

Conference Report

The 52nd EUCHEMS Conference on Stereochemistry:
Bürgenstock Conference 2017, Brunnen, April 30th–May 4th, 2017

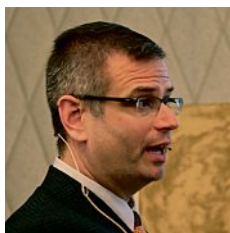
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There is no conference like the Bürgenstock. What makes it unique is not only history, prestige or traditions, it is that in every single one of its 52 editions, it has succeeded at bringing scientific excellence to an idyllic location, fostering a particularly collegial atmosphere in which scientific discussion flourishes. The significance of this conference can be summarized by paraphrasing a lecturer of this year “If you are invited to the Bürgenstock and you had other plans, you change your plans”.

The 52nd Bürgenstock conference started on April 30th and took place on the shores of Lake Lucerne (Vierwaldstättersee) in Brunnen, Switzerland. The welcome dinner was the occasion for an introductory speech by this year’s president of the conference **Bert Meijer** (Eindhoven University of Technology), who presented the guest of honor **François Diederich** (ETH Zurich). The organizing committee of this year included **Christian Bochet** (University of Fribourg), **Alain de Mesmaeker** (Syngenta), **Guido Koch** (Novartis), **Jérôme Lacour** (University of Geneva), **Cristina Nevado** (University of Zurich), and **Helma Wennemers** (ETH Zurich).



Paul Chirik

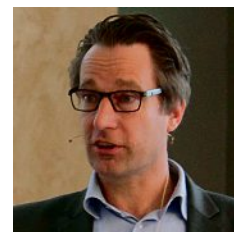
After dinner, moderator Christina Moberg (KTH Royal Institute of Technology) introduced the first speaker of the conference, **Paul Chirik** (Princeton University). In an authentic tour de force, he took us from the basic chemistry of (redox) non-innocent ligands to how to pair them with iron, cobalt and nickel to create catalysts that enable a variety of challenging transformations. Using small feedstock hydrocarbons and iron complexes, he demonstrated applications in [2+2] and [4+2] cycloaddition reactions of unactivated alkenes and dienes, as well as hydrovinylations to produce structurally simple, yet otherwise difficult to synthesize skipped dienes. With cobalt-based catalysts, he showed impressive borylation reactions, including rare 1,1-hydroborylations of alkynes, sequential and stereodefined addition of electronically different borane substituents, and synthesis of 1,1,1-triboryl alkanes. Many examples of C–H activation methods were presented, mostly utilizing cobalt pincer complexes, which have reactivities that are orthogonal to iridium complexes. He closed his talk with surprising discoveries in cobalt-mediated hydrogenation reactions in methanol and the use of zinc as an activating agent in the production of competent bimetallic species for catalysis.

The Monday morning session, chaired by Anja Palmans (Eindhoven University of Technology), started off with a presentation by **Kay Severin** (EPF Lausanne) on novel chemistry using nitrous oxide as reagent in organic chemistry. He presented how this potent greenhouse gas, which arises as a byproduct in nylon manufacturing, can serve as a mild oxidizing agent, enabling both the homo- and hetero-dimerization of Grignard reagents. Moreover, by sequestering it with *N*-heterocyclic carbenes it can serve as a source of nitrogen, which opens new avenues to azoimidazolium dyes. He then introduced the audience to the yet uncharted chemistry of alkenyl- and alkynyl-triazines, which are readily obtained from nitrous oxide, lithium amides and Grignard reagents. The lecture concluded with an outlook on a number of exciting transformations, which can be accessed from these unusual intermediates.



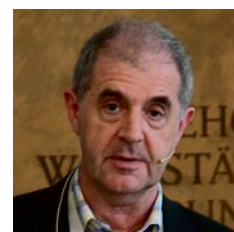
Kai Severin

The second talk was given by **Joost Reek** (University of Amsterdam). By introducing judicious supramolecular interactions into his ligand designs, he has managed to orient substrates to control selectivity in transformations ranging from ruthenium-mediated hydrogenations within self-assembled cages to hydroformylation reactions. A major theme of the talk was the effect of confinement in cages and effective concentration, in particular of metal ions. By employing some of the Fujita cages, he showed that they could generate multinuclear complexes in which both the catalyst and substrate are pre-organized in the nanosphere. He finished his talk by introducing hydrogenase models in which the diiron active site of the natural enzyme is embedded within Fujita cages to obtain proton reduction at significantly decreased overpotentials.



Joost Reek

The Monday afternoon session was chaired by Donald Hilvert (ETH Zurich). The hunt for natural products in exotic places is a dangerous endeavor, as demonstrated in an entertaining talk by **David Craik** (University of Queensland). Ultra-stable, plant-derived cyclic peptides known as cyclotides were his hunting prey. These cyclotides provided a versatile and stable scaffold for grafting biologically active peptide-epitopes. These constructs are metabolically inert peptides that can be expressed in a genetically modified plant and hold great promise as potential drug candidates. In an extension of these findings, he also presented how the pharmaceutically interesting peptide Conotoxin could be stabilized through cyclization and cysteine cross-linking of the conserved epitope, resulting in IMB-007, a drug candidate to treat neuropathic pain.



David Craik

The first poster session took place on Monday afternoon, which started with five short presentations by junior faculty, in-

cluding **Philipp Heretsch** (Free University of Berlin), **Rafal Klajn** (Weizmann Institute of Science), **Jiří Míšek** (Charles University of Prague), **Robert Phipps** (University of Cambridge), and **Pablo Rivera-Fuentes** (ETH Zurich).



Tanja Weil

The evening session was chaired by Patricia Dankers (Eindhoven University of Technology) and featured a very dynamic presentation by **Tanja Weil** (Max Planck Institute for Polymer Research). Using a peptide-decorated copolymer, she demonstrated the formation of fibril aggregates that recruit viral particles to its surface and facilitate their entry into hematopoietic stem cells, which are notoriously difficult to infect. Additionally, dendrimer G2b, a small globular dendrimer composed of multiple aromatic rings could form a supramolecular complex with adenovirus 5 particles to facilitate their entry into cells independently from the typical CAR receptor-mediated mechanism. This strategy allows the infection of cells even in the presence of the coagulation factor X, which normally blocks entry of viruses into cells. Applications of this technology include induction of nerve growth and intracellular delivery of anticancer drugs. In the last part of her talk, she introduced her recent work in the field of nanodiamonds doped with nitrogen-vacancy centers and presented some recent application of these monodisperse, light emitting nanocrystals as sensors of magnetic fields.



Thorsten Bach

Tuesday morning started with a session chaired by former president Paul Knochel (LMU Munich). The first speaker was **Thorsten Bach** (Technical University Munich), who delivered an insightful talk on enantioselective synthesis using light. In a very didactic manner, Bach demonstrated how triplet induction using a chiral sensitizer is an efficient way to impart enantioselectivity in [2+2] cycloadditions. He also showed that using bathochromically shifted sensitizers increase the selectivity of the reactions by avoiding direct excitation of the substrate. Further extensions of this concept include the use of chiral Lewis acids, which upon complexation with α,β -unsaturated ketones induce a red-shift in absorbance and generation of thioketoxonium intermediates from dithianes, which also provide good spectral separation and improve catalytic performance. Interestingly, this strategy can also be used to induce enantioselectivity in photochemical reactions that occur primarily through the singlet manifold.



Jörn Piel

The quest for new taxa of bacteria, which are talented producers of biologically active natural products, and the characterization of their biochemical machinery was at the center of the presentation of **Jörn Piel** (ETH Zurich). He showed how the discovery of *Entotheonella* symbionts and the complex natural products produced by these bacteria led to the identification of very unusual biosynthetic pathways and the underlying enzymatic modification machinery. He also demonstrated how the power and promiscuity of these enzymes can be harnessed for protein engineering. Very unusual post-translational modifications were described, including a rare peptide-splicing transformation. In another impressive example, an *entotheonella*-derived epimerase was able to invert the stereochemistry of specific amino acids

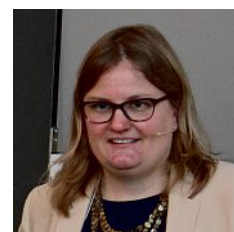
with great selectivity in glucagon or defensin peptides. These and other newly discovered enzymes from uncultured bacteria are opening new perspectives for post-translational modification in protein engineering.

A day with gorgeous weather and views of snowcapped mountains was rounded off in the last session, chaired by Syuzanna Harutyunyan (University of Groningen), with a presentation by **Timothy Jamison** (Massachusetts Institute of Technology) on the advantages and pitfalls of doing chemistry in continuous flow. A call was made to educate the next generation of chemists not only in 'batch-mode'-thinking, which deals with systems changing over time but also in 'flow-mode'-thinking where a system in steady-state changes over space. The impact of engineering in this field was highlighted by several useful tools presented like in-line separators for continuous phase separation, smaller and more powerful pumps to allow for shrinking the required lab-space or continuous solvent evaporation, which allows for connecting more chemical steps in sequence. Providing examples of chemical transformations that benefit from large surface areas, exact temperature control, 'extreme' conditions, and 'end-to-end' manufacturing of pharmaceutical ingredients in a single machine, the evening lecture convinced the audience that chemical transformations in continuous flow will be an integral part of chemistry in the future



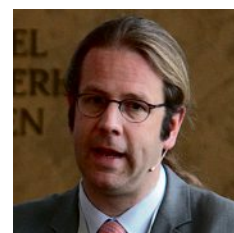
Timothy Jamison

The first session on Wednesday morning was chaired by Christian Hackenberger (Leibniz Institute for Molecular Pharmacology) and started with a lecture by **Jennifer Prescher** (University of California, Irvine) on new bioorthogonal reactions and bioluminescent systems. After introducing the state of the art in bioorthogonal chemistry to introduce 'clickable' functional groups, she presented their development of cyclopropene units as strained alkenes for bioorthogonal reactions with tetrazines. The advantages of cyclopropenes are multifold: they are metabolically stable, sterically small and electronically tunable. In yet another important contribution to bioorthogonal chemistry, she introduced reactions between cyclopropenones and triaryl phosphines. By appending a nucleophile close to the phosphine, they were able to develop a new ligation reaction and demonstrated this method in cell lysates. In the second part of her talk, she described the directed evolution of new luciferin/luciferase pairs for multi-signal imaging. These new luciferin/luciferase pairs hold great potential for whole-animal imaging of cell mobility and cell-cell contact visualization, and some proof-of-principle applications have already been realized.



Jennifer Prescher

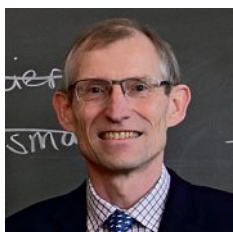
Luc Brunsveld (Eindhoven University of Technology) presented how multivalent interactions leading to the spatial organization of proteins in the form of dimers or more complex aggregates can be manipulated by drug-like small molecules. Taking advantage of host-guest chemistry involving phenylalanine residues and the small-molecule receptor cucurbit[8]uril, control over protein-protein interactions was achieved. A proof-of-principle application of this methodology was presented by demonstrating the as-



Luc Brunsveld

sociation of fluorescent proteins by resonance energy transfer as well as by a split luciferase complementation assay. Additionally, small-molecule regulation of caspase-9 activity *via* induced dimerization on the 14-3-3 protein scaffold was disclosed.

On Wednesday evening, the attendees of the Bürgenstock were offered a musical treat. The Quadrivium ensemble of students from Eindhoven University of Technology performed a series of well-known classical and modern pieces, ranging from Mozart's 'Eine kleine Nachtmusik' to Randy Newman's 'You've got a friend in me'. After the concert, there was an opportunity to meet the young artists, some of whom are scientists as well.



Karl-Heinz Altmann

On the final day of the Bürgenstock, session chair and president elect Ilan Marek (Technion – Israel Institute of Technology) introduced **Karl-Heinz Altmann** (ETH Zurich). Paying great attention to experimental details, Altmann described the synthesis and biological evaluation of mycolactones A and B, which are macrocyclic, polyketide natural products of bacterial origin. Using a robust synthetic strategy, these products could be obtained in sizable quantities for downstream applications. For example, a biotinylated derivative was used to identify that these molecules destabilize the mTORC1 complex, likely through FKBP12 signaling. In the second part of the talk (–)-zampanolide and (+)-dactylolide were introduced. Both compounds stabilize tubulin polymerization but, curiously, their macrocyclic cores are enantiomeric. By developing a modular synthesis, structure–activity relationships could be established and (–)-zampanolide was used to obtain the first X-ray diffraction structure of a polymerization stabilizer bound to tubulin.



Motomu Kanai

Development of organic transformations that are compatible with conditions found in living cells and their subsequent application in protein modification was the theme of a talk by **Motomu Kanai** (University of Tokyo). A nitroxide radical-based (ketoABNO) system allowed not only a serine site-selective method for peptide cleavage but also opened up the possibility to exploit tryptophan residues as novel sites for bioconjugation with minimal perturbation of protein structure. How surface patterns of large biopolymers like β -amyloid plaques can be used for achieving highly selective delivery of a therapeutic agent was beautifully demonstrated with a singlet oxygen generating catalyst, which is only active if bound to the target protein surface.



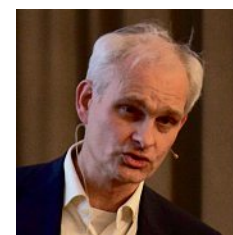
Frank Würthner

Rainer Haag (Free University of Berlin) moderated the final session of the conference. Dye development was an early driving force of synthetic chemistry in the 19th and 20th centuries, and **Frank Würthner** (University of Würzburg) guided us through the world of 21st century supramolecular dye chemistry. Using perylenes as a platform, he has developed supramolecular assemblies in which stacking of the monomeric chromophores is controlled. In cyclophanes, the nature and orientation of the guest determine the photophysical properties of the assembly by HOMO-LUMO band gap tuning. Moreover, the properties of cyclic oligomers were shown to be modulated not only by the nature of the guest,

but also by the number of monomeric units and their conformational flexibility, which has an effect on the efficiency of energy transfer. Stacks of merocyanine dyes were engineered through backbone-supported self-assembly. The strong electrostatic forces in this class of dyes ensured H-stacking through very strong dipolar interactions. Using tailored backbones, multiple stacks and heterostacks were created and characterized by exciton coupling theory. The goal of mimicking natural light harvesting systems may still be far, but this work has certainly taken us closer.

On Thursday afternoon, another five young scientists presented eight-minute talks as appetizers for the second poster session. Presenters were **Pol Besenius** (University of Mainz), **Thomas Hermans** (University of Strasbourg), **Frank Kotch** (Pfizer), **Corinna Schindler** (University of Michigan, Ann Arbor), and **Corey Stephenson** (University of Michigan, Ann Arbor).

The last presentation of the 52nd Bürgenstock conference provided a dazzling outlook on the rapid progress towards life-like systems based on artificial cells. From biodegradable polymersome capsules to multicompartmentalized nanoreactors, **Jan van Hest** (Eindhoven University of Technology) elegantly demonstrated how increasing levels of organizational and functional complexity can be built into artificial polymer-based systems. Achieving control of polymersome surface topology to generate stomatocytes not only allowed to load larger and more complex assemblies of proteins into nanoreactors but also to generate oxygen-propelled molecular motors. Irrespective of how long it will still take to generate fully biomimetic, synthetic cells, this final lecture highlighted again that there are few limits to where the imagination of curious, scientifically minded spirits can lead.



Jan van Hest

The 52nd Bürgenstock conference was a tremendous success and the authors thank the organizing committee, president Bert Meijer, and the Junior Scientist Participation fellowship (P. R.-F.) for the wonderful experience. We also want to express our gratitude to the two outgoing members of the organizing committee, Jérôme Lacour and Helma Wennemers, for their passionate dedication to this conference over many years. We look forward to the next Bürgenstock, which, under the presidency of Ilan Marek will certainly be another unforgettable meeting.

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