

Conference Report

The 57th Bürgenstock Conference

Amidst the Giants

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The Swiss Chemical Society (SCS) Conference on Stereochemistry, or the Bürgenstock Conference, was hosted in Brunnen, Switzerland surrounded by mountainous summits, including that which serves as the namesake of the conference. These natural giants framed the scene of this prestigious event where giants in the field of chemistry are invited to present their pioneering work and contributions under the theme of stereochemistry. At the base of these peaks is the Vierwaldstättersee (Lake Lucerne), an expanse of blue water reminiscent of the strategy later described by *Timothy Noël*, to pursue research ideas in uncharted waters. This was a common theme emanating from each talk, the courage of each speaker to trailblaze new research areas, and their ultimate recognition for exceptionalism.

The Bürgenstock Conference has a long history of bringing together the world's top minds in chemistry every year for nearly six decades. Only two years have been missed, making this the 57th occurrence of this renowned meeting. The theme, stereochemistry, bridges many scientific disciplines, broadening the keynote presentation sessions into a cornucopia of stellar chemistry-oriented talks. From the stereochemistry that dictates biological processes, to biological processes that give rise to stereoselective transformations, to how we as chemists can mimic the chemistry evolved by nature, and finally the development of methodologies not yet known from nature to generate magnitudes of stereochemically complex molecules, this conference never ceases to impress.

The organization of this year's Bürgenstock Conference was led by President **Erick M. Carreira** of ETH Zurich with support from the Vice President **José Luis Mascareñas** (Universidade de Santiago de Compostela) and the organizing committee members **Karl Gademann**, (University of Zurich), **Fabrice Gallou** (Novartis), **Francesca Paradisi** (University of Bern), **Maud Reiter** (Firmenich), **Thomas Ward** (University of Basel), and **Jérôme Waser** (EPFL). The team put together an exceptional line-up of speakers who, until the first day of the conference, the 28th of April, were unknown to the remainder of the participants. In addition to the keynote speakers described in detail below, other invited guests included a handful of promising young scientists selected to join the Bürgenstock Conference and supported by the Junior Scientists Participation (JSP) Fellowship. Coming from industry (3) and academia (14), the fellows were incredibly international, representing Germany, Italy, Sweden, Switzerland, France, USA, Spain, Japan, and China. Whether from near or far, they emanated enthusiasm for the opportunity to participate in this prestigious event, and many added to the discussions with stimulating questions.

The 57th Bürgenstock Conference opened with a thought-provoking evening seminar centred on how chemistry gave rise to biology in the context of non-enzymatic RNA replication. **Jack Szostak** (University of Chicago), 2009 Nobel Laureate in Physi-



The Vierwaldstättersee.

ology and Medicine, walked the audience through a tale of template copying chemistry driven by a covalent dinucleotide.^[1] The geometry of the imidazolium bridge poised for primer extension was beautifully visualized in crystal structures, and the extension was observed *via* elegant time course reactions. In describing recent work from his group, Jack Szostak detailed the discovery that catalytic amounts of Mg²⁺ can induce stereospecific primer extension by coordinating the non-bridging phosphate oxygen, or the oxygen of the reactive phosphate centre, on the imidazolium-bridged dinucleotide substrate.^[2] Moderated by Vice President José Luis Mascareñas, a discussion on the kinetics of base pairing ensued, with an emphasis on achieving optimal fidelity by allowing enough time for dissociation of mismatches and subsequent proper re-matching. A central question from Peter Chen (ETH Zurich) arose, “How reversible is the extension?” because the ability to catch the reversal could open new avenues for fixing mismatches. The seminar concluded with a brief dip into the group's work on model protocells,^[3] utilizing flow to optimize oligomerization with the goal to ultimately assemble ribozymes from shorter oligos.



Prof. Szostak presentation (left) and Prof. Peter Chen in the Q&A session (right).

Moderated by Konrad Tiefenbacher (University of Basel), the morning session of the first full day of the Bürgenstock Conference opened with a seminar from **Charlotte Williams** (University of Oxford). She welcomed the audience into a story of how poly-

mers permeate our everyday lives. The current polymer production methods focus on end-of-life solutions such as mechanical and chemical recycling, and Charlotte Williams emphasized that we should be rethinking the process as well as the raw material input. As an example, she detailed her group's substrate-focused strategy to develop new Co(III)/alkali-metal(I) heterodinuclear catalysts for ring opening co-polymerization of CO₂ and propylene oxide.^[4] She then delved into catalysts capable of achieving higher molar mass plastics, such as Zn(II)Mg(II) catalysts,^[5] a process that is highly dependent on the ring size. The incorporation of 5-membered rings was more suitable for the production of large polymers, and the observed epoxide ring opening selectivity for the trans-configuration was postulated to be due to the different abilities of 5 *versus* 6 membered rings to flip.^[6]

The second speaker of the morning, **Niveen Khashab** (King Abdullah University of Science and Technology) introduced her research group by first presenting herself as someone who is driven by promoting scientific discovery and advocating for women in science in places that truly need it. She applies this conviction in supramolecular chemistry, focusing on molecular level recognition and higher order assemblies formed by non-covalent interactions. She touched on a number of applications of her group's work including host-guest interactions in organic cages,^[7] as well as their *exo*-functions or what is happening beyond the cage. She then started a discussion of how her work is applied to issues in human health such as protein aggregation diseases and humidity responsive sensors for touchless screens and password managers.^[8] To conclude the talk, she circled back to applications of polycage membranes for molecular separation and catalysis.^[9]



Prof. Charlotte Williams (left) and Prof. Niveen Khashab (right) presenting their work.

We were welcomed into the afternoon session with poetry from moderator Yamuna Krishnan (University of Chicago) and a dive into chemistry inspired by biology from **Rebecca Buller** (Zurich University of Applied Sciences). Her group is taking biocatalysis to the next level by incorporating machine learning-guided enzyme engineering for higher activity and regioselectivity.^[10] In this realm, Rebecca Buller's group achieved halogenation of noticeably different substrate classes (macrolides *versus* native indole alkaloids) and are planning to expand the non-heme iron catalyzed chlorination of free substrates beyond the welwitindolinone-type compounds to other terpene-based substrates. Traversing into other kingdoms of life, from bacteria and later into plants, Rebecca Buller then told the story of her group's investigations into the biosynthetic production of anthocyanidins.^[11] They re-defined the role of glutathione transferases as the last catalytic step in anthocyanidin biosynthesis and achieved production of the pigmented compounds in yeast 'microbial cell factories'.

For the remainder of the afternoon, Jérôme Waser moderated a selection of short presentations to highlight work featured in



Prof. Rebecca Buller with moderator Prof. Yamuna Krishnan after the Q&A session.

the poster session to follow. **Christine Le** (York University, JSP Fellow) walked the audience through some of her early career achievements centred on carbamoyl fluorides in C-C bond forming reactions.^[12] We gained insight into high throughput experimentation chemistry to accelerate medicinal chemistry programs in industry *via* a talk by **Fabio Lima** (Novartis, JSP Fellow). Following on the pharmaceutical trend, **Francesco Mutti** (University of Amsterdam) described the synthesis of chiral amines as intermediates to active pharmaceutical agents.^[13] **Michel Rickhaus** (University of Geneva, JSP Fellow) detailed his group's use of molecular topography to build 2D models, and **Daniel Strand** (Lund University) reported on his group's efforts to synthesize dithiosilvatin natural products. **Julien Vantourout** (Syngenta, JSP Fellow) concluded the session by describing methods for merging electrochemistry and Ni catalysis.^[14]

The first full day of the Bürgenstock Conference was appropriately concluded with a poetic entrance by moderator Yamuna Krishnan and an enlightening seminar by **Corey Stephenson** (University of Michigan, soon University of British Columbia) focused on redox catalysis strategies for chemical synthesis. He detailed the challenges associated with scaling-up photocatalytic reactions and solutions found in high-throughput photochemical reactions in flow.^[15] He then delved into radical aryl transfer strategies for C-C bond forming reactions,^[16] and aminoarylation of alkenes with arylsulfonyletacetamides. To conclude his talk, Corey Stephenson emphasized his group's contributions to bifunctional reagents^[17] and aryl sulfonamide reagents that facilitate stereoretentive coupling.^[18]



Prof. Corey Stephenson during his talk (left) and after the Q&A session with moderator Prof. Yamuna Krishnan (right).

On the second day, the shining sun, albeit turbulent wind, set the stage for the ground-breaking work to be described throughout the day. The first speaker, **Mariola Tortosa** (Universidad Autónoma de Madrid) was introduced by moderator Louis-Charles

Campeau (Merck Sharp and Dohme). She opened with the central theme of ‘Escaping from Flatland’^[19] and the importance of chiral centres and molecular complexity in this context. Consequently, her seminar focused on stereoselective synthesis of sp^3 -rich building blocks. An apt comparison of the mountains mirrored in the Vierwaldstättersee was used to describe enantiomers, however the waves and wind on this second full day provided a parallel analogy to the challenges associated with synthesis of these complex molecules. Mariola Tortosa went into detail describing her group’s preparation of chiral spirocyclic building blocks *via* diastereo- and enantioselective diborylation of spirocyclobutenes, followed by the achievement of structural diversity with amines,^[20] and ending with an overview of their work on visible light-mediated hydro- and deuterodeamination reactions.^[21]



Prof. Mariola Tortosa and moderator Dr. Louis-Charles Campeau after the Q&A session.

Sereina Riniker (ETH Zurich) then took the stage to discuss the conformational flexibility of biomolecules and the impact of computational research. Four short stories were used to epitomize these impacts. She started with describing a collaborative project on proline-based crosslinking methods with **Helma Wennemers** (ETH Zurich), who was also attending the conference and a key contributor to the discussion sessions. The team combined molecular dynamics (MD) simulations and experimental data to validate the mechanism of stabilization of triple helical collagen model peptides.^[22] Sereina Riniker then migrated into the topic of other MD-coupled projects including with gas phase transition metal ion Förster Energy Resonance Transfer and with ion mobility-mass spectrometry.^[23]

She then circled back to the peptide theme to focus on conformations of cyclic peptides that are conducive to entering and crossing the lipid membrane.^[24] Lastly, she detailed how mechanistic and computational studies can be combined with spectroscopic data to solve stereochemical challenges associated with structural elucidation of natural products, and in this particular case for the structural assignment of mutanobactin D in collaboration with Erick M. Carreira (President of the 57th Bürgenstock Conference).^[25]

Following an afternoon break with time for local outdoor activities, the day concluded with an evening seminar by **Corinna Schindler** (University of Michigan, soon to be at the University of British Columbia) moderated by Karl Gademann (University of Zurich). This tour-de-force lecture began with a background on traditional methods for carbonyl-olefin and olefin-olefin metathesis strategies, then narrowed down to Fe(III) catalysis methods developed in the Schindler group.^[26] She focused on ‘super-electrophiles’ consisting of a singly bridged Fe(III)-dimer and their functionality as more powerful Lewis acid catalysts,^[27] then diverged into aluminum(III)-ion pairs that allow access to six- and seven-membered rings.^[28] Schindler then described how imines were used by her group for scope expansion. Indeed, tri-



Prof. Sereina Riniker presenting her work (left) and Prof. Helma Wennemers during the Q&A session (right).

plet energy transfer catalysis and visible light-enabled intramolecular Axa Paternò Büchi reactions^[29] led to the use of cyclooxime substrates to quench the luminescence of the photocatalyst for synthesis of azetidines^[30] and the applications of this chemistry for bioconjugation and labelling of RNA.



Prof. Corinna Schindler and Prof. Karl Gademann after the Q&A session.

Another full day followed on Wednesday the 1st of May, where the opening talk on the combination of synthetic chemistry and chemical engineering was delivered by **Timothy Noël** (University of Amsterdam) and moderated by Thomas Ward (University of Basel). Following a discussion on the advantages of microscale flow reactors and their implications for medicinal chemistry efforts, he described how he chooses his project areas: aiming for the uncharted ‘Blue Water’ areas rather than the more crowded and treacherous water or the ‘Red Ocean’ full of sharks.

This was clearly his strategy when he approached the undirected C–H functionalization challenge of functionalizing methane.^[31] He also described heteroarylation enabled by a continuous flow reactor^[32] and automation and self-optimization of photocatalysis in flow achieved with RoboChem.^[33]

Next up, **Manuel Alcarazo** (Georg-August-University Göttingen) offered insights on the synthetic applications of sulfuranes and sulfonium salts. Herein he described the implementation of sulfuranes towards many reaction types including electrophilic cyanation and alkylation, chlorocyanation of alkynes, electrophilic thiolation of non-functionalized (hetero)arenes and initiating cationic cyanocyclization cascades.^[34] A key emphasized point here was to beat the instability by finding a reaction that is faster than the decomposition process. As for sulfonium salts, his group has applied them toward the synthesis of triazoles, and used them as substrates for Rh-catalyzed addition of sulfoniocarbene



Prof. Timothy Noël (left) and Prof. Manuel Alcarazo (right) during their talks.

moieties to olefins.^[35] He ended with a discussion on his group's efforts in sulfonitrene chemistry^[36] and the complementarity of their reactions with aryl cyclobutenes to the iodinitrene methods of the group of Bill Morandi, who was also in attendance and a plenary speaker.

Following lunch, Marcos G. Suero (ICIQ) moderated an inspiring talk by **Antonia Stepan** (Roche Innovation Centre Basel) who describe how Roche's Design Hub supports decision making in medicinal chemistry. They implemented virtual screening in a combinatorial space and tested a late-stage functionalization platform for C–H borylation.^[37] Antonia Stepan also emphasized the ability to improve pharmacokinetics and intrinsic potency by understanding the pathophysiological mechanisms of toxicity and tuning this *via* high-throughput pharmacokinetic modelling.^[38] She also drew attention to the importance of lipophilicity. She defined the lipophilic metabolism efficiency (LipMetE) or the parameter describing the impact of lipophilicity and metabolic stability^[39] and applied this metric to preclinical GABA_A targeting projects.^[40] What was evidently clear from the talk is that “lots of chemical space remains untapped and AI is helping us to get there.”



Dr. Antonia Stepan during her presentation.

The rest of the afternoon was filled with six exciting short talks moderated by Jérôme Waser starting with **Daniel Gryko** (Polish Academy of Sciences) discussing his group's work on gold-catalysed 1,2-aryl shift and double alkyne benzannulation.^[41] This was followed by a seminar given by **Line Næsborg** (University of Münster, JSP Fellow) focused on micelle effects in photocatalysis.^[42] **Ydna Questell Santiago** (Bloom Biorenewables SA, JSP Fellow) then presented her work at a start-up company aimed at using biomass as a renewable carbon source. Staying on the industrial side, **Fabrice Robvieux** (dsm-Firmenich, JSP Fellow) then described route-scouting and development of new perfumery ingredients. Merging back into academic space, **Christof Sparr** (University of Basel) detailed his group's work on catalyst control over pentavalent

stereocenters.^[43] Finally, **Yang Yang** (University of California, Santa Barbara, JSP Fellow) finished the session with energizing new strategies for stereoselective biocatalysis.^[44]

The last full day of the Bürgenstock Conference came to an end with **Franziska Schönebeck** (RWTH Aachen) guiding the audience through methods for accessing privileged scaffolds by drawing on new catalytic strategies and physical chemistry. Her group's work with Pd(I) dimers was accentuated with problem-specific refinement, or stabilizing ligands, discovered through unsupervised machine learning.^[45] She then crossed over to talk about Ni(I) catalysis, focusing on machine learning-guided development of trialkylphosphine Ni(I) dimers for selective C–I arylations and olefin migration.^[46] The next stage of the seminar focused of the Schönebeck group's advances in aryl germane chemistry, invoking Pd nanoparticle catalysis and light-activated gold catalysis for the formation of C–C bonds and achieving the first germane centred C–heteroatom bond formation (C–O)^[47] followed by nitration (C–N bond forming) and recently expanding into C_{sp3} space.



Prof. Franziska Schönebeck during (right) and after (left) her presentation.

Alois Fürstner (2023 President of the Bürgenstock Conference, MPI für Kohlenforschung) moderated the last session of the 57th Bürgenstock Conference. **Thomas Magauer** (University of Innsbruck) presented his chemical ‘odyssey’, a journey to synthesize complex natural products such as the diterpenoid waixenicin A where his group navigated the challenges of achieving the 9-membered *trans*-fused oxabicyclo[7.4.0]tridecane ring system.^[48] He then moved into the tetracyclization strategy of a dual nucleophilic aryl enol ether to access the pimarane natural products and an enantioselective route to the *ent*-pimaranes. In the same polyolefin cyclization chapter of this odyssey, his group also accessed sesquiterpene alkaloids Greenwayodendrines and polysin *via* bioinspired indole *N*-terminated cationic tricyclization^[49] and expanded into methyl-initiated polyene cyclizations for triterpenoids by mimicking biosynthetic methyltransferases that initiate terpene cyclization *via* methylation followed by carbocation migration. In describing the latest stages of this odyssey, he reported the first synthesis of chartspirotion, and spiro-fused benzofuran lactone.

Bill Morandi (ETH Zurich) closed the 2024 Bürgenstock Conference with a tale of new concept development for atom and functional group transfer. He started with his group's work on hydrocarbon amination including iron-catalysed aminochlorination to generate primary amines from alkenes^[50] and methods to access core amination. He detailed how his group achieved chemical diversification *via* ring expansion and ‘late-stage scaffold hopping’ *via* *N*-atom insertion and their latest work toward synthesis of pyridones through oxidative amination of cyclopentenones.^[51] Other protocols developed by the group that were covered in this expansive seminar were for HCN-free hydrocyanation alkene transfer or the ‘oxo-walk’ for ketone transposi-



Prof. Thomas Magauer during (left) and (after) the Q&A session.

tion,^[52] and how his group is addressing challenges in transfer difunctionalization.^[53] He closed the seminar with recent work in shuttle HAT catalysis to generate Co(III)–H and mild alkene transfer hydrofunctionalization to introduce functional handles.



Prof. Bill Morandi presenting his work (left) and after the Q&A session with Prof. Alois Fürstner.

To bring this odyssey of the 57th Bürgenstock Conference to a close, the seminars inspired all in attendance to search for the blue ocean space, perhaps develop fleets to tackle problems requiring multi-disciplinary approaches and expand into new horizons on the quest for stereo-selectivity/-specificity.

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