

Conference Report

Report from the 47th EUCHEMS Conference on Stereochemistry: The Bürgenstock Conference

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The small town of Brunnen on the Vierwaldstättersee is hallowed ground for chemists. For forty-seven years luminaries of the chemical community have converged once a year either on the mountaintop or at lakeside for a week of vigorous scientific exchange. The talks are legendary, the question sessions even more so. This year's conference took place at lakeside, from April 29 to May 4, 2012; and the president, *Andreas Pfaltz*, did not disappoint.

The proceedings opened with a welcome from *Andreas Pfaltz* and the introduction of the guest of honour: *Prof. Albert Eschenmoser*, whose long-standing contribution in the field of organic chemistry, including the monumental synthesis of vitamin B12 and his seminal investigations into the possible origins of nucleic acids, continue to inspire new generations of chemists. Even at this opening dinner the weather foreshadowed the wonderful week to come, as the sun was shining and a warm *Föhn* wind opened up a spectacular view of the Alps.



In the first evening lecture, under the kind moderation by past president *Jeremy Sanders*, *Roger Tsien* (University of California at San Diego) outlined his longstanding effort in building molecules capable of imaging electric fields, cellular distribution of important proteins, as well as spatial localization of distinct tissues or tumours inside organisms. We witnessed numerous fascinating results of a technique for selectively delivering molecules to tumour cells – activatable cell-penetrating peptides (ACPPs). There, a poly-arginine tag covalently bound to the molecule of interest is linked via a protease-sensitive linker to a poly-glutamate. Only after the linker is digested by a protease secreted exclusively by the neoplastic cells does the remaining part of the construct become cell-permeable. Precise spatial localization of that process only in the proximity of the targeted cells enables much more effective delivery than in previously used methods. Various modifications

of this technique allow for optical or MRI visualization of neoplastic cells in real time with a precision far overcoming standard medical procedures. All of this delivered with Prof. *Tsien's* inimitable intellectual brio.



The second day started off with the two morning lectures under the moderation of *Clément Mazet*. *Frank Glorius* (Westfälische Wilhelms-Universität Münster) began with a fascinating talk dealing with 'Stories on design and surprise: C–H activation, asymmetric arene hydrogenation and NHC organocatalysis'. He first presented recent developments in his research group on C–H activation, which culminated in him describing the first post synthetic modification of metal-organic frameworks. The second part dealt with Ru-NHC complexes catalysing asymmetric arene hydrogenation. Intriguing X-ray structural data of the pre-catalyst was displayed along with an interesting mechanistic proposal and this led to an exciting and interactive question session.

The second part of this session featured an outstanding lecture by *Vy Dong* (University of Toronto). Given the alpine setting, her lecture had a delightfully apropos title: 'A few of my favorite rings: Catalysis inspired by lactones and lactams'. In the first part she described her C–H activation strategy for enantioselective lactone synthesis. A very efficient enantioselective process was presented involving Rh(I) and enantiopure chiral phosphine ligands. Theoretical mechanistic studies were performed to rationalize the asymmetric induction, and this understanding allowed further refinement of the method. *Vy* then described a new method for the synthesis of cyclic peptides that aimed to avoid the major drawbacks of the currently established synthesis. Her strategy involves first constructing a linear dehydropolypeptide that adopts a β -turn conformation. Cyclisation of this peptide leads to the cyclic dehydropolypeptide in high yield despite running the reaction at high concentration. Finally asymmetric hydrogenation of this compound gives rise to the desired cyclopeptide in high yield and outstanding selectivity. The efficiency of the new method was highlighted through an economical synthesis of the complex natural cyclopeptide, *mahafacycline b*.



Among the 21 posters of the first session, 6 were selected for short (8 min) oral presentations. Contributors included *Manuel Alcarazo* (Max-Planck-Institut für Kohlenforschung), *Stuart Conway* (University of Oxford), *Syuzanna Harutyunyan* (Stratingh Institute, University of Groningen), *Ruben Martin* (Institute of Chemical Research of Catalonia), *Nuno Maulide* (Max-Planck-Institut für Kohlenforschung), and *Jérôme Waser* (Ecole polytechnique fédérale de Lausanne). This was followed by two hours of passionate discussion at the posters, involving all participants.



Properties and applications of functional structures prepared by self-assembly were demonstrated in the Monday evening lecture by *Luisa de Cola* (Westfälische Wilhelms-Universität Münster), vice-president of the Conference. Her broad research interest varies from phosphorescent metal complexes arranged in micelles to spatial arrangement of cargo inside zeolite channels. She beautifully demonstrated how to make minerals biocompatible. Zeolite crystals with directionally exposed charged molecules constructed in her lab can adhere to the oppositely charged surface of bacteria, resulting in nanoscale ‘carts’ propelled by the microorganisms.

Sarah O'Connor (John Innes Centre and University of East Anglia) kicked things off on Tuesday morning, in a session moderated by Bernd Giese, by taking us on a tour through her efforts in elucidating a number of alkaloid and terpenoid biosynthetic pathways in plants. The secrets of plant biosyntheses are often hidden in non-clustered pathways and so one of the great challenges is connecting the dots in a given pathway. Sarah described how her group approaches this problem with enabling technologies such as virus-induced gene silencing and co-expression analysis of whole transcriptomes. Through such analyses she was then able to annotate a number of unknown steps in important natural product biosynthetic pathways, such as, for example, the N-methylation step in vinca alkaloid biosynthesis.



The second morning talk on bioorganic chemistry was delivered by *Virginia Cornish* (Columbia University). The yeast two-hybrid system has proven to be essential in the characterization of protein-protein interactions. Virginia taught us that the potential of this exciting technology is far from tapped. She described how her group has retooled the yeast two-hybrid system to create a directed evolution platform for evolving new enzymes for reactions not observed in Nature. She also described how to combine traditional transformation methods with sexual reproduction as a new approach for creating molecular diversity in yeast with minimal experimental effort.

The third evening lecture, moderated by Mohammad Movassaghi, was given by *Paul A. Wender* (Stanford University) and carried the ambitious title: ‘Transformative therapies and the ideal synthesis: strategies to eradicate AIDS, treat Alzheimer’s disease and overcome resistant cancer’. At the beginning of his talk Paul threatened us with a 3 or 4 hour lecture, but given the eloquence of his delivery none of us would have been disappointed had this occurred. His lecture began by discussing the interesting biological activity of the complex natural product bryostatin. Neither isolation from natural sources nor synthetic approaches have been able to sustain a supply of bryostatin for clinical studies. Employing a different tack Paul then described his group’s development of the ‘bryologues’: molecules that resemble bryostatin but do away with any functionality unnecessary for its biological activity. Through this approach he has not only found molecules that



seem to have greater cancer-fighting activity than bryostatin, but may also improve cognition and therefore could also find use in Alzheimer’s treatment. With cancer and Alzheimer’s out of the way, Paul then described his approach to eradicating AIDS. Modern antiviral treatments do a wonderful job of reducing viral load in patients, but latent reservoirs of the virus always lay in wait for any opportunity to proliferate. Prostratin is a promising molecule in the treatment of this disease because it purges latent virus, making it susceptible to standard courses of antivirals. But prostratin is also available in short supply. No problem. The Wender group took advantage of their expertise in phorbol chemistry to achieve a semisynthesis of prostratin in only 4 steps and 16% overall yield from abundantly available phorbol.

On Thursday morning, in a session moderated by Bernhard Kräutler, *Bernhard Jaun* (ETH Zürich) discussed his investigations into the mechanism of an important enzyme responsible for methane formation and functionalization in *archaea* – methyl coenzyme-M reductase (MCR). MCR’s prosthetic group consists of nickel hydrocorphinato, a partially saturated porphyrinoid. The active state of the enzyme contains an oxygen sensitive Ni(I) radical, making the isolation and study of these enzymes a tricky affair. However, after proper handling procedures were developed, it was possible by thorough investigation of fate of isotopically labelled MCR substrates (methane and ethane) to propose a convincing kinetic model which rationalizes observed substitution patterns and measured kinetic isotopic effects.



The second speaker of the morning, *Milan Mrksich* (University of Chicago) delivered a fabulous talk, entitled ‘Label-free screening for the discovery of chemical and biochemical reactions’. In dynamic and convincing style, Milan began his lecture with the study of interfacial reactions. A Diels-Alder reaction between a benzoquinone group fixed on a monolayer and cyclopentadiene was monitored in real time by electrochemistry. Then the problem of characterization of the product was discussed and he presented a powerful method, involving MALDI-TOF spectroscopy to characterize monolayers. This method has led to the discovery of a new phosphine-catalysed reaction whose scope and mechanism was explored. Then a new strategy for solid-supported oligosaccharide array synthesis with direct SAMDI-TOF mass spectrometry detection of the synthesis process was described. Automated preparations handling of the arrays combined with rapid scanning allow the analysis of up to 90000 spots/day. Milan then described his work studying the post-translational regulation of histone, and an early example of methylation-acetylation cross-talk by a single enzyme was reported.

For the musical evening *Jeanne Roth* accompanied by *Andres Joho* used her vocal talent to invite us for a musical journey from Brunnen around the world. ‘Bonsoir’ composed by George Enescu commenced our evening voyage through Swiss landscapes pictured by Othmar Schoeck. Then the music of Calixa Lavallé, Aaron Copland and Scott Joplin moved us to the New World. Subsequently we were impressed by musical pictures of Japanese wind forests, leaving us with a vision of mysterious Orient. Next, Edward Elgar’s music gave us a short stop in the America on our way back to Europe. A tour through Germany commenced with Beethoven’s sonata. Then Jeanne Roth expressively performed



'Erdas Warnung' from Wagner's 'The Rhine Gold', which led into a short sung epigram of Goethe; finally Giuseppe Verdi's 'Stornello' completed our musical journey. The concert was finished with two pieces performed with extraordinary passion dedicated to the conference President – Andreas Pfaltz.

Under the moderation of the vice president Luisa de Cola, the Thursday morning session began with a captivating lecture of *Douglas W. Stephan* (University of Toronto) who presented how his group has developed the concept of frustrated Lewis pairs as a new avenue to small molecule activation and catalysis. After a historical perspective, the metal-free activation of H₂ by frustrated Lewis pairs was described and the nature of this reaction was discussed based on computational and experimental studies. The scope of this reaction was extended to other small molecules like alkynes, alkenes, carbone dioxide, and cyclopropane. The system also proved efficient for the catalytic hydrogenation of imines without a transition metal. Additional highlights of his lecture include the reduction of N-heterocycles and the capture of CO₂ with frustrated Lewis pairs.

Stefan Grimme (Westfälische Wilhelms-Universität Münster) tackled the very challenging task of delineating the role of dispersion interactions in computational chemistry. After a short introduction on the different theoretical approaches used for calculations performed on chemical systems of various sizes, he explained to us the origin of dispersion energy as the consequence of long-range electron correlation. Stefan convincingly explained that in simple systems containing only a few atoms dispersive interactions are usually negligible, but with complex multiatomic systems they play a more significant role and misleading results are often obtained, if the dispersion energy is neglected in calculations.



During the introduction for the second poster session of the conference we heard short presentations delivered by *Takahiko Akiyama*, *Martin Albrecht*, *Yujiro Hayashi*, *Hayato Tsuji*, *Corey Stephenson* and *Christian Hackenberger*. The topics ranged from chiral phosphoric acid catalysts for enantioselective C(sp³)-H bond activation, exploiting carbenes in metalloenzymes, applications of organocatalysis in total synthesis of Tamiflu® and other bioactive molecules in context of 'pot economy', efficient semiconducting materials based on fused furans, synthesis of natural product by means of visible light-mediated radical reactions, to the application of sialic acid derivatives for glycan-specific metabolic oligosaccharide engineering.



For the final evening lecture moderated by *Shu Kobayashi*, *Ei-ichi Negishi* (Purdue University) delivered an unforgettable lecture on the early experiments that led to his now famous cross-coupling process.



But he didn't stop there! He also described his group's seminal contributions and continuing development in a process he terms 'ZACA', Zr-catalysed asymmetric carboalumination of alkenes.

The final session of the 47th Bürgenstock conference was conducted under the moderation of *Jieping Zhu*. In a fascinating lecture entitled 'Molecular design of organic ion pairs for asymmetric catalysis', *Takashi Ooi* (University of Nagoya) presented the latest results from his group on the combination of 1,2,3-triazoles and chiral structures to create efficient asymmetric phase-transfer catalysts. He then focused on asymmetric silicon-based nucleophilic halogenations, showing how his group achieved highly enantioselective halide ring-opening of aziridines. Finally, the use of supramolecular ligands for metal-based asymmetric catalysis was described. He illustrated how simple chiral molecules and achiral ligands can be associated *via* electrostatic interactions to achieve asymmetric palladium-catalysed allylic alkylation. In the spirit of the Bürgenstock Conference most of the results he described were very recent or unpublished results.

Homogeneous and enzymatic catalysis may seem like disparate areas but *Thomas Ward* (University of Basel) delivered a convincing case that there is much to be gained from a fusion of these two disciplines. He described his group's early contributions in recognizing the potential of genetic diversity to tailor protein space for the optimization of catalytic reactions. He then revealed some of his chemical dreams for the future of this technique; at first these hopes seemed very pie-in-sky, but by the end of this wonderful lecture we were convinced that he was already halfway there.



From its opening lecture by *Roger Tsien* into the potential of chemistry for solving medical problems, to its close where *Tom Ward* described how biology can help chemists solve some of our own intractable problems, this year's Bürgenstock was a truly wonderful and diverse scientific event. Although *Luisa de Cola* performed her job as vice-president admirably, delivering wonderful weather the whole week, her job as next year's president promises to be much more difficult as the bar has been set very high this year. Well done *Andreas*!

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