

Conference Report

The 50th EUCHEM Conference on Stereochemistry (Bürgenstock Conference 2015),
Brunnen, April 26th–May 1st, 2015

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Keywords: Bürgenstock conference 2015 · EUCHEM · Stereochemistry

The legendary and outstanding EUCHEM Conference on Stereochemistry – the ‘Bürgenstock Conference’ – celebrated its 50th anniversary in the charming town of Brunnen at the shore of Vierwaldstättersee (April 26th to May 1st 2015). As one can only expect from a Bürgenstock Conference, also this year a group of world class scientists has gathered together in Brunnen to present and discuss top-notch science and, at least on lecture-free afternoons, to enjoy the breathtaking views of the Swiss Alps. The guests were immediately rewarded for a long trip by a sunny Sunday afternoon in Brunnen.

The scientific party was opened by this year’s president **Antonio Togni** from the ETH Zürich. On the occasion of the traditional conference dinner on Sunday, **Dieter Seebach** (ETH Zurich), whose research on stereochemistry has coined the field of organic synthesis and this conference in particular for many decades, was introduced as the Guest of Honor. The organizing committee of this year’s Bürgenstock Conference consisted of **Christian Bochet** (University of Fribourg), **Alain De Mesmaeker** (Syngenta), **Jérôme Lacour** (University of Geneva), **Reto Naef** (Novartis), **Philippe Renaud** (University of Bern) and **Helma Wennemers** (ETH Zurich).



Dieter Schlüter

The spectacular week of scientific excellence started on Sunday evening, as chairman David Reinholdt introduced **Dieter Schlüter** from the ETH Zürich as the first speaker. His group has produced an impressive body of work on creation and physicochemical characterization of one monomer unit thick macromolecules, the two-dimensional polymers (2DPs), that may soon have a tremendous impact on the field of material sciences. Schlüter presented an upscalable synthetic strategy that allows photochemically induced growth of chiral 2DP crystals from enantiomeric single crystals. The created crystals, which can be obtained on gram scale from three-bladed anthracenes, can be exfoliated into nanosheet sheets and can also be reverted into monomers simply by heating, thus opening new avenues towards applications in membrane and non-linear optics technologies. As it is traditionally the case at the Bürgenstock meetings, the presentation was followed by intense discussions that were continued until late into the evening.

The Monday morning session began with a fascinating journey to the world of fluoroalkylation reagents and reactions presented by **Jinbo Hu** from the Shanghai Institute of Organic Chemistry

(SIOC), who was introduced by chairman Klaus Müller (Hoffmann-La Roche). Hu first provided an extensive overview over his group’s past achievements in difluoromethylation, difluoromethylenation and monofluoromethylation reactions. The speaker also presented some of the newest fluoroalkylation reactions developed in his laboratory such as the use of TMSCF_2Br as a general difluorocarbene source for the difluoromethylenation of alkenes, alkynes as well as the O-, S-, N-, and P-nucleophiles. The mild reaction conditions also allow difluoromethylation of sensitive substrates, such as (thio)alcohols, sulfonates, heterocyclic amines and even hydrophosphine oxides. Furthermore, Hu presented an *in situ* AgF-mediated *gem*-difluoroolefin fluorination/intermolecular alkenyl C-H functionalization cascade reaction, a highly innovative method that provides facile access to $\alpha\text{-CF}_3$ alkenes and $\beta\text{-CF}_3$ ketones, which are otherwise challenging to prepare. Also, a novel approach was demonstrated that allows the synthesis and, most importantly, also the separation of the *Z*- and *E*-monofluoroalkenes simply by liquid–liquid extraction. Considering the ever growing importance of fluorination and fluoroalkylation reactions in modern drug design, Jinbo Hu’s novel reactions and reagents will surely find broad use in the pharmaceutical industry.



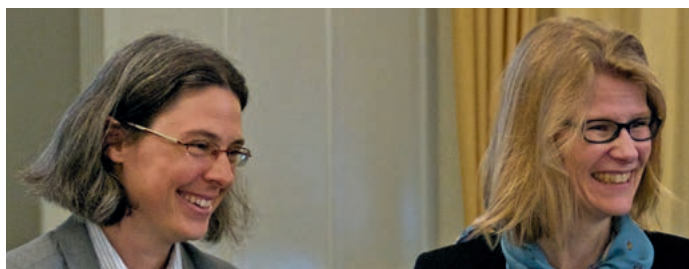
Jinbo Hu

Following the coffee break, **Cristina Nevado** (University of Zurich) delivered a highly dynamic and fast-paced talk on mechanistic diversity in late transition metal catalyzed reactions. The speaker presented two novel radical-mediated transformations of activated alkenes, an arylphosphonylation and arylazidation, to obtain the corresponding $\alpha\text{-aryl-}\beta\text{-phosphonyl}$ and $\alpha\text{-aryl-}\beta\text{-azido}$ amides in a highly regioselective fashion. In yet another two dizzyingly complex and highly stereoselective radical cascade reactions, densely functionalized indanes and dibenzocycloheptadienes were obtained from *ortho*-vinyl- and *ortho*-vinylaryl-substituted *N*-(arylsulfonyl)acrylamides. In the last part of her talk, Nevado switched from synthetic methodology to medicinal chemistry and presented a novel chemical class of receptor tyrosine kinase inhibitors. In collaboration with Amedeo Caffisch (University of Zurich), her group has developed highly promising nanomolar inhibitors of Eph kinases that are now being further investigated in *in vivo* models.



Cristina Nevado

Prior to the first poster session, five promising young European scientists and recipients of a fellowship from the Junior Scientists Participation Program were given the opportunity to present their research in a short oral presentation. The short talks on chemical modification of cysteines (Alexander Adibekian; University of Geneva), iron-catalyzed amination of alcohols (Katalin Barta, University of Groningen), total synthesis of Sarpagine alkaloids (Tanja Gaich, Leibniz University Hannover), total synthesis of Leucosceptroids (Thomas Magauer, LMU Munich) and organo-



Tanja Gaich and Helma Wennemers

catalytic atroposelective aldol condensation (Christof Sparr, University of Basel) were followed by a lively two-hour poster session involving all participants.



Thomas O'Halloran

The Monday evening session was chaired by Luisa De Cola (University of Strasbourg), who introduced **Thomas O'Halloran** (Northwestern University) as the speaker. Professor O'Halloran gave an exciting, colorful presentation on how the inorganic chemistry in cells can control the cell fate decisions. Using a fluorescent zinc probe and state-of-the-art imaging techniques, such as scanning transmission electron microscopy, energy-dispersive spectroscopy, X-ray fluorescence microscopy and three-dimensional elemental tomography, O'Halloran and coworkers investigated the dynamics of zinc sparks that are being created during fertilization of a mammalian egg. These zinc sparks arise from thousands of zinc-loaded vesicles, each containing 10^6 zinc atoms. Moreover, the speaker demonstrated that these vesicles undergo dynamic movement during oocyte maturation and exocytosis at the time of fertilization.



Markus Ribbe

The Tuesday morning session, chaired by Jan Bäckvall and Peter Kündig, was opened by **Markus Ribbe** (UC Irvine), who provided a detailed overview over the most recent achievements from his laboratory in the nitrogenase field. Nitrogenase is a uniquely versatile metalloenzyme that catalyzes the reduction of various substrates, such as N_2 , CO and CN^- at its cofactor site. Using radiolabeling experiments, the carbide group in the M-cluster, a metal-sulfur cluster in the active site of the nitrogenase, was shown to originate from S-adenosylmethionine (SAM) and to be inserted into the M-cluster by protein NifB. Amazingly, the nitrogenase cofactors can be extracted into organic solvents and are still capable of catalyzing the reduction of cyanide, carbon monoxide and carbon dioxide without using ATP, but with samarium(II)iodide and 2,6-lutidinium triflate as a reductant and a proton source, respectively. Needless to say that also this thought-provoking lecture was followed by long and intense discussion.



Ben Feringa

After the coffee break, it was **Ben Feringa's** (Rijksuniversiteit Groningen) turn to entertain the audience with his dynamic molecular systems. For example, by covalently attaching glucose oxidase and catalase to carbon nanotubes glucose was converted into H_2O and O_2 to power autonomous movement of the nanotubes. As yet another example, a series of light-driven molecular motors with rigid substituents was synthesized to act as 'molecular stir-

ers' in a variety of solvents. The rotary speed can be modulated by the rigidity and also the length of the substituents. Most impressively, Feringa has created a unique scientific blend by combining molecular motors with asymmetric catalysis. A chiral bisphosphine with a molecular motor core structure was used as a chiral switchable ligand for Pd catalysis and the stereoselectivity in a catalytic reaction was modulated by switching the helicity of the bisphosphine ligand on irradiation.

On Tuesday afternoon, moderator Lia Addadi (Weizmann Institute) introduced **Ayusman Sen** (Pennsylvania State University) as the speaker of the evening session. Sen's lecture was dedicated to self-powered dynamic materials, such as nanomotors and nanobots. His group has designed autonomous motors that are powered by depolymerization of poly(2-ethyl cyanoacrylate) (PECA), an FDA-approved polymer. These motors are capable of moving in various media, even including salt solutions and artificial serum. Amazingly, surface-immobilized enzymes, such as catalase, lipase, urease and glucose oxidase, can function as self-powered micropumps in the presence of their respective substrates. Sen believes that the flow is driven by a gradient in fluid density generated by the enzymatic reaction. Thus, the pumping velocity increases with increasing substrate concentration and reaction rate. One could envision usage of these systems for delivery of small molecules, such as drugs, in response to specific chemical stimuli.



Ayusman Sen

The first organic synthesis session on Wednesday morning was moderated by this year's vice president Paul Knochel (LMU Munich). The lecture of **Sarah Reisman** from the California Institute of Technology was dedicated to novel synthetic strategies for the construction of complex alkaloids and terpenoids. Using a directed C-H functionalization and an elegant [4+2] cycloaddition/Prins cascade reaction, a major part of the meroterpenoid psiguadial B could be constructed. For the synthesis of hasubanane alkaloids, the use of a diastereoselective 1,2-addition to benzoquinone-derived *tert*-butanesulfinimines was presented. The third part of the talk was dedicated to a [2+2] cycloaddition retro-aldol approach for the synthesis of the complex alkaloid acutimine. Using the benzoquinone *tert*-butanesulfinimine strategy, the retro-aldol precursor could be synthesized in a concise manner. Careful structural modifications enabled the envisioned retro-aldol reaction to give a highly functionalized precursor of the target molecule. A large proportion of the results presented was unpublished and stimulated a lively and intense discussion with the audience.



Sarah Reisman

The next speaker, **Richmond Sarpong** from UC Berkeley, continued the theme of alkaloid total synthesis and presented innovative routes to lyconadin A, complanadine A and B, liljestrandinine and weisaconitine. The selective C-N bond formation in the synthesis of lyconadin A could be accomplished *via* a novel oxidative coupling of dianions using iodine. For the synthesis of the complanadines, the chemistry of methoxy pyridines was investigated in detail. This allowed the



Richmond Sarpong

regioselective C–H borylation of highly functionalized building blocks for fragment coupling. A biosynthetic network analysis of the aconitine framework led to a strategy, which disconnects the highly substituted central ring. This tactic was realized for the synthesis of liljestrandinine and weisaconitine and enabled the construction of a major part of the complex alkaloid aconitine. This lecture was followed by another fruitful discussion.

On Wednesday afternoon, Jack D. Dunitz, Albert Eschenmoser and Duilio Arigoni joined the aperitif and pre-dinner event to share their memories from previous Bürgenstock Conferences. After the gala dinner and a wonderful musical evening with Eliana Burki and the Alpinisti – a musical journey with the Alphorn around the world – the participants enjoyed the post-concert get-together with the musicians.



David O'Hagan

On Thursday morning, moderators Alan Krief (IOCD) and Bernhard Kräutler (University of Innsbruck) introduced **David O'Hagan** from the University of St. Andrews, who presented a spectacular lecture on synthesis and chemical properties of polyfluorinated cyclohexane derivatives. The stereoelectronic and conformational effects observed for several fluorinated muscone and civetone derivatives using X-ray crystallography were investigated. For linear all-*cis* alkylfluorides, a helical structure due to electronic repulsion was described. Using a generalized strategy based on nucleophilic fluorination, all-*cis* 1,2,3,4,5,6-hexafluorocyclohexane could be synthesized for the first time. Using ^{19}F NMR spectroscopy, it was beautifully demonstrated that the highly polar all-*cis* 1,2,4,5-tetrafluorocyclohexane shows strong interaction with toluene.



Matthew Francis

In the next session, **Matthew Francis** from UC Berkeley gave an impressive talk on the chemical modification of *N*-terminal peptides by using 2-PCAs (2-pyridinecarboxaldehydes). This strategy allows for the controlled and site-specific protein modification that does not require any genetic engineering and avoids traditional methods based on the modification of lysine and cysteine residues. This method was used for the bio-conjugation of a wide range of proteins with polymer supports and PEG-linkers. For the removal of endocrine-disrupting pollutants from water the soluble domain of the human estrogen receptor could be conjugated. An environmentally-friendly access to biofuels was presented using lignocellulosic biomass. Based on the selective bio-conjugation approach, thermoresponsive polymers allow for the recycling of heat-stable cellulase. In addition, the added polymer increases cellulase activity over time by directly interacting with the substrate. In addition, the bio-conjugation was extended to viral capsid DNA aptamer conjugates (bacteriophage MS2) as multivalent cell-targeting vehicles constructs.



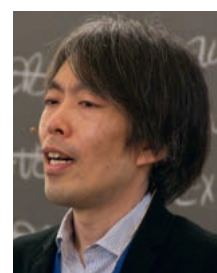
Cynthia Burrows

During the second poster session, five eight-minute poster appetizer talks were given by excellent young researchers: Juraan Huskens (University of Twente) on self-assembly of nanoparticles, Henning J. Jessen (University of Zurich) on inositol polyphosphate analogs, Mamoru Tobisu (Osaka University) on cross-coupling reactions via C–O-bond activation, Oliver Trapp (University of Heidelberg) on ste-

reodynamic catalysis and Jerome Waser (EPFL) on hypervalent iodine reagents. The exciting lectures were followed by a lively and intense discussion during the second poster session.

Thursday evening speaker **Cynthia Burrows** from the University of Utah was introduced by Donald Hilvert and continued the chemical biology theme. In her lecture, she took the audience on a journey through adventures in oxidative damage, G-quadruplex topology and gene expression. The mechanism of oxidative DNA damage and the enhanced reactivity of guanine over adenine, cytosine and thymine were elucidated. In addition to 8-oxoguanosine which was identified to facilitate base rotation and G to T transversion, the structures and mechanisms of formation of several of the additional oxidation products were uncovered. The role of guanine oxidation was then presented for the oxidative damage of telomers in G-quadruplex structures. Finally, the mechanistic and kinetic aspects of the formation of guanidinohydantoin and spiroiminodihydantoin were elucidated.

Andrea Vasella (ETH Zurich) and Samir Zard (Ecole Polytechnique) opened the final session on Friday. **Masayuki Inuo** from Tokyo University gave a spectacular presentation on radical-based approaches to highly oxygenated terpenoids. For the construction of ryanodol, a C_2 -symmetric bicyclic ring system was designed for the synthesis of the central core of the target molecule. Desymmetrization via Mukayama's oxidation protocol and generation of a bridgehead nucleophilic radical allowed the stereocontrolled assembly of the highly congested polyhydroxylated framework. This radical approach was then extended to the three-component coupling of acetals and applied for the synthesis of resiniferatoxin, a polycyclic terpenoid. The same strategy could be used for the synthesis of manzacidin A.



Masayuki Inuo

Jieping Zhu from EPFL held the last lecture of the 50th Bürgenstock Conference on stereochemistry. Inspired by the biosynthesis of monoterpenoid alkaloids, a unified route to several indole alkaloids was presented. By forming the indole at a late stage of the synthesis, the natural products goniomitine, aspidospermidine and kopsihainanine A could be accomplished from the same synthetic intermediate. A similar strategy was presented for the construction of leuconolam–leuconoxine–mersicarpine family of monoterpene indole alkaloids. Mersicarpine could be converted to scholarisine G and the latter could be efficiently transformed to leuconoxine. In addition, an efficient method for the decarboxylative coupling of carboxylic acids with vinyl triflates was presented. Finally, the concept of self-induced diastereomeric anisochronism (SIDA) was elegantly demonstrated for the natural product melodinine E.



Jieping Zhu

The authors thank the Organizing Committee, the Junior Scientists Participation Program and the President Antonio Togni for a wonderful birthday party and wish the next president Paul Knochel (LMU Munich) another spectacular and successful conference. Jack D. Dunitz said that “if something turns 50, it is likely that it will also turn 100.” We all hope to meet at the Bürgenstock Conference in 2065!

Received: June 25, 2015