and joined Professor Binghe Wang’s research group in 2009 as a postdoctoral research associate where her research interest focused on mass spectrometry. In 2014, she joined Veritas Laboratories LLC, where she is now a senior scientist at the company.

Yueqin Zheng was born in 1988 in Fujian (P. R. of China). He received his B.S. degree in materials chemistry from the University of Science and Technology of China (USTC, P. R. of China) in 2011, and joined Professor Binghe Wang’s lab as a graduate student at Georgia State University (USA) in 2012. His research interests include prodrugs of gasotransmitters (organic CO prodrugs and organic H$_2$S prodrugs) and developing novel chemical-reaction-based drug delivery systems.

Geert-Jan Boons received his M.Sc. and Ph.D. degrees in chemistry from the State University of Leiden (The Netherlands) under the direction of Professor Jacques van Boom. He spent seven years in the UK, first as a postdoctoral fellow at Imperial College London and the University of Cambridge in the research group of Professor Steven Ley, and then as a lecturer and professor at the University of Birmingham. In 1998, he joined the faculty of the Complex Carbohydrate Research Center of the University of Georgia (USA), where he is a Distinguished Professor in Biochemical Science. A hallmark of his research is a seamless integration of method development for complex glycoconjugate synthesis, application of the new methods for the preparation of biologically important targets, and innovative use of the resulting compounds in biological studies.

Siming Wang is the Director of mass spectrometry facilities at Georgia State University (USA). She obtained her B.S. degree in medicinal chemistry from Beijing Medical College (Now Beijing University Health Sciences Center, P. R. of China) in 1982, and her Ph.D. degree in medicinal chemistry from the University of Kansas, School of Pharmacy (USA), in 1991 (Ph.D. mentor: Professor Robert P. Hanzlik). Subsequently, she did postdoctoral work with Professor Ronald T. Borchardt of the University of Kansas and Professor Francis J. Schmitz of the University of Oklahoma (USA). She then moved to North Carolina (USA) and worked at North Carolina State University, ManTech Corp/US EPA, and the National Institute of Environmental Health Sciences before assuming her current position. Dr. Wang has published over 40 papers in the area of medicinal chemistry, mass spectrometry, and biosensing.
Binghe Wang is Regents’ Professor of Chemistry, Associate Dean for Natural and Computational Sciences in the College of Arts and Sciences, and founding Director of the Center for Diagnostics and Therapeutics at Georgia State University (USA). He also holds an endowed chair as Georgia Research Alliance Eminent Scholar in Drug Discovery and Georgia Cancer Coalition Distinguished Cancer Scholar. Professor Wang obtained his B.S. degree in medicinal chemistry from Beijing Medical College (Now Beijing University Health Sciences Center, P. R. of China) in 1982, and his Ph.D. degree in medicinal chemistry from the University of Kansas (USA), School of Pharmacy, in 1991 (Ph.D. mentors: Professors Matt Mertes and Kristin Bowman-James). Subsequently, he did postdoctoral work with Professor Victor Hruby of the University of Arizona (USA) and Professor Ronald T. Borchardt of the University of Kansas. He started his independent career in 1994 as an Assistant Professor of Medicinal Chemistry at the University of Oklahoma, College of Pharmacy (USA). In 1996, he moved to the Department of Chemistry, North Carolina State University (USA), and was promoted to Associate Professor with tenure in 2000. In 2003, he moved to his current institution at Georgia State University (USA), as Professor of Chemistry, Georgia Research Alliance Eminent Scholar in Drug Discovery, and Georgia Cancer Coalition Distinguished Cancer Scholar. He served as the Chemistry Department chair from 2011–2013 before his current appointment as Associate Dean. His research interests include drug design and delivery, molecular recognition, chemosensing, and new diagnostics. His work has been continuously funded by the NIH for the past 20 years. He was the recipient of the Distinguished Alumni Professor award (2007), which is the highest award that GSU bestows upon a professor for lifetime achievement in scholarly activity, teaching, and service. Professor Wang has published over 230 papers and given over 170 invited lectures worldwide, is the Editor-in-Chief of the high-impact journal Medicinal Research Reviews, and founding serial editor of ‘Wiley Series in Drug Discovery and Development,’ which has published over 20 volumes. He has edited books in the areas of drug design, drug delivery, pharmaceutical profiling, chemosensing, and carbohydrate recognition. Internationally, Professor Wang serves on many panels and editorial boards including his current membership on the Synthetic and Biological Chemistry-A Study Section (SBC-A) at the NIH. He has also organized and presided over many international symposia and conferences.

REFERENCES

Catalytic N-Radical Cascade Reaction of Hydrazones by Oxidative Deprotonation Electron Transfer and TEMPO Mediation

Nat. Commun. 2016, 7, 11188

N-Centered radical reactions have been established as one of the most powerful and versatile methods for C–N bond formation towards the assembly of valuable and diversely functionalized N-containing compounds. Typically, the generation of reactive N-radical intermediates has relied mainly on reductive scission of the relatively weak N–O, N–N or N–X (X = Br, I) bonds by high-energy UV irradiation or radical initiators. In contrast, the direct catalytic conversion of ubiquitous N–H bonds to N-centered radicals is an economic and attractive, but challenging, strategy for synthetic chemists. Recently, Professor Jia-Rong Chen’s group at the Central China Normal University (Wuhan, P. R. of China) has been interested in visible-light photoredox-controlled reactions of N-radicals. Employing this strategy, they developed a novel visible-light photocatalytic N-radical cascade reaction of β,γ-unsaturated hydrazones by combining oxidative deprotonation electron transfer (ODET) and hydrogen-atom transfer (HAT), which provided efficient access to various structurally diverse 1,6-dihydropyridazines (Scheme 2, Path B). One of the most important outcomes of our current 6-endo radical cyclization is the mild generation of N-centered radicals directly from the recalcitrant N–H bonds via ODET under visible-light irradiation,” said Professor Chen. The addition of a common base is essential to this process, which enables a facile SET oxidation of the resultant nitrogen anion intermediate 1-A to form N-radical intermediate 1-B. 2,2,6,6-Tetramethylpiperidine-N-oxyl (TEMPO) served as an H-atom acceptor to facilitate the subsequent formation of C–C double bonds by a HAT process.

In 2014, Professor Chen’s group achieved a mild hydroamination of β,γ-unsaturated hydrazones for the first time via a visible-light-induced 5-exo cyclization of N-radical intermediate 1-B (Scheme 2, Path A). “The remarkable feature of the current reaction is the exclusive 6-endo regioselectivity of the N-radical cyclization achieved by rational design of catalytic system and substrates,” said Professor Chen. “Actually, the substitution patterns of the alkene moiety of hydrazones proved to be critical to the reaction’s regioselectivity.”

Scheme 1 The direct oxidative generation of N-centered radicals from N–H bonds

Scheme 2 Visible-light photocatalytic N-radical cascade reaction of unsaturated hydrazones
Professor Chen continued: “The 5-exo and 6-endo selectivity of N-radical cyclization is dependent on the activation free energy and the stability of the newly formed C-centered radical intermediates. For example, the 5-exo cyclization is much more favored than the 6-endo process when R1 is an H-atom as shown by their activation free energy (8.8 vs 13.5 kcal/mol) (Scheme 2, Path A). In contrast, the 6-endo cyclization of the N-radical is more feasible than the 5-exo process when R2 is a phenyl group, due to the stability of the newly generated benzyl radical 1-D, which is consistent with the results of DFT calculations (11.4 vs 8.7 kcal/mol) (Scheme 2, Path B).”

“The reaction exhibits a remarkably wide substrate scope, and various aromatic and aliphatic unsaturated hydrazones can be well tolerated, affording the corresponding biologically important 1,6-dihydropyridazines in generally good yields (Scheme 3a),” said Professor Chen. He continued: “Moreover, 1,6-dihydropyridazines can be further applied to the synthesis of diazinium salts through two simple operations, and preliminary biological evaluation showed that these compounds display promising activities against four common clinical pathogenic fungi such as Candida albicans, C. neoformans, C. glabrata and C. parapsilosis (Scheme 3b).” To gain insight into the role of TEMPO and the reaction mechanisms, a series of control experiments, luminescence quenching experiments, 1H NMR and electrochemical analysis were performed. Based on these results, a visible-light-induced ODET process was established for the conversion of N–H bonds into N-radicals (1 to 1-B).

Professor Chen concluded: “We have developed an efficient photocatalytic N-radical cascade reaction of β,γ-unsaturated hydrazones via a visible-light-induced ODET/HAT strategy, enabling the efficient synthesis of various valuable 1,6-dihydropyridazines with good regioselectivities and yields.” He continued: “This straightforward and mild technique has great potential in the catalytic direct generation of other types of reactive N-radicals from N–H bonds, rendering it ideal for applications in the field of N-radical-based nitrogen installation.” Exploiting this strategy, the Chen group has also reported a general and selective oxidative radical oxyamination and dioxygenation of β,γ-unsaturated hydrazones and oximes.4

Scheme 3 Selected substrate scope and synthetic application
### About the authors

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<th>Institution</th>
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Young Career Focus: Dr. Florian Beuerle (Julius Maximilian University Würzburg, Germany)

**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. Florian Beuerle (Julius Maximilian University Würzburg, Germany).

**Biographical Sketch**

Florian Beuerle was born in Bayreuth (Germany) and grew up in the rural area of Upper Franconia in southern Germany. He studied chemistry at Friedrich Alexander University in Erlangen (Germany) and graduated with a diploma in 2005. After working under the guidance of Professor Dr. Andreas Hirsch on the regioselective functionalization and antioxidant properties of [60]fullerene derivatives, he obtained his PhD in 2008. Afterwards, he moved as a Feodor Lynen fellow of the Humboldt Foundation to the group of Sir Fraser Stoddart at Northwestern University in Evanston, IL (USA). During his postdoctoral stay, he worked on various projects in the area of mechanically interlocked molecules, including supramolecular catenanes and rotaxanes as well as theoretical investigations on toroidal carbon nanotubes. In 2010, he returned to Germany and started his independent academic career as a junior research group leader at Julius Maximilian University in Würzburg (Germany) supported by a Liebig fellowship of the Fonds der Chemischen Industrie. Current research interests of the Beuerle group include covalent organic cage compounds, porous materials, supramolecular and nanosystems chemistry.

**INTERVIEW**

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

Dr. F. Beuerle Research in our group is centered around the design and synthesis of complex molecular architectures utilizing the repetitive self-assembly of small organic building blocks under reversible conditions. Following a molecular design approach, we aim for tailor-made control of the structure and function of these functional materials by means of suitable building block design and appropriate choice of dynamic coupling reactions. Furthermore, we aim for new design paradigms beyond traditional synthetic protocols including self-sorting of complex reaction mixtures, and precise control of molecular hierarchy and morphology, as well as stimuli-responsive systems allowing for spatiotemporal control of assembly and function. In particular, we are interested in porous materials, for example, covalent organic cage compounds and metal-organic, covalent organic or supramolecular frameworks, in order to obtain novel materials for applications in areas such as organic electronics, host-guest interactions or energy-related issues.

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

Dr. F. Beuerle From the very beginning of my undergraduate studies, I was always fascinated by the two-sided nature of chemistry as the molecular science that fruitfully combines both theoretical knowledge on reactivity and properties of molecules and the practical aspect of actually making compounds which might never have been made before. During my further education towards supramolecular and materials chemistry, I realized more and more that good synthetic skills still remain very essential for all aspects of chemistry, since any deeper understanding of structure–function relationships depends strongly on the availability of suitable model
compounds or novel derivatives exhibiting improved properties, neither of which would be accessible without profound knowledge of chemical synthesis.

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

Dr. F. Beuerle Chemists like me who, by training, have a more applied approach towards synthesis, sometimes have the naïve notion that the main problems of synthesis have already been solved decades ago and almost any imaginable molecule can be synthesized at will. However, after some failures in the lab you will learn the hard way that the devil is in the details and that there is still a great need for improvement and development of new synthetic methods. On the other hand, I believe that, in the future, synthesis has to be seen in a much broader sense than traditional step-by-step modifications on small molecules. For example, dynamic and combinatorial approaches towards synthesizing complex systems based on multi-component mixtures will surely enlarge the chemical space greatly. Alongside this, growing interest in chemical systems out of equilibrium will force scientists to rethink traditional concepts of product stabilities and selectivities. Nevertheless, I am still a strong advocate for keeping courses on modern synthetic chemistry as integral parts of the curricula for advanced organic chemistry students and for pursuing basic research on new synthetic methodologies to further enhance the art of organic synthesis in the future.

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

Dr. F. Beuerle Our current research activities are focused on the design and synthesis of novel porous materials such as covalent organic cage compounds as well as covalent organic or metal-organic frameworks. Based on a hierarchical approach, we aim to modify these molecular architectures on various hierarchy levels. Therefore, synthetic modifications on the lowest level of the small molecule precursors are at the centerpiece of our daily lab work. On this basis, we try to obtain integrative systems with a precise spatial arrangement of multiple functional units utilizing self-sorting phenomena and directional approaches. Furthermore, we would like to get better control over solid-state arrangements of such complex molecular architectures in order to correlate molecular function with bulk properties, ultimately leading to functional devices and materials. For these purposes, we implement organic scaffolds possessing unusual geometries, for example, tribenzo-triquinacenes or [60]fullerene hexakis adducts, into complex hierarchical assemblies. In particular, we are interested in porous molecular architectures in order to develop new materials for areas such as gas storage and separation, energy production and storage, sensing or specific host–guest interactions.

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

Dr. F. Beuerle Recently, we reported on a series of covalent organic cage compounds based on catechol-functionalized tribenzo-triquinacenes and diboronic acids (Angew. Chem. Int. Ed. 2015, 54, 10356). The geometrical shape of the cages can be rationally tuned by simply changing the angular disposition of the ditopic linkers. Moreover, in the case of complex reaction mixtures containing two different boronic acids, both narcissistic self-sorting into segregated cages as well as social self-sorting with the exclusive formation of unprecedented three-component assemblies were observed. The latter case represents the first example for social self-sorting of covalent
cage compounds and represents an important step towards the targeted synthesis of integrative systems and the next generation of cage molecules with a precise spatial orientation of multiple functionalities.

[Signature]
Coming soon

- Literature Coverage
Catalytic Asymmetric Addition of Grignard Reagents to Alkenyl-Substituted Aromatic N-Heterocycles

- Literature Coverage
Palladium/N-Heterocyclic Carbene Catalyzed Regio- and Diasteroselective Reaction of Ketones with Allyl Reagents via Inner-Sphere Selective Mechanism

- Literature Coverage
Total Synthesis of Atropurpuran

Further highlights

Synthesis  Review: Synthetic Approaches to Coronamic Acid, Coronamic Acid and Coronatine (by A. J. B. Watson and co-workers)

Synlett  Account: Introduction of Functionalized Difluoromethylated Building Blocks Mediated or Catalyzed by Copper (by X. Pannecoucke and T. Poisson)

Synfacts  Synfact of the Month in category “Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions”: Copper-Catalyzed Asymmetric Nucleophilic Addition to Ketones