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Conference Report

The 58th Bürgenstock Conference

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The 58th Bürgenstock Conference took place from May 4–8, 2025, in Brunnen, a picturesque Swiss village in the canton of Schwyz. Attendees were hosted at the Seehotel Waldstätterhof, which offers stunning views of Lake Lucerne and the Swiss Alps. Many attendees describe the Bürgenstock Conference as one of the most prestigious and unique gatherings in the field.

The Swiss Chemical Society (SCS) Conference on Stereochemistry, commonly known as the Bürgenstock Conference, has a rich history dating back to 1965. It attracts international academic and industrial experts from various chemistry disciplines. This invitation-only event is renowned for its immersive setup, featuring top-tier speakers. The attendee list is kept confidential until the event begins, adding an element of anticipation and excitement.

Delivering a plenary talk at this conference is considered a rare honor, typically reserved for those who have made significant contributions across different fields. The high level of expertise among the relatively small number of attendees fosters a unique atmosphere and elevates the quality of discussions during the Q&A sessions following each talk. The conference also offers numerous formal and informal networking opportunities, enhanced by the fact that the conference hotel serves as the venue.

The organization of this year's Bürgenstock Conference was led by President **José Luis Mascareñas** from the University of Santiago de Compostela with support from the Vice President **Paolo Melchiorre** (University of Bologna). The Guest of Honor was **Miquel A. Pericàs** (University of Rovira i Virgili) and the organizing committee members included **Rebecca Buller** (ZHAW Wädenswil), **Karl Gademann** (University of Zurich), **Fabrice Gallou** (Novartis), **Francesca Paradisi** (University of Bern), **Lionel Saudan** (DSM-Firmenich), and **Jérôme Waser** (EPFL). They were supported by assistants Daniela Schaub (Buller group), Helena Solé Àvila (Waser group), Glenn Bojanov (Paradisi group) and Erik Jung (Gademann group), who were also instrumental in making this edition such a success.

In addition to the keynote speakers described in detail below, selected scientists in the early stages of their academic or industrial careers were awarded Junior Scientists Participation (JSP) fellowships to attend the Bürgenstock conference. This was made possible with the support of the Division of Fundamental Research of the Swiss Chemical Society and sponsors, including Arxada, Dottikon, dsm-firmenich, Givaudan, Idorsia, Johnson & Johnson Innovative Medicine, LifeMine, Lilly, Lonza, Microsoft Research, Novartis, Roche, Siegfried, Solvias, Syngenta, Thieme and Nature. The JSP 2025 fellows were Claudia Bonfio (University of Cambridge, UK), Ala Bunescu (University of Bonn, DE), Julius Hillenbrand (Bayer, DE), Sascha Hoogendoorn (University of Geneva, CH), Muhammad Jbara (Tel Aviv University, IL), Fabio Julia (Universidad de Murcia, ES), Koji Kubota (Hokkaido University, JP), Marcin Lindner (Warsaw Institute of Organic Chemistry, PL), Gregory Mann (Novartis, CH), Hugh Nakamura (Hong Kong University of Science and Technology, HK), Manuel Nappi (CiQUS, ES), Giulio Ragazzon (University of Strasbourg, FR), Courtney C. Roberts (University of Minnesota, US), Philippe Schwaller (EPFL, CH), Mattia Silvi (University of Nottingham, UK), Erin Stache (Princeton University, US) and Simon Wagschal (Lonza, CH) (Fig. 1).

Fig. 1. The 2025 JSP fellows.

The scientific program featured a stellar line up of speakers over five days, with a broad range of topics and discussions that spanned various areas of chemistry and related disciplines, including synthetic methodologies, transition-metal, photo- and biocatalysis, main group and organometallic chemistry, chemical biology, process chemistry, and material chemistry.

The conference started with a lecture by Nobel Prize winner ***David McMillan*** (University of Princeton) on the latest results of his group on photochemistry. Introduced by Paolo Melchiorre (University of Bologna), McMillan is one of the few speakers who has presented twice at the Bürgenstock conference (the first time in 2003 on organocatalysis) (Fig. 2).

The first part of the talk focused on the identification of biological interactions of proteins using the micromapping technology that employs Dexter energy transfer from a photocatalyst to activate diazirines in close proximity. Leveraging this novel

Fig. 2. (Left) From left to right: Prof. José Luis Mascareñas, Sir David McMillan, Prof. Miquel A. Pericàs and Prof. Paolo Melchiorre, and (right) Prof. McMillan enjoying the social activity after his lecture.

approach, the team could capture new interactions with known immunoregulatory receptors.[1] The second part of the presentation delved into the formation of reactive radicals using visible light. Requiring only commercially and widely available starting materials, photoredox chemistry has become widespread over the last two decades. The most recent developments included deoxygenative processes that extend photoredox cross-coupling to alcohol starting materials.[2] By merging metallaphotoredox C(sp^2)–C(sp^3) cross-coupling with intramolecular Minisci-type radical cyclization, a variety of previously unexplored spirocyclic, bridged and substituted saturated ring types could be obtained.[3]

The next day the morning session was moderated by Rebecca Buller and started with a lecture from ***Claudia Höbartner*** (University of Würzburg) on the molecular architectures and mechanisms of RNA-alkylating ribozymes (Fig. 3). First, their groundbreaking work towards the creation of chemically diverse ribozymes using *in vitro* selection was highlighted. In a first example, m^{6}G was used as a small-molecule methyl group donor, and a ribozyme, named MTR1, catalyzing the site-specific methylation of adenosine at position N1 was identified.[4] Next, the development of SAMURI, a SAM analogue-utilizing ribozyme, was discussed. This ribozyme provides a powerful tool to install a propargyl group to a target adenosine both *in vitro* and in cells, allowing its downstream detection using click chemistry.[5] Recently, the crystal structure of SAMURI in the post-catalytic state was solved, allowing detailed understanding of the catalytic mechanisms and paving the way for the discovery of alternative RNA-modifying RNA enzymes.[6]

Fig. 3. Prof. Höbartner's presentation (left) and with moderator Prof. Buller (right).

Andrey Klymchenko (University of Strasbourg) then delved into the chemistry of dyes at the nanoscale to shed light on biological systems (Fig. 4). The properties of biological membranes are important determinants of cellular activity, and therefore as chemical tools to probe membrane organization they are highly valuable.[7] The first part of the talk focused on the work that leveraged the solvatochromic properties of NileRed to measure variations in lipid order. Through incorporation of targeting units, the probe could be specifically delivered to a variety of different cellular compartments, allowing the study of cellular responses to chemical or physical stimuli, at the level of the membranes of individual organelles.[8] Next, their work on developing covalent strategies for plasma membrane labeling was discussed. The Memgraft probes consist of a fluorescent dye, a chemical reactive group such as an NHS ester, and a lipid anchor, which leads to much more efficient localization and therefore reactivity at the cell membrane. Varying the color of the dye allows for the barcoding and tracking of cells over time.[9]

On Monday afternoon, Karl Gademann (University of Zurich) introduced ***Jonathan Burton*** (University of Oxford) (Fig. 5), who presented the synthesis and applications of oxoniums ions.[10] The first part of the talk focused on the conversion of triaryloxonium ions into arynes under mild basic conditions at room temperature and subsequent cycloadditions with a broad functional group tolerance.[11] The application of oxonium ions in total synthesis was then discussed, as several halogenated natural products isolated from Laurencia species are proposed to arise biosynthetically *via* complex trialkyl oxonium ion intermediates. The synthesis and characterization of some of these biosynthetically relevant trialkyloxoniums ions was then presented, resulting in the biomimetic total synthesis of 25 complex natural products.

Fig. 4. Prof. Klymchenko (left) and together with moderator Prof. Buller after the Q&A session (right).

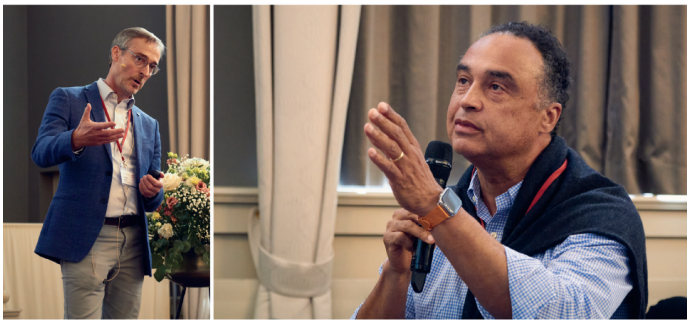

Fig. 5. Prof. Burton (left) and Prof. Lacour during the Q&A session (right).

After the break, the session continued under the moderation of Jerome Waser with six short talks – ***Hagan Bayley*** (University of Oxford), ***Ala Bunescu*** (University of Bonn, JSP Fellow), ***Michal Juricek*** (University of Zurich), ***Gregory Mann*** (Novartis, JSP Fellow), ***Philippe Schwaller*** (EPFL, JSP Fellow), and ***Simon Wagschal*** (Lonza, JSP Fellow) – and a very interactive poster session.

During the evening session, ***Rebecca T. Ruck*** (MSD) started with the observation that recent active pharmaceutical ingredients (APIs) are getting more and more complex and showed how enabling technologies could support the discovery process and development efforts in industry (Fig. 6). For instance, a macrocyclic peptide medicinal chemistry program could be accelerated *via* the synthesis of non-canonical amino acids such as 3-hydroxy proline. The initial 8-step synthesis route could be replaced by a single biocatalytic step using a protein-engineered enzyme using proline as substrate and resulting in a 175-fold increase in yield. Solid-phase peptide synthesis (SPPS) has been employed for decades to synthesize peptide fragments. By performing this approach in a hydraulically controlled continuous-flow SPPS, MSD chemists could optimize and deliver multigram quantities of peptide fragments with drastic reductions in development efforts, process execution timelines, and waste generation.[12] Flow technology was also applied to the synthesis antibody-drug conjugates (ADCs) and similar target attributes and significantly shortened reaction-step times were obtained compared to batch-produced ADCs.[13]

Fig. 6. Dr. Rebecca Ruck with Prof. Gademann after the Q&A session (left) and (right) Prof. Weckhuysen during his presentation.

The Tuesday morning session was introduced by Gilles Gasser (Chimie ParisTech, PSL), and started with a presentation by ***Bert Weckhuysen*** (University of Utrecht) on catalytic processes to make the chemicals and fuels of the future (Fig. 6). Fossil fuels are the primary source of global energy and products, but their use significantly contributes to carbon dioxide emissions and climate change. To achieve a carbon-neutral society by 2050, renewable electricity can replace fossil-fuel energy, while electrifying refinery processes and using alternative raw materials like carbon dioxide and waste can close the carbon cycle. Developing a completely fossil-free refinery will require substantial resources and renewable energy for hydrogen production and carbon dioxide capture, supported by long-term commitment and technological advancements.[14] Towards more sustainable catalysis, enhanced mechanistic understanding is essential, and the Weckhuysen group has developed advanced *in situ* and *operando* spectroscopy methods to study the catalytic mechanisms of heterogenous catalysts in real time: 'seeing is believing'.[15] One important reaction parameter in the reactor is the temperature, and recently they showed that it is possible to monitor temperature fluctuations of catalyst particles and relate them to their morphological evolution.[16]

The second talk of the morning was delivered by ***Diego Peña*** (University of Santiago de Compostela) with an inspiring story on the visualization of intricate molecular structures on metal surfaces (Fig. 7). Arynes are privileged organic intermediates for the formation of structurally defined polyaromatic hydrocarbons with high molecular complexity. However, the insolubility of these compounds largely prevents their characterization by conventional methods such as NMR spectroscopy. In a longstanding collaboration with IBM, the Pena group has pioneered the bottom-up synthesis of nanographenes and their structural characterization with a combined scanning tunneling microscope/atomic force microscope (STM/AFM).[17] A variety of nanographenes with ever increasing complexities were presented, as well as new avenues that include on-surface chemical reactions and the application of STM for simultaneous tip-induced selective rearrangement cascades and reaction visualization.[18,19]

The afternoon was free to explore the beautiful -if cloudy- surroundings (Fig. 8), and the evening of the second day was dedicated to a different type of magic: illusions beyond chemistry.

Fig. 7. Prof. Peña during his presentation (left) and together with Prof. Mascareñas and Prof. Gasser (right).

Fig. 8. The beautiful but cloudy scenery surrounding the conference venue.

The Wednesday morning session was moderated by Ollala Vásquez (Philipp University of Marburg). The first speaker, ***Anat Milo*** (Ben-Gurion University of the Negev) (Fig. 9) started by reminding us about the importance of data visualization and how Florence Nightingale leveraged it to demonstrate that improving hygiene and living standards in hospitals reduced death rates during the Crimean War. In Milo's research, data visualization has proven instrumental to identify the key parameters behind the reaction rate and enantioselectivity enhancement observed when adding boronic acids to a benzoin reaction. This study reveals that boronic acids (BAs) as secondary-sphere modifiers in *N*-heterocyclic carbene (NHC) organocatalysts enhance reaction rates and maintain enantioselectivity through a water-assisted hydrogen atom transfer mechanism.[20] While often ignored by the community, the importance of reporting the substrates that did not work in a scope was emphasized, as those bring useful information for readers, and are most important as training data for machine learning approaches. In the last part of the talk, a new approach was discussed to develop molecular representation models building on foundation models. The resulting MoleCLIP, a molecular image representation learning framework, needed significantly less pretraining data to match the performance of existing models.[21] In conclusion, an important take-home message was that even with little amount of data, relevant conclusions can be drawn using statistical tools combined with data visualization and intuition.

In the second part of the morning session, ***Eva Hevia*** (University of Bern) presented how highly reactive organometallic species can be tamed for arene functionalization and catalysis (Fig. 9). Compared to the widely used organolithium reagents, organosodium and organopotassium species are more abundant, more reactive but less thermally stable and non-commercially available. The Hevia group recently achieved the Pd-catalyzed cross coupling of aryl halides with a range of aryl and benzylpotassium

Fig. 9. (Left) Prof. Milo and (right) Prof. Hevia during their talks.

species, generated *in situ* by direct C–H metalation.[22] Organosodium compounds could also be used as cross coupling partners in iron-catalysed oxidative homocoupling and cross-coupling with alkyl halides.[23] Furthermore, to make these syntheses more accessible to the community, a detailed synthetic procedure for the generation of sodium organometallics was shared.[24]

The afternoon session was opened with a talk by ***Kathrin Lang*** (ETH Zurich), highlighting the power of chemical tools to interrogate biology (Fig. 10). The incorporation of non-canonical amino acids into cellular proteins through genetic code expansion allows for their subsequent functionalization with a variety of chemical reporters, such as fluorophores or biotin. Moreover, the introduction of reactive groups such as photo-crosslinkers enables interactome profiling.[25] Proteins are often post-translationally modified, and it is challenging to understand the nature and function of such PTMs. Using genetic code expansion, the Lang group has investigated the influence of lysine succinylation and glutarylation on the enzymatic activity of metabolic enzymes. For this, the negative charge was temporarily masked as a thioester derivative.[26] Recently, a technical limitation for genetic code expansion in bacteria, namely the limited uptake of the non-canonical amino acids, was overcome through the use of isopeptide-linked G-XisoK tripeptides that serve as an excellent ligand for active transport *via* the periplasmic protein OppA. The terminal glycine is cleaved off enzymatically, allowing the installment of a wide variety of functional group-containing ‘X’, such as bio-orthogonal handles, novel PTMs or crosslinkers.[27]

Fig. 10. Prof. Lang (left) and together with session moderator Prof. Vásquez (right).

Moderated by Jérôme Waser, the session continued with six flash talks – ***Joshua Barham*** (University of Strathclyde), ***Lorena De Luca*** (Givaudan), ***Muhammad Jbara*** (University of Tel Aviv, JSP Fellow), ***Esteban Mejia*** (LIKAT), ***Courtney C. Roberts*** (University of Minnesota, JSP Fellow), and ***Stephan Rummelt*** (Roche) – followed by the second lively poster session.

For the Wednesday evening session, Erick Carreira (ETH Zurich) introduced ***Shu-Li You*** (Shanghai Institute of Organic Chemistry) (Fig. 11) whose group developed novel synthetic methodologies focusing on enantioselective C-H bond direct functionalization processes and catalytic asymmetric dearomatization (CADA) reactions, mediated by either chiral phosphoric acids, transition metals or photocatalysts and subsequently applied to the total synthesis of natural products.[28] The presentation then delved into the synthesis of *Z*-olefins, a motif frequently encountered in bioactive compounds but thermodynamically less stable than their *E*-type counterparts and more challenging to reach. By capturing the transient *anti*-π-allyl-Ir complex with an external nucleophile, the *Z*-configuration of the double bond could be retained in the target products (>20:1 *Z*/*E*).[29]

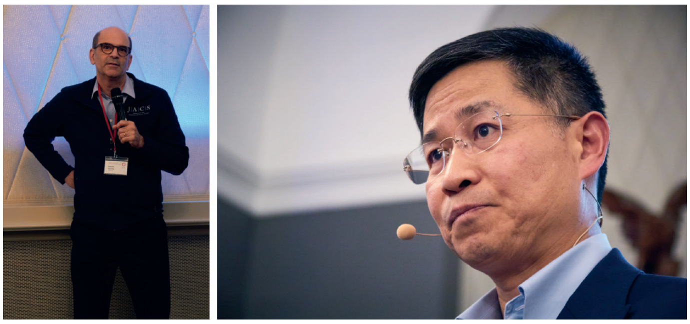

Fig. 11. Prof. Carreira (left) and Prof. You (right).

The Thursday morning sessions were moderated by Francesca Paradisi (University of Bern). ***Belèn Martin-Matute*** (University of Stockholm) (Fig. 12) started with a presentation on C-H bond functionalizations and activations for selective organic synthesis, with the aim to enable late-stage modifications of biologically active molecules. These molecules pose significant challenges in terms of selectivity, as they are often complex and contain multiple C–H bonds. An important characteristic of the catalysts used for C–H bond functionalization in their research is that they need to be simple, safe, and easy (commercially accessible), to allow sustainable drug discovery. Several examples were shared, including the iridium-catalyzed carboxylate-directed *ortho* C–H methylation of benzoic acids, which, when applied to known drugs, led to increased metabolic stability due to the ‘magic methyl’ effect.[30] Another important area is the late stage incorporation of a synthetic handle, such as an amine, for further conjugation reactions. Using a high-throughput experimentation strategy, an iridium-catalyzed directed C–H amination was developed and used on complex substrates, which enabled miniaturization of the reaction as well as the establishment of guidelines for the applicability of the reaction.[31] While not discussed in detail during the talk, the last slide was dedicated to heterogenous rather

Fig. 12. Prof. Martin-Matute (left) and Prof. Hyster (right) presenting their work.

than homogenous catalysis, to celebrate this year's guest of honor Miquel A. Pericàs.

The closing talk, centered on emergent mechanisms in photoenzymatic catalysis, was delivered by ***Todd Hyster*** (Princeton University) (Fig. 12). While enzymes have specific roles in nature, they can be engineered to enable new chemistries using directed evolution. Taking inspiration from small molecule catalysis, where the catalyst can employ different mechanisms depending on the substrate, the question arises how an enzyme – typically set out to do a single reaction – can be evolved in that direction. Combining photoexcitation with flavin-dependent 'ene'-reductases was found to change their catalytic function, allowing these enzymes to perform asymmetric radical cyclization.[32] This enzyme could furthermore be evolved to improve catalytic function and broader wavelength compatibility. Next, a recent example of an engineered mono-oxogenase for photoenzymatic alkene hydroamination was shared, as a beautiful illustration of the potential of enzymes to access unique mechanistic solutions for challenges in organic synthesis.[33] Finally, these enzymes can provide the platform for enantioselective free radical transformations when coupled with exogenous photoredox catalysts, through tuning of the redox potential of the substrates within the enzyme's active site.[34]

Fig. 13. (Left, right) Participants having a good time during the sessions and (middle) moderator Prof. Paradisi.

While the job of the Vice-President is to ensure good weather did not fully go as planned, the participants left the premises after 5 days invigorated by inspiring talks highlighting the many exciting research directions in organic chemistry in its broadest sense. Many ideas were exchanged throughout the discussions (Fig. 13) – often continuing during coffee or meal breaks – and collaborations fostered, making this edition of the Bürgenstock conference a true success.

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