Conference Report

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Scientific Fireworks to Celebrate the 50th Anniversary of the Bürgenstock Conference**

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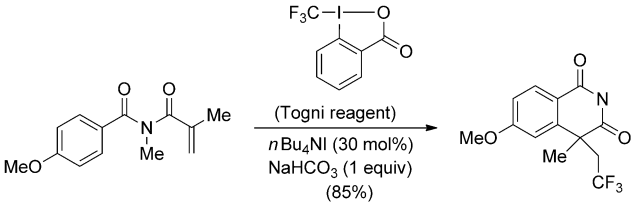
For half a century, the Bürgenstock Conference has held a very special position in the chemistry landscape, just as the eponymous Swiss mountain ridge on Lake Lucerne does in the natural landscape. The conference has remained unique in many respects, as a set of basic rules stimulates the in-depth reflection on a small number of selected topics, and vibrant discussions by the participants from various disciplines. The traditionally outstanding list of speakers is not announced in advance, creating a distinctive atmosphere that is receptive for the unexpected. Ample time is reserved for questions after each lecture, thus allowing a discourse on the subject from many different perspectives. The spirit and unparalleled character of this legendary conference was already excellently described in the Essay by Klaus Müller (F. Hoffmann-La Roche, Basel) and the Editorial by Jay Siegel (Tianjin University).[1]

The Seehotel Waldstätterhof in picturesque Brunnen served as the stunning setting for the conference. It was immediately clear when reading the eagerly awaited program that this year's President, Antonio Togni (ETH Zurich), exceeded all expectations by compiling a spectacular program. Topics ranging from catalysis, polymer chemistry, inorganic chemistry, fluorine chemistry, and dynamic molecular systems to natural product synthesis and chemical biology were flavored with events to celebrate the anniversary of the conference.

Togni opened the meeting with a warm welcoming address and a moving speech for the guest of honor, Dieter Seebach (ETH Zurich), who gave a delightful overview of the rich history of the conference. The scientific program began with a fulminant lecture by Dieter Schlüter (ETH Zurich) on synthetic, two-dimensional macromolecules. In a particularly elegant strategy, three-bladed anthracene monomers were preorganized to form layers by a templated crystallization. A subsequent photochemical polymerization by means of a strategic [4+4]-cycloaddition reaction delivered novel two-dimensional polymer crystals, which were studied in detail by X-ray crystallography after an annealing process. Nanometer-thin all-carbon polymer sheets and occasionally single sheets were obtained by exfoliation, representing a remarkable achievement considering the structural changes occurring during polymerization.[2]

The first morning session started with Jinbo Hu (Shanghai Institute of Organic Chemistry), who impressively demonstrated the merits of sulfur-based reagents for the selective incorporation of fluoroalkyl groups beyond the classic bioisosteres. By modulating the reactivity of fluorinated organosulfur compounds, exceptional transformations that are often distinct from their nonfluorinated counterparts were achieved. Hu proceeded to describe an alternative installation of trifluoromethyl groups by a remarkable AgF-mediated *gem*-difluoroalkene fluorination, concomitantly triggering an olefin cross-coupling process.[3] Cristina Nevado (University of Zurich) followed with a fascinating lecture illustrating the mechanistic diversity of late-transition-metal-catalyzed reactions such as alkene difunctionalizations by Au^{I}/Au^{III} catalytic cycles. A mechanism-based journey through complex cascade reactions to form densely functionalized carbocylic structures led to an astonishing metal-free non-radical carbon trifluoromethylation reaction by virtue of activating the Togni reagent with catalytic amounts of tetrabutylammonium iodide (Scheme 1).[4]

After the afternoon break, the participants reassembled for short presentations by junior researchers prior to the first of two highly stimulating poster sessions on a broad range of topics. In a captivating evening lecture, Thomas O'Halloran (Northwestern University) focused the attention on the inorganic chemistry of mammalian cell fertilization. Using dynamic live-cell fluorescence imaging with specifically designed chemical probes, zinc fluxes occurring during mammalian cell fertilization were locally mapped. Intriguingly, fertilization-induced zinc sparks essential for control-



Scheme 1. Metal-free carbon trifluoromethylation by using the Togni reagent.[4b]

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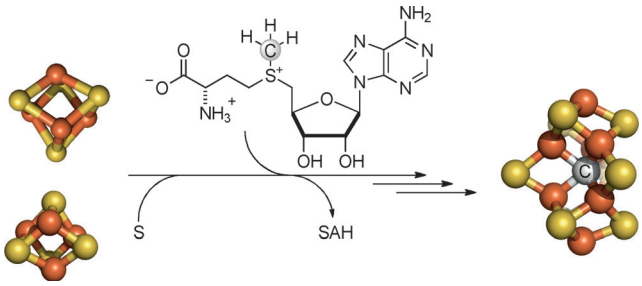
ling cell cycle progression were identified and the underlying molecular mechanism was deciphered in combination with complimentary physical approaches.[5]

The Tuesday morning session was opened by Markus Ribbe (University of California, Irvine), who emphasized the role of carbon in nitrogenase cofactors. The interstitial carbide found in the catalytically active metal–sulfur M-cluster of nitrogenase posed the question of the biosynthetic origin of this carbon atom. Ribbe described the elucidation of an outstanding *S*-adenosylmethionine (SAM) based carbide insertion mechanism responsible for nitrogenase M-cluster assembly (Scheme 2). Furthermore, this catalytically active metallocluster was isolated from the enzyme by extraction and used in Fischer–Tropsch-like reactions to transform CO and even CO_2 into short hydrocarbons.[6]

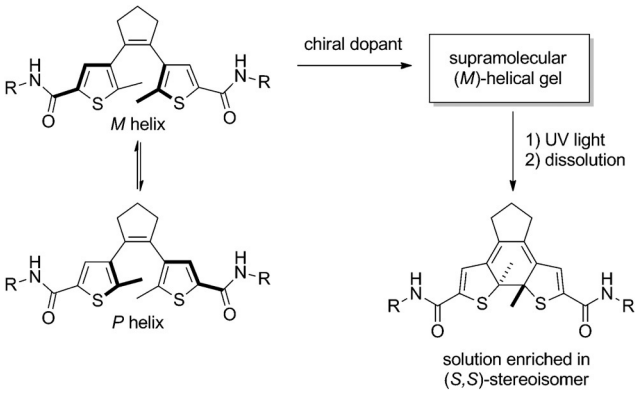


Scheme 2. SAM-dependent incorporation of a carbon atom into the nitrogenase L-cluster, precursor of the nitrogenase M-cluster.[6a]

Ben Feringa (University of Groningen) continued with an incredibly multifarious lecture on dynamic molecular systems. In order to combat adverse effects and the emergence of resistance, precise spatiotemporal control over pharmacological activity was reached by photochemical regulation. In another exceptional example, a supramolecular assembly into helical fibers controlled by chiral dopants resulted in autoamplification of molecular chirality locked by a photochemical diarylethene ring closure (Scheme 3).[7]

The evening was set in motion by Ayusman Sen (Pennsylvania State University) in a lecture on catalytically driven movement of small objects. Sen started with an excellent overview on the main physical principles operating on small length scales and elaborated on how substrate specific reactions leading to different gradients can be exploited to engage in translational motion. In his fascinating illustrations, catalyst units moved into domains with higher substrate concentration, bone cracks became detectable, and enzymes were separated based on their activity.[8]

The Wednesday morning session was dedicated to cutting-edge natural product synthesis. Sarah Reisman (California Institute of Technology) started with a captivating talk on new strategies and methods for the assembly of intricate polycyclic terpenoids and alkaloids. By adding organometallic reagents to a chiral benzoquinone monoketal-derived sulfinyl imine and a subsequent photochemical [2+2]-cycloaddition, the propellane core of acutumine was efficiently constructed. A subsequent retro-aldol reaction, triggering a tautomerization and ketalization sequence, systematically established extra-



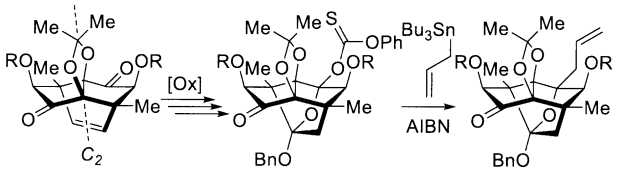
Scheme 3. Autoamplification of molecular chirality induced by a supramolecular assembly into helical fibers, locked by a photochemical ring closure.[7b]

ordinary caged structures.[9] Richmond Sarpong (University of California, Berkeley) highlighted ideal retrosynthetic disconnections of complex natural products by network analysis. With this scrutiny, methods for the rapid generation of molecular complexity were identified and consequently developed. For instance, Sarpong devised strategic pyridine functionalization methods for the synthesis of the pseudodimeric alkaloid complanadine B and a remarkable oxidative C–N bond formation by C,N-dilithium chelates as a key step en route to lyconadin A.[10] The celebrations marking the 50th anniversary of the Bürgenstock Conference reached their summit with the reception for Duilio Arigoni, Albert Eschenmoser, and Jack Dunitz, who passionately shared anecdotes about the origins of the conference and how this famous meeting was initiated by André Dreiding.

On Thursday morning, David O'Hagan (University of St. Andrews) convincingly demonstrated the control reached over the topology of acyclic and cyclic molecular scaffolds by utilizing fluorine conformational effects. Occasionally, the altered properties of the products became immediately evident to the researchers, as a clear change in olfactory properties was sensed upon fluorination. The lecture culminated with the synthesis of all-*cis* multivicinal hexafluorocyclohexane, the aliphatic compound with the largest molecular dipole moment reported to date.[11] Matthew Francis (University of California, Berkeley) followed with an account on state-of-the-art bioconjugation. Transamination reactions with pyridoxal phosphate allowed a site-selective, N-terminal protein modification set up for a ligation with aminooxy-functionalized peptides to make hybrid materials for various applications. Francis made another persuasive case by a specific imidazolidinone formation with 2-pyridinecarboxaldehydes for the detection of endocrine-disrupting compounds in drinking water.[12] The last evening lecture by Cynthia Burrows (University of Utah) was devoted to systematic structural investigations of highly mutagenic hydantoin lesions resulting from the oxidative damage of DNA. In her intriguing studies, the absolute configuration of spiroiminohydantoin lesions was elaborated and first implications for the underlying biological factors were established. This represents an important realization as the mutational profile is

dependent on the exact structure of the lesion. Burrows concluded her talk with a remarkable analysis of the subtle topological changes in G-quadruplex folds of the human telomer by single-molecule detection within a protein nanopore.[13]

The closing session on Friday began with a lecture by Masayuki Inoue (University of Tokyo) on a spectacular strategy for the total synthesis of the densely oxygenated polycyclic natural product ryanodol. Pairwise functionalization to a highly advanced C_2-symmetric intermediate prepared for an oxidative desymmetrization with a subsequent key α-alkoxy bridgehead radical reaction (Scheme 4). Moreover, the methodology was elaborated to a versatile multicomponent coupling by a radical decarbonylation reaction of α-alkoxyacyl tellurides.[14]



Scheme 4. Oxidative desymmetrization and selective α-alkoxy bridgehead radical reaction in the total synthesis of ryanodol.[14a] AIBN = 2,2′-azobisisobutyronitrile.

The honor of the final lecture was given to Jieping Zhu (École Polytechnique Fédérale de Lausanne), who showcased the integration of oxidation, reduction, and cyclization steps for the efficient one-pot construction of characteristic polycyclic scaffolds. An oxidative scission of alkenes followed by highly chemoselective reduction processes triggered numerous astonishing cyclization events, directly leading to complex monoterpene indole alkaloids. The skeleton of the substrates is completely reorganized in this sequence abbreviated IORC, allowing late-stage structure diversification by precise control over the oxidation and reduction processes.[15]

The outstanding quality of the research presented, the diversity of the selected topics, as well as the unique format encouraging vigorous discussions made the 50th Bürgenstock Conference an extraordinary success. With great anticipation for the continuation of this tradition, the conference was closed with enthusiastic words of acknowledgment addressed to the President Antonio Togni and the organizing committee: Christian Bochet (University of Fribourg), Alain de Mesmaeker (Syngenta, Stein), Jérôme Lacour (University of Geneva), Reto Naef (Novartis, Basel), Philippe Renaud (University of Bern), and Helma Wennemers (ETH Zurich). The Bürgenstock Conference from May 1–6 2016 under the Presidency of Paul Knochel (Ludwig-Maximilians-Universität München) is undoubtedly in the best hands to begin another prosperous 50 years of this legendary meeting.

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