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Conference Report

A Ray of Light Piercing through the Clouds
The 49th EUCHEMS Conference on Stereochemistry Bürgenstock Conference 2014

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It is common to conclude that a conference was great, wonderful or amazing, but these words are not good enough to describe the 49th EUCHEMS Conference on Stereochemistry (May 4–9, 2014), much better known as the Bürgenstock conference. As the title (a quotation of a regular participant of this meeting) says, the event has its own spirit. It might be its rather long history or somewhat unique rules or a splendid location, but it certainly is a blend of many distinctive factors, which make you feel that you want to come back. And for the younger participants, it is difficult to believe, that just six years ago, this conference used to take place some 30 km away from Brunnen. Interestingly, even those who witnessed the editions at the original location in the Bürgenstock resort, highly appreciated the qualities and advantages of the current venue. Will the conference ever move back?

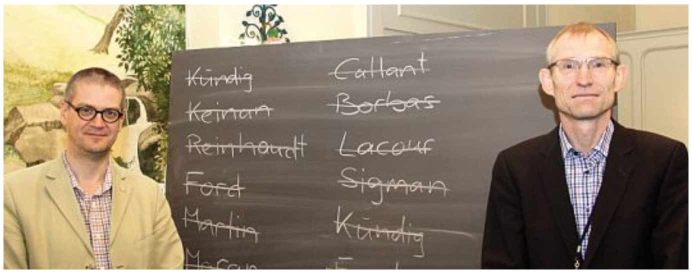
This year's president of the conference, ***Antonio M. Echavarren*** (ICIQ) welcomed the participants at the opening dinner and introduced a guest of honor, his compatriot and colleague ***Javier de Mendoza*** who was the first Spanish speaker (1994) and also the first Spanish president (1999) of the Bürgenstock conference. He also highly praised the work of the organizing committee, ***Alain De Mesmaeker*** (Syngenta), ***Jérôme Lacour*** (University of Geneva), ***Reto Naef*** (Novartis), ***Philippe Renaud*** (University of Bern) and ***Helma Wennemers*** (ETH Zürich), who made this spectacular meeting possible.


Antonio Echavarren

Right after the Sunday dinner, Paolo Melchiorre (ICIQ) introduced ***Peter R. Schreiner*** from the Justus-Liebig University of Giessen who gave an outstanding opening talk on reactions that follow the Swiss model of tunneling through barriers rather than climbing over the hill. His group devised routes for the synthesis and isolation of the new class of hydroxycarbenes from common starting materials. Remarkably, these carbenes undergo facile [1,2]hydrogen tunneling shifts to the corresponding aldehydes through large energy barriers. His experiments in combination with powerful computational approaches demonstrate that tunneling must be included to fully understand chemical reactivity. Schreiner emphasized that tunneling is not only a correction of reaction rates, but that it rather represents a third paradigm of chemical control in addition to thermodynamic and kinetic control. Chemical selectivity is thus not only governed by the relative heights of kinetic barriers but also by the widths of the reactions paths. As in all cases throughout the whole week, a great talk was followed by an intense discussion. The chatter then continued at a get together where all the participants could enjoy a nice glass of wine. As usual, debates ended at the hotel bar.


Paolo Melchiorre and Peter R. Schreiner

The moderation of the Monday morning session was in the hands of Karl-Heinz Altmann (ETH Zürich). The first speaker ***Christophe Copéret***, also from ETH, explained how one can control the chemistry on oxide supports to generate well-defined supported catalysts, thus bridging the gap between homogeneous and heterogeneous catalysis. Applying molecular approaches and spectroscopies, he explained how his research group clarified the structure of some relevant industrial catalysts, *e.g.* for metathesis and polymerization, which have been used for decades, and even how it was possible to design novel well-defined catalysts with superior performance. He also demonstrated how new techniques such as Dynamic Nuclear Polarization Surface Enhanced NMR spectroscopy could help characterize surface species at the atomic level in a short time (decreasing experimental times by several 10'000). He finally described that this molecular approach was applicable not only to catalyst design and preparation, but also to the development of imaging technologies.



Christophe Copéret and Karl-Heinz Altmann

Right after a coffee-break served at the shore of the lake, ***Anna Mapp*** (Michigan University) entered the stage for the second morning talk. Dysregulation of genes causes diseases including cancer. The transcription machinery contains proteins displaying multiple protein-protein interactions (PPIs) that could be suitable for small molecule targeting. However, these interfaces fall in the category of the so-called 'undruggable genome'. In her lecture, Anna nicely demonstrated the power of unbiased high throughput screening methodologies and identified depside natural products as suitable small molecules to target the

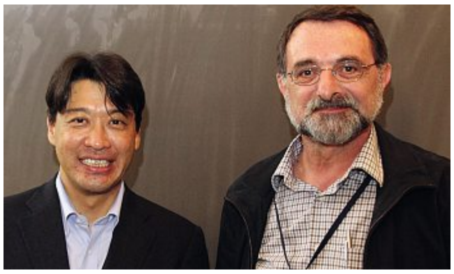

Anna Mapp

dynamic interface of the transcriptional co-activator CBP/p300. Furthermore, Anna showcased tethering strategies, a covalent chemical capture strategy that enables the identification of specific small molecule fragment inhibitors of PPIs. Ultimately, such biochemical approaches accelerate the process of drug discovery by identifying otherwise unanticipated PPIs inhibitors.

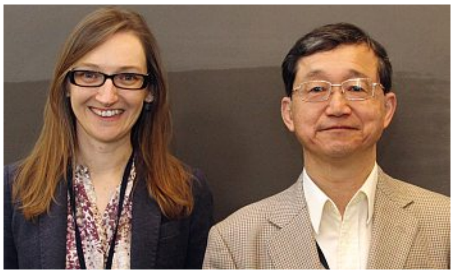
The low ratio of total 14 scientific talks given in six days is probably another factor which makes this conference so unique. But it perfectly serves its purpose of communicating chemistry in a relaxed and creative atmosphere. There is just enough time to exchange ideas, challenge existing dogma, introduce new concepts and set new goals. Therefore, the other researchers “had to resort” to present their great achievements “only” *via* a poster. No harm done! On later Monday afternoon, five recipients of the JSP fellowship, John Bower (University of Bristol), Dennis Gillingham (University of Basel), Nathalie Katsonis (University of Twente), Andrew Lawrence (University of Edinburgh) and Daniel Summerer (University of Konstanz) provided a great appetizer (eight-minute short talks carefully regulated by Helma’s popular cow) for an intense two-hour poster session visited by all participants.

The evening session was opened by Jerome Lacour who sadly reminded us that last year, the chemical world lost the *Man behind the Bürgenstock conference*, Professor André Dreiding (June 22, 1919, Zurich – December 24, 2013, Herrliberg). He then invited ***Wolf-Dietrich Woggon*** (University of Basel), a former habilitand of André Dreiding, to the stage to pay tribute to this outstanding person. Although being a Swiss citizen, Professor Dreiding obtained most of his education in the US (Master at Columbia University in New York, Ph.D. at University of Michigan in Ann Arbor with professor Bachmann in 1947, postdoctoral fellow at the same institution). He started his academic career as an assistant professor at Wayne University from 1949 to 1954. Then he returned to his homeland and became a professor at University of Zurich where he stayed even after his retirement in 1987 as Emeritus Professor. His research activities were broad and ranged from stereochemical problems, synthesis of unusual compounds via structure elucidation of natural products to total synthesis. A complete list is far beyond the limits of this report, but two facts should be reminded. It was Dreiding who in 1958 invented a skeletal molecular model (named Dreiding stereomodels) made of stainless tubes and rods to be used for many years as a powerful tool primarily in stereochemistry; and it was André Dreiding who initiated and became the first president of the Bürgenstock conference. *Requiescat in pace*.

Antonio Togni (ETH Zurich) then introduced ***Kenichiro Itami*** (Nagoya University) who delivered an uplifting overview of his broad research activities. The first part focused on the development and understanding of the nickel-catalyzed C–H activation processes with emphasis on arylation reactions. Being a cofounder and a director of the Institute of Transformative Bio-Molecules, in the second part he demonstrated how such a synthetic expertise can be exploited in the rapid synthesis of pharmaceutically relevant molecules *via* a late-stage C–H functionalization. The last part of his talk was dedicated to the development of efficient methods for the construction of various structurally uniform nanocarbons. For example, the Itami group thus established protocols for the synthesis of a wide range of cycloparaphenylenes (from [7] to [16]), which can be used as nanoring templates for the bottom-up synthesis of carbon nanotubes. They also designed a two-step sequence to nanographenes containing 26(!) aromatic rings. Interestingly, such structures become grossly warped resulting in improved solubility and modified electronic and optical properties.


Kenichiro Itami and Antonio Togni

The Tuesday morning session was moderated by Cristina Nevado (University of Zurich) and the first speaker, ***Naoto Chatani*** from the Osaka University summarized his expertise in C–H functionalization reactions. It should be emphasized, especially to the younger generation readers, that back in 1993 it was the contribution from his laboratory on the first efficient alkylation *via* a ruthenium-catalyzed directed carbon–hydrogen bond cleavage, which inspired other scientists all over the world. Professor Chatani reported on the development of N,N-bidentate directing groups as a promising platform for the discovery of new transformations. He discussed some of his recent achievements in the field of C–H functionalization with emphasis on carbonylation, arylation and alkylation (including methylation) reactions catalyzed by ruthenium or nickel. Extensive studies showed that depending on the oxidation state of the metal, different mechanisms are operating in the C–H functionalization step (σ-bond metathesis for M(0) and concerted metallation-deprotonation pathway for M(II)).


Cristina Nevado and Naoto Chatani

After a coffee break second speaker, ***Marcy Waters*** (University of North Carolina) revealed the efforts and strategies of her group towards understanding recognition of histone protein modifications. The genetic material of eukaryotic cells is packed as a nucleoprotein complex named chromatin. Histones proteins are further chemically modified by post-translational modifications (PTMs) including methylated lysine residues, which orchestrate the expression of genes. Marcy first introduced the molecular basis of supramolecular interactions with particular emphasis on cation-π interactions. She then provided solid evidence that recognition of specific marks using antibodies raised against these marks are drastically affected by the combinatorial nature of PTMs. Her work, based on dynamic combinatorial chemistry, takes advantages of disulfide chemistry to build selective receptors for lysine and polymethylated lysine residues with the ultimate goal of replacing antibodies with small molecules to decipher the histone code, a challenging endeavor.


Marcy Waters

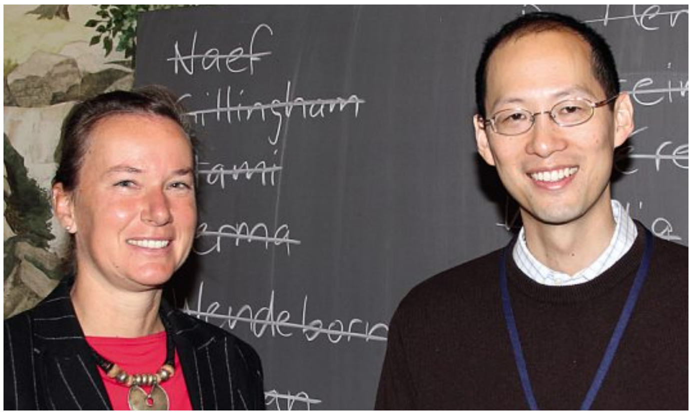
The evening session was moderated by Masashiro Murakami (Kyoto University) who delivered a very entertaining performance.

Masashiro Murakami

John Porco (Boston University) described his recent work on the total synthesis of densely functionalized natural products including rocaglamide, forbaglin, silvestrol, aglain and associated biological properties. These syntheses feature a remarkable photogeneration of oxidopyrylium intermediates, obtained from hydroxyflavones by means of Excited State Intramolecular Proton Transfer (ESIPT) followed by [3+2] dipolar cycloadditions yielding aglain core structures. An asymmetric version of the photocycloaddition in the presence of chiral Brønsted acids (*e.g.* TADDOLs) was also presented. John then elaborated on the use of parallel fluorescence quenching assay using microplates to rapidly and reliably identify suitable dipolarophiles. Finally, the synthesis and absolute structural assignment of (+)-ponapensin and (+)-elliptifoline were highlighted, fulfilling the very purpose of the Bürgenstock Conference, a beautiful lecture!

John Porco

Wednesday morning session was moderated by Ruth Gschwind (University of Regensburg). The cellular detection of metabolites and metal ions *in vivo* is critical and represents a considerable challenge. ***Christopher Chang***, HMMI investigator from the University of California, Berkeley, introduced a subset of the research ongoing in his lab including the development of small molecule sensors of reactive oxygen species (ROS) and metal ions. In particular, Chris described small molecule probes containing boronic esters, which upon exposure to hydrogen peroxide release the corresponding fluorescent aromatic phenols. Remarkably, the probes can detect hydrogen peroxide in cells and living organisms including the zebrafish. This creative approach revealed a rather unforeseen role of reactive oxygen species in promoting neurogenesis. Finally, Chris described recent work on metal sensors with particular emphasis on BODIPY-derived copper probes, which revealed a calcium-dependent delocalization of copper from the cell body to its periphery upon activation, thereby establishing unprecedented metal ions signaling pathways. It is conceivable that such strategies could be generalized to the detection of other metal ions and metabolites for live cell imaging, a major landmark in the field.



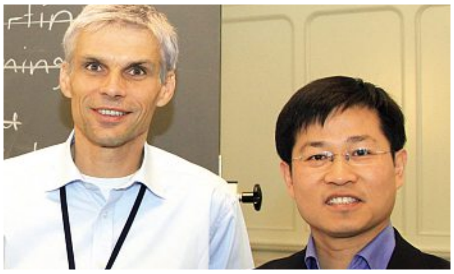
Ruth Gschwind and Christopher Chang

After a coffee-break the audience enjoyed an amazing trip to the very origin of systems which are important for the existence of life. ***John Sutherland*** from the MRC Laboratory of Molecular Biology in Cambridge demonstrated how his group sheds light on the prebiotically plausible syntheses of pyrimidine nucleotides, sugars, amino acid precursors and lipids from simple molecules under conditions which are consistent with potential early-Earth geochemical models. These include cyanide, cyanamide, acetylene, ammonia and inorganic phosphate as possible prebiotic feedstock molecules. The strategies rely on mixed oxygenous and nitrogenous chemistry as well as photoredox systems. Professor Sutherland also proposed how to circumvent the thermodynamically disfavored and kinetically sluggish polymerization of nucleotides. His work suggests that RNA could be assembled *via* ligation facilitated by chemoselective acetylation of the 2'-hydroxyl group of oligoribonucleotide-3'-phosphates in water.

John Sutherland

The afternoon was left free so that the participants could rest their minds before another intense series of insightful lectures and discussions. On Wednesday evening the lecture hall was rearranged to a concert venue as the chemistry gave way to music. Asasello Quartet, composed of Rostislav Kozhevnikov (violin), Barbara Kuster (violin), Justyna Sliwa (viola) and Teemu Myöhänen (cello), coddled our ears with Shostakovich's String quartet no. 9 and Tchaikovsky's String quartet no. 3. After a massive applause, the artists returned for an encore presenting a Canzonetta from Mendelssohn's String quartet no. 1. It did not escape our notice that some participants skipped this delightful musical event to play table football in a bar 'down-town'.

Shuli You from the Shanghai Institute of Organic Chemistry opened the Thursday morning session by introducing ***Armido Studer*** (WWU Münster) who develops processes catalyzed by electron. These include cross dehydrogenative coupling reactions occurring *via* base-promoted homolytic aromatic substitution for the synthesis of fluorenones or a novel transformation for the preparation of trifluoromethylated phenanthridines from suitable isonitriles. As the arene ring is formed during the reaction, a perfect control of the position of the trifluoromethyl group was achieved. He also demonstrated on the central role of TEMPO in his group which can for example be used as an organic oxidant to initiate a radical/anionic polymerization for preparation of conjugated polymers *via* transition metal-free homocoupling of bis-Grignard reagents. Alternatively, the TEMPO-anion can act as a mild reducing reagent for the generation of carbon-centered radicals which are oxidatively trapped by the TEMPO radical formed in the first step. Such redox chemistry can be applied to trifluoromethylaminoxylation, azidooxygenation or carboaminoxylation of terminal alkenes.



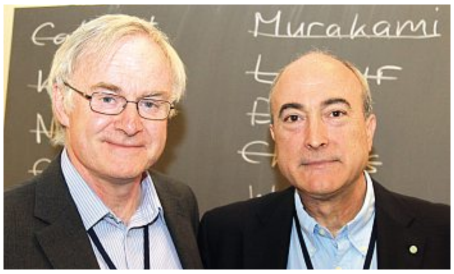
Armido Studer and Shuli You

Michelle Chang (University of California, Berkeley) showcased her recent work on synthetic biology, the use of designer enzymes to fine tune the production of otherwise inaccessible metabolites such as biofuels and fluorinated natural products for biomedical applications. Remarkably, Michelle and co-workers took advantage of the microbe *Streptomyces cattleya* with evolved fluoroacetyl-CoA thioesterase (FIK) activity to selectively produce natural product scaffolds that contains fluorine at specific positions with a defined stereochemistry. This illustrates the power of synthetic biology to produce complex structures including biologically active polyketides. Furthermore, Michelle described some groundbreaking results with the high yielding production of butanol using chimeric pathways from different organisms. Cell factories can be used to produce biofuels and relevant chemicals by means of microbial fermentation, an important milestone.


Michelle Chang

During the afternoon, a second and final poster session took place and the poster teasers were offered by Jonathan George (University of Adelaide), Bernhard Kräutler (University of Innsbruck), Clement Mazet (University of Geneva), Raphaël Rodriguez (CNRS) and Daniel Strand (Lund University).

The evening program of the penultimate day was moderated by John Murphy (University of Strathclyde). ***Nazario Martín*** (University Complutense of Madrid) gave a general overview of his very inspirational contribution to the field of supramolecular chemistry with particular emphasis on allotropes of carbon, namely fullerenes, carbon nanotubes and graphenes. This included the enantioselective synthesis of chiral fullerene as well as fullerene functionalized with π-extended tetrathiafulvalene (exTTF) exhibiting versatile donor-acceptor electron transfer properties. Mechanically interlocked single-wall carbon nanotubes (SWNTs) were also described along with the preparation of rotaxane-containing carbon nanotubes and exTTF. The main challenge of designing organic compounds that display effective convex-concave recognition ability has been met, as exemplified by a large diversity of supramolecular devices such as C60-functionalized optical tweezers.



John Murphy and Nazario Martín

The final morning session was chaired by Rubén Martín (ICIQ). The first speaker ***Jesus Jiménez-Barbero*** (CIB-CSIC, Madrid) gave a remarkable insight into the potential of modern NMR spectroscopy for molecular recognition. The outer part of cell membranes is loaded with a series of lipids, proteins and glycoconjugates that cells use to communicate with one another, to attach and move within tissues, internalize nutrients and further promote intracellular signaling that is critical for cell survival and fate. A clear understanding of roles and crosstalk between cell surface markers could provide strong basis for therapeutic intervention. Then he demonstrated the power of NMR spectroscopy to elucidate the mode of binding of macromolecules with particular focus on carbohydrates and glycoconjugates including lectins. He also described the nature of sugar-π interactions with the requirement for three axial hydrogen atoms on the sugar to interact with an aromatic surface, a rather unexpected feature. TR-NOESY can reveal which atoms of biomolecules and small molecules engage supramolecular interactions within complexes highlighting its value to elucidate biological processes.


Jesus Jiménez-Barbero and Rubén Martín

Although ***Matthew Sigman*** (University of Utah) expressed a slight dismay at being the last speaker of the conference, the audience appreciated that the splendid program had been crowned with his spectacular lecture on analyzing and predicting selectivity in asymmetric catalysis. Matthew emphasized the importance of choosing proper mathematical representation of properties, which affect reactivity and selectivity. He presented case studies in which a different set of parameters led to strong correlations although other parameters failed. Following these activities, his group developed a new parameter system based on the vibrational response of a molecule to infrared radiation. In comparison to classical systems, their parameters address and evaluate simultaneous changes to steric and electronic properties. Professor Sigman also introduced a three-dimensional free energy relationships, which correlates steric and electronic effects for the design and optimization of a ligand class in catalytic enantioselective transformations. With such a tool, they can even predict that a satisfactory asymmetric induction cannot be achieved with a certain catalyst and thus alternative ligand scaffold has to be evaluated.


Matthew Sigman

From its opening lecture by ***Peter Schreiner*** on quantum mechanical tunneling as a new model for the control of chemical reactions, to its close where ***Jesus Jiménez-Barbero*** demonstrated the potential of NMR spectroscopy to unravel complex supramolecular interactions, this year's Bürgenstock covered, once again, an impressive diversity of science of exceptional quality. Although, the vice president ***Antonio Togni*** performed his job almost perfectly (three sunny days out of five), as next year's president his job to match such an exceptional atmosphere and fantastic research will certainly be a lot more challenging. But is there any doubt?


Antonio Togni

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