doi:10.2533/chimia.2016.563 Chimia 70 (2016) 563–566 © Swiss Chemcial Society

# Conference Report

## The 51st EUCHEMS Conference on Stereochemistry: The Bürgenstock Tradition Continues

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**Keywords**: Bürgenstock conference · EUCHEMS · Stereochemistry

One year has passed since the EUCHEMS Conference on Stereochemistry, known as the 'Bürgenstock Conference', celebrated its 50th anniversary. This year, the legendary conference began the next 50 years of tradition that brings scientists to the shore of Lake Lucerne to engage in vigorous discussions. The magnificent view across the lake from the Seehotel Waldstätterhof, where the conference took place, merely reflected the view from the seats inside the lecture hall. It was this site in Brunnen where the attendees enjoyed most of the breath-taking views, the views on stereochemistry.

Paul Knochel

The list of speakers, composed by the President ***Paul Knochel*** (Ludwig-Maximilians-University Munich) and concealed until the first day of the conference, affirmed that the participants were about to start the long-awaited week of thought-provoking and rigorous dialogues. The gathering began on Sunday evening with an opening dinner and a warm welcome speech of Paul Knochel, who introduced the Guest of Honor, ***Dieter Seebach*** (ETH Zürich). The organization of the meeting was in the expert hands of ***Christian Bochet*** (University of Fribourg), ***Alain De Mesmaeker*** (Syngenta), ***Guido Koch*** (Novartis), ***Jérôme Lacour*** (University of Geneva), and ***Helma Wennemers*** (ETH Zürich), whose dedicated efforts from the start to the end guaranteed that the Bürgenstock Conference would once again become an unforgettable experience.

Oliver Trapp

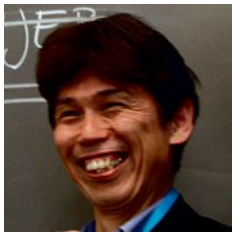
Sunday dinner was followed by the opening talk of ***Oliver Trapp*** (University of Heidelberg), who delivered new insights into the self-amplification of chirality in catalytic processes and design of enantioselective autocatalytic reactions. He illustrated the working principles of a bidirectional enantioselective catalyst, based on stereolabile axially chiral biaryl ligands that can be modified with a chiral auxiliary to shift the initial 1:1 equilibrium partially in favor of one diastereomer. In this stereodynamic system, the diastereomeric ratio can be locked at lower temperatures upon formation of a metal complex, in which it can be switched towards the initially less favored diastereomer at higher temperatures. As a result, one metal complex selectively catalyzes formation of each enantiomer depending on temperature, with high selectivities governed by positive non-linear amplification of chirality. In the second part of his talk, Trapp demonstrated a direct visualization of spatial arrangements of atoms in a chiral epoxide, which is directly connected to the unambiguous determination of the absolute configuration of (+)-glyceraldehyde, by using foil-induced Coulomb explosion imaging technique that can be applied to small gas-phase molecular ions or their fragments.

Olivier Baudoin

Monday scientific suite began with a delightful morning session on C–H activation opened by ***Olivier Baudoin*** (University of Basel), who gave a presentation on construction of four- and five-membered rings, where the key to success is a cleavage of an unactivated $C_{sp3}$–H bond. From discovery of palladium-catalyzed activation of benzylic geminal dialkyl groups to applications in the synthesis of natural products, Baudoin described stage by stage the developments from his group in the synthesis of cyclobutanes and cyclopentanes fused to an aromatic ring. Detailed mechanistic understanding of the crucial steps and reaction intermediates allowed for a control of the course of the reaction that proceeded either through a five- or a six-membered palladacycle. This methodology was extended to the synthesis of valuable precursors of biologically active compounds, such as bicycles, indanes, or γ-lactams, possessing up to three stereogenic centers. By screening various chiral catalysts, these reactions were optimized to proceed with high diastereo- and enantioselectivities and applied in the general and scalable syntheses of alkaloids, coralydine, or aeruginosin marine natural products.

Lutz Ackermann

In the spirit of the C–H functionalization theme, ***Lutz Ackermann*** (Georg-August-University Göttingen) demonstrated during his talk the perspectives of ruthenium(II) complexes as catalysts for unactivated $C_{ar}$–H bonds. His strategy capitalized on substrate coordination to the catalytically competent ruthenium catalyst, a step that initiates the C–H activation, which played a key role in the development of efficient procedures for versatile carbon–carbon bond formations. Of particular interest were Ackermann's alkylation of arenes with alkyl halides bearing β-hydrogen atoms, hydroarylation of methylenecyclopropanes, which occurred with a complete conservation of the cyclopropane rings, or C–H functionalization of alkenes and arenes by a single-component phosphinous acid ruthenium catalysts. Switching the gears towards the use of less expensive metals, Ackermann showed examples, where complexes of cobalt, copper, manganese, iron, or nickel performed remarkably well as catalysts. The use of copper iodide, for example, was employed in an unprecedented photoinduced arylation of both aromatic and nonaromatic heteroarenes, providing a step-economical access to the alkaloid natural products balsoxin and texamine.


Itaru Hamachi

After lunch, ***Itaru Hamachi*** (Kyoto University) introduced the world of proteins and highlighted the potential of a chemistry approach to understand the structure, function, dynamics, and localization of proteins in the complex environment of living cells. The chemical strategy relies on ligand-directed labeling of selected proteins with a probe, which allows their monitoring, however, it often suffers from disruption of the protein's native function. Hamachi and his group developed a new tactic to overcome this limitation, known as 'traceless affinity labeling', which involves attachment of a probe to the protein-specific ligand *via* a linker that can be easily cleaved once the probe is covalently bound to the protein in close proximity to the active site. Hamachi demonstrated various applications of their method, including determination of binding affinities of a labeled sugar-binding protein lectin with various saccharides, which were similar to those of native lectin, indicating that its function was not compromised. An elegant synthetic advancement was achieved by labeling the target protein through an $S_N2$-type reaction with the concomitant release of the ligand molecule, which allowed monitoring of ligand–protein and protein–protein interactions, and the lifetime of an endogenous protein *in vivo* without gene manipulation.

Before the afternoon gathering at the posters, the participants could enjoy five 'appetizer' talks by young principal investigators. The eight-minute presentations were served by ***Jovica Badjic*** (Ohio State University), ***Christopher Cordier*** (Imperial College London, Junior Scientists Participation (JSP) Program), ***Ali Coskun*** (Korea Advanced Institute of Science and Technology), ***Bill Morandi*** (Max Planck Institute for Coal Research, Mülheim, JSP Program), and ***Yu Zhao*** (National University of Singapore), while Christian Bochet was strictly keeping an eye on the time limit. The short talks were followed by two hours of vivid discussions with all participants at the poster session in the Rütli Saal and then at dinner.


Stephen Kent

The evening lecture completing the Monday program was presented by ***Stephen Kent*** (University of Chicago), who offered a glance 'through the looking glass' into a new world of D-proteins—the mirror-images of natural L-proteins—composed of D- instead of L-amino acids and achiral glycine. These unnatural molecules are proposed to be near-optimal human and animal therapeutics, as they are resistant to digestion by proteases *in vivo* and are anticipated to be non-immunogenic. In his talk, Kent briefly described the development by his group of the native chemical ligation method, the first practical approach to D-proteins utilizing condensation of unprotected protein segments in a series of 'one pot' reactions. The access to D-enantiomers of natural protein targets, such as D-VEGF-A, allowed their collaborators to use 'mirror image' phage display screening to first find a high-affinity L-protein ligand for D-VEGF-A and for the Kent group to then generate the D-protein form of this ligand—with high affinity to the natural L-VEGF-A—which inhibits the binding of L-VEGF-A to the VEGF-R1 receptor. Kent also highlighted the role of D-proteins in high-resolution crystallographic analysis of proteins that is facilitated by use of racemic mixtures of L- and D-proteins.

Tuesday morning started off with a lecture from ***Giuseppe Resnati*** (Polytechnic University of Milan), who first clarified the concept and definition of the halogen bond, which is an interaction between electrophilic region associated with a halogen atom and an electron-rich site. Resnati then continued with a demonstration of assorted examples, where halogen bonding governs supramolecular assembly of halogen-bond donor and acceptor molecules that dictates the properties of the formed halogen-bonded networks. Resnati's collection box involved systems, where halogen bonding outcompetes hydrogen bonding, trapping of virtually unknown tetrahalide species $[I_4]^{2-}$, $[I_2Br_2]^{2-}$, and $[I_2Cl_2]^{2-}$ in porous organic salts, as well as halogen-bond-assisted inclusion of perfluoroalkyl halides in a synthetic cavity. The prospect of halogen bonding to create the 'tipping point' in gel formation was beautifully shown in a two-component 'co-gel' made of bis(pyridyl urea) and 1,4-diiodotetrafluorobenzene, where halogen bonding was strong enough to compete with gel-inhibitory interactions in polar media. In addition, Resnati revealed that halogen-bond donors as small as trifluoroiodomethane can serve as 'single-carbon' anion transporters across bilayer lipid membranes.


Giuseppe Resnati


Valery Fokin

A wave of holistic interrogation filled the lecture hall when ***Valery Fokin*** (University of Southern California) unveiled the scenes behind his investigations of complex catalytic systems during the second morning talk. Set off to clarify the mechanism of one of the most widely used reaction, the copper-catalyzed azide–alkyne cycloaddition, he manifested an elegant yet simple solution to solve the intricate mechanistic riddle. By using real-time heat-flow reaction calorimetry and crossover experiments with isotopically enriched copper, Fokin demonstrated that the reaction involves intermediates containing two copper centers: a catalytically active complex with two discrete copper atoms that become chemically equivalent in an intermediate formed upon the first C–N bond formation. This mechanistic insight unifies the reaction pathway of electronically rich σ-acetylides, including haloacetylenes and soft-metal acetylides, with 1,3-dipoles, *via* a complex formed by weak and reversible π-interaction of a copper(I) catalyst with the acetylide. Fokin also presented a base-catalyzed 'click-type' condensation between aromatic bis(silyl ethers) and bis(fluorosulfates) that provides high-molecular-weight polysulfates in nearly quantitative yields.


Janine Cossy

Tuesday lunch was followed by synthetic variations of ***Janine Cossy*** (ESPCI, Paris) to synthesize small and large heterocycles, available through intriguing ring-closing steps and catalysis by a variety of metals. Her examples included an eco-friendly iron(III)-catalyzed synthesis of piperidines and tetrahydropyrans with high diastereoselectivities observed for the *cis*-2,6-disubstituted product or cross-couplings with Grignard reagents and bromoglycosides catalyzed by cobalt(II). Cossy's non-catalyzed approach to [*n*]paracyclophanes, taking advantage of sequential Diels–Alder/retro-Diels–Alder reactions, was an elegant demonstration of the so-called 'ring-distortion reactions', involving a tetracyclic 1,4-diene intermediate in between the key Diels–Alder steps. In addition, Cossy illustrated the principles of ring-formations utilizing the smallest possible

ring, cyclopropene, which were employed in the synthesis of six- and eight-membered heterocyclic rings, through gold(I)- and rhodium(II)-catalyzed generation of metala-carbenoids. The metala-carbenoids generated by gold(I) chloride are the first examples to mediate an intramolecular cyclopropanation of an alkene produced by electrophilic ring-opening of cyclopropenes.

As the day before, five short presentations by young group leaders started off the Tuesday poster session. The appetizer talks by ***Suzanne Blum*** (University of California, Irvine), ***Ivana Fleischer*** (University of Regensburg, JSP Program), ***Michal Juríček*** (University of Basel, JSP Program), ***Kathrin Lang*** (Technical University Munich, JSP Program), and ***Uday Maitra*** (Indian Institute of Science, Bangalore) continued with stimulating dialogues and exchange of ideas at the posters in the Rütli Saal joined by all participants.

Jonas Peters

In his talk finalizing the program of Tuesday, ***Jonas Peters*** (Caltech, Pasadena) set out to bring insight into the role that iron plays in the conversion of nitrogen to ammonia catalyzed by nitrogenase enzymes in nature. In an effort to validate that a single iron site may be capable of catalyzing this process, Peters and his group carried out an in-depth investigation of the ammonia formation from nitrogen by using a tris(phosphine)borane-supported iron model complex as a catalyst. In this complex, the flexible iron–boron interaction seemed to be important for efficient catalysis, indicating that the interstitial carbon atom recently assigned in the nitrogenase MoFe-cofactor may have a similar role. Peters further highlighted an unexpected robustness of their synthetic iron nitrogenase, which retains its high-turnover activity even after multiple reloadings, and presented *in situ* freeze-quench $^{57}$Fe Mössbauer spectroscopy data, which revealed a likely candidate for the resting state of their catalytic system. These hydride resting species were previously thought to be primarily a 'catalytic sink', but they can reenter the catalytic pathway emphasizing the importance of metal hydride reactivity in iron-mediated nitrogen-fixation processes.

Annette Beck-Sickinger

During the first talk on Wednesday morning, ***Annette Beck-Sickinger*** (Leipzig University) summarized the efforts of her research group in search for optimal tools to diagnose and treat tumors, such as breast cancer. Based on a finding that over 90% of breast tumors express predominantly G protein-coupled receptor $Y_1$ while healthy cells express mainly receptor $Y_2$, she and her team designed and synthesized a protein ligand labeled with rhenium(I) that showed nanomolar binding selectively to receptor $Y_1$ *in vitro*, an excellent match for tumor targeting. For radiolabeling studies *in vivo*, $^{99m}$technetium(V) was used instead of rhenium(I), which allowed to target tumor cells in four patients with different stages of disease, by following the uptake of the synthetic ligand. Moving forward, a bioconjugate comprising a high-affinity ligand for $Y_1$ receptor and a synthetic drug that inhibits microtubule polymerization connected *via* a labile disulfide linker was synthesized and tested for target-specific drug delivery. Beck-Sickinger showed that this bioconjugate selectively internalized in tumor cells, where it displayed high cytotoxic activity upon the cleavage of the disulfide linker and release of the drug, namely, cytolysin, into the cytoplasm.

Judith Klinman

The second and last talk on Wednesday was presented by ***Judith Klinman*** (University of California, Berkeley), who shared the fruits of her quest to find the missing link between protein dynamics and function, a central contemporary issue in enzyme catalysis. In contrast to the earlier model based on the transition-state stabilization by static protein structures, newer findings imply the role of protein dynamics, or 'conformational sampling', needed to reach that state. Klinman revealed experimental evidence that a quantum mechanical hydrogen tunneling associated with enzymatic C–H bond cleavage requires protein dynamics for achieving optimal catalysis, in line with the proposed model. As hydrogen tunneling strongly depends on the barrier width, and not just the height, a kinetic isotope effect allows to correlate the distance between the hydrogen donor and acceptor with the reaction rate. By using the enzyme soybean lipoxygenase, a prototype for hydrogen-tunneling reactions, and its double mutant analogue possessing larger cavity and so an increased donor–acceptor distance, Klinman demonstrated how enzyme's flexibility and the ensuing generation of close donor–acceptor distances can contribute to the enormous rate enhancements.

Wednesday afternoon was dedicated to outdoor discussions in the mountains surrounding the Lake Lucerne, followed by a musical evening featuring a piano performance of Tatjana Živanović-Wegele.

Hiroyuki Isobe

On Thursday morning, the attendees fastened their seatbelts and ***Hiroyuki Isobe*** (Tohoku University, Sendai) took them for a spin inside his molecular bearings, the skeleton of which is made exclusively of carbon atoms. Isobe's design of molecular bearings is based on finite and discrete carbon 'belts', subunits of single-walled carbon nanotubes, which represent the outer ring and fullerenes that represent the inner ring, or the journal. Isobe stressed that for achieving an efficient rolling motion, the outer ring must hold the journal tightly to avoid its running out and, in the presence of such holding constraint, the friction must be low so the journal can roll. The first condition was met by creating a sufficiently large π-surface of the carbon belts, by linking four chrysene units into a circle, which consequently displayed high binding affinities of up to $K_a \sim 10^{12}$ M$^{-1}$ to fullerene $C_{60}$ on account of van der Waals interactions. By using $^1$H NMR spectroscopy and based on the number of observed signals and symmetry arguments, it could be concluded that fullerene $C_{60}$ rolls inside the belt in this carbonaceous bearing. Isobe further showed that even higher fullerenes, such as $C_{70}$, can be held tightly and roll in a belt featuring anthanthrene instead of chrysene subunits.

Michinori Suginome

In the second morning talk, ***Michinori Suginome*** (Kyoto University) explained the concept of the chirality-switchable catalyst developed in his group, which can change its helicity sense upon applying a stimulus and thus catalyze formation of either enantiomer of a product. The catalyst has a screw-like poly(quinoxaline-2,3-diyl) backbone and can be synthesized by living polymerization from respective 1,2-diisocyanobenzenes. Notably, the use of chiral alkyl side chains attached to the monomeric units prior to polymerization results in a solvent-dependent

main-chain helix inversion of the polymer. Suginome illustrated that incorporation of metal-binding phosphine groups into the backbone yields a polymeric ligand that upon metal complexation catalyzes enantioselective hydrosilylation of styrenes. The most unique feature of this catalytic system is that each enantiomer can be made at will by choosing the right solvent and that both enantiomers are formed with high selectivities. Furthermore, chirality amplification has been observed when the catalyst was made from monomers with low enantiopurity, which sufficed for induction of a pure single-handed helical structure of the catalyst, providing high enantiopurity of the product.

Stuart Schreiber

The lecture by ***Stuart Schreiber*** (Broad Institute, Harvard University) on Thursday evening finalized the program of the Bürgenstock Conference. Its scientific diversity was nicely reflected in this last contribution, in which Schreiber highlighted the future prospect of diversity-oriented synthesis and the 'real-time' biological characterization of its products towards the development of new therapeutics. In contrast to the traditional approach to drug discovery *via* total synthesis, the diversity-oriented synthesis aims to easily access compounds having structural features often found in the ensemble of natural products. The strategy relies on a protocol, which creates a variety of skeletons in just a few steps, such that multiple derivatives of each structural type can be made without having to face a synthetic challenge. Most importantly, the access to skeleton-wise unrelated pool of molecules allows, upon biological screening, for a discovery of unprecedented relations to targets, leading to drugs with new modes of action. These new modes of action can now be discovered by chemists nearly concurrent with the chemical reactions used to make the compounds, for example, by simple annotation of compounds' effects on cells using six dyes and a microscope ('cell painting'). Schreiber also pointed out that cell painting can be performed analogous to how chemists routinely annotate their compounds using NMR, and in so doing enable chemists to directly impact biology and medicine without relying on slow and ad hoc measurements by biologists, usually many years later.

The 51st Bürgenstock Conference began the next 50 years of ritual, where scientists serve and digest views on stereochemistry, and thanks to all attendants and their active participation in discussions, it fulfilled all expectations. I would like to thank the Organizing Committee, the Junior Scientists Participation (JSP) Program, and the President Paul Knochel for the opportunity to be part of this memorable event and wish the next President ***Bert Meijer*** (Eindhoven University of Technology) yet another successful conference.

Received: July 22, 2016