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Conference Report

The 53rd EUCHEMS Conference on Stereochemistry: Bürgenstock Conference 2018, Brunnen, April 29th – May 3rd, 2018

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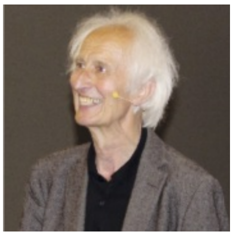
"*Chemistry is marked by magic moments*," *Yves Chauvin*

Set on the picturesque shore of Lake Lucerne, with a backdrop of the Swiss Alps, the 53rd Bürgenstock Conference (April 29th – May 3rd, 2018) was indeed a collection of magical moments.

Under the masterful direction of president ***Ilan Marek*** (Technion – Israel Institute of Technology), the unwritten theme of this year's meeting seemed to be "science meets art". It was in this spirit, and thanks to the hard work of the organizing committee – Christian Bochet, Alain de Mesmaeker, Fabrice Gallou, and Cristina Nevado – that the 53rd Edition was a showcase of cutting-edge chemistry, ranging from the fundamental to the applicative; from the elegantly simple to the beautifully complex.

In true Bürgenstock style, Marek opened the conference from the balcony in the Fronalp Saal of the Waldstätterhof Seehotel in Brunnen, welcoming guest of honor ***Yitzhak Apeloig*** (Technion) and all of the attendees.

The inspiring presentations were augmented by the open, stimulating discussions and the warm atmosphere that are characteristic of this special meeting. The combination is perhaps best described with a quote from the first speaker of this year's meeting, Helmut Schwarz: "The baguette is more than the sum of its crumbs."


Helmut Schwarz

The opening session of the 53rd Bürgenstock Conference was moderated by vice-president ***Veronique Gouverneur*** (Oxford), who introduced the first speaker, ***Helmut Schwarz*** (Technische Universität Berlin). Schwarz gave a compelling account of the complex challenges involved in transforming the simplest of organic compounds – methane – in a sustainable and viable way. His talk focused specifically on hydrogen atom transfer (HAT), and addressed both experimental and computational investigations into the metal-oxide based mechanism, aimed at elucidating the role of relativistic effects and spin states in C-H activation. Starting from Li/MgO systems, he showed that doping with Ga enables probing of the apparent and intrinsic barriers for H-activation. Coupled with conclusions from ligand-effect studies, a deformation-energy based tool was proposed for predicting whether HAT or proton-coupled electron transfer will occur. Schwarz then showed how coinage-metal oxides are "the same but not the same" (to quote R. Hoffmann) and can highlight the importance of excited states in thermal rearrangements. He then smoothly transitioned to discussing the use of carbides as probes for elementary steps. Tying together all of the threads into an elegant bow, he concluded his talk by proposing that the future of smart reagents lies in the use of oriented electric fields, pointing out that many effects (for example, endo-selectivity in Diels-Alder reactions) can be explained by assuring such a field.


James P. Morken

Monday morning began with a session moderated by ***Mark Gandelman*** (Technion) and dedicated to the chemistry of rearrangements. The first presentation was given by ***James P. Morken*** (Boston College), who began by demonstrating the broad utility of boron functional groups to afford enantioselective, efficient, simple, and environmentally benign transformations. He then presented his approach to the construction of such organoboron compounds, *via* a metal-induced metallate rearrangement concomitant with a C–Pd bond formation. This reaction, termed *catalytic conjunctive cross-coupling*, uses a chiral Pd catalyst to enantioselectively merge an organolithium species, an organoboronic ester, and an organotriflate into a chiral organoboronic ester which leads to a secondary alcohol after deborylation. A kinetic investigation of the reaction showed the metallate pathway to be favored over the carbo-palladation route. Subsequent optimization of the process enables use of commercially available vinyl-Grignard reagents.


Nuno Maulide

Nuno Maulide (University of Vienna) had the distinction of being the youngest speaker at this year's meeting. He presented an impressive overview of his accomplishments thus far, with the development of methodologies involving keteneiminium intermediates as the main thread. The first part was focused on polarity reversal at the α-position of a carbonyl group *via in situ* generation of an enolium species stemming from the reaction between a keteneiminium and LNO (Lutidine-N-Oxide). This enolium can then undergo several transformations, such as diastereoselective intramolecular cyclization (formal oxidative C–C coupling), enolate addition, α-fluorination, or oxidation into 1,2-ketoamides. The second part of his talk was dedicated to sulfur; in particular, he described the access to α-arylated thioesters and amides by a [3,3]-sigmatropic rearrangement with chirality transfer from a sulfonium to a carbon atom. Finally, in the last minutes he presented an elegant method to access functionalized cyclobutenes *via* a two-step sequence: a photoisomerization of 2-pyrone into a bicyclic lactone and its metal-catalyzed-opening into cyclobutene. These building blocks can then be utilized as diene precursors, as they can undergo a retro-electrocyclization under thermal conditions.


Shigehiro Yamaguchi

The Monday afternoon session, chaired by ***Jérome Waser*** (EPFL Lausanne), began with a talk by ***Shigehiro Yamaguchi*** (Nagoya University), who talked about a main-group strategy for photostable fluorescent and NIR dyes. Current microscopic techniques are limited by the performance of organic dyes, which necessitates design of new fluorophore skeletons in order to enable high-resolution and dynamic imaging. While existing techniques utilize steric bulk to effect rigidity, the design principle applied by Yamaguchi is based on planar, π-system structural motifs, in combination with main group atoms, including boron, sulfur, phosphorus, silicon. Specifically, the introduction of boron doping affords remarkable stability of extended π-framework carbon radicals. For near-IR (NIR), he has designed tropylium-core based systems, which have the dual advantage of small size and an extended π-system, rendering them soluble and stable. The versatile nature of this strategy enables red-shifting of the dye by changing the substituent – from 510 nm with oxygen to 582 nm with silicon to 627 nm with phosphoxide – without affecting the core, which means that the solubility is not adversely affected. Another successful structural motif is the phosphole indole, which allows selective staining of lipid droplets and affords much enhanced signal-to-noise ratio. All of the systems presented by Yamaguchi demonstrate high spatial resolution and exceptional photobleaching resistance, allowing for repeated scanning over time. The lecture was concluded with a remarkable presentation of high-resolution, dynamic imaging of living cells.

The first poster session took place on Monday afternoon, starting with flash talks by five junior faculty: ***Job Boekhoven*** (TU München), ***Charles E. Diesendruck*** (Technion), ***Han Sunkyu*** (KAIST), ***Monica Perez-Temprano*** (Institute of Chemical Research of Catalonia), and ***Maros G. Suero*** (ICIQ), all recipients of the Junior Scientist Participation award.


Andreas Marx

The day concluded with a presentation by ***Andreas Marx*** (University of Konstanz), who began with an entertaining and humbling lesson in biology: While humans boast 20,000 genes and approximately 3,300,000 base pairs in our genome, onions have about five times as many base pairs and about 50% more genes, demonstrating that human development is not linearly related to the number of genes or nucleotides. Indeed, there is a wealth of information beyond the DNA sequence, collectively termed epigenetics, including mechanisms such as nucleic acid modifications and protein modification. In his talk, Marx presented his work on identification of proteins interacting with Ubiquitin chains and, in particular, Ub chains linked via K27, K29, or K33, which are still underexplored. To do that, a method for obtaining all seven homogeneous K-linked Ub chains was developed and these were utilized to identify interaction partners of the linkage type K27, K29, and K33 *via* affinity-based proteomic profiling. Another part of his lecture dealt with protein Poly-(ADP-ribos)ylation (PARylation). PARylation is a complex post-translational protein modification and is involved in many processes, in particular in DNA repair. In this context, new tools were presented to study the PARylation dynamics within the cell, based on the development on fluorescent NAD+ analogues. Finally, Marx talked about biomarkers for epigenetic and the development of modified nucleotides to discriminate cytosine from the epigenetic marker 5-methylcytosine (5mC), which may cause damages in various cellular processes.


Helma Wennemers

Tuesday's morning session was chaired by ***Virginie Vidal*** (Chimie ParisTech) and was launched with a fascinating lecture by ***Helma Wennemers*** (ETH Zürich) that began with a short teaser on oligo-proline based supramolecular assemblies, showing how they self-assemble to form triaxial, kagome-like, molecular weaves. Wennemers then shifted gears to talk about smaller compounds – tripeptides – and their role in asymmetric catalysis. Tripeptides lie at the intersection between enzyme catalysts and synthetic catalysts, and provide advantages from both types. They have the stereoselectivity and chemoselectivity of the former, and the small size and ease of synthetic access that are typical of the latter. In addition, the use of peptides entails modularity, which in turn enables the tuning of functionality and adaptation to specific reactions. Specifically, Wennemers discussed the utility of the Pro-Pro-Xaa motif for two reactions: Xaa = Asn for conjugate addition of aldehyde to maleimide, and Xaa = Glu for addition of aldehydes to nitro-olefins, which her group has succeeded in performing with high stereoselectivity. Structure-activity relationship and kinetic studies led to subsequent optimization of the reaction conditions, including a reduction of the catalyst loading to 0.05 mol% – the lowest reported for such reactions. Conformational NMR studies highlight the importance of the balance between flexibility and rigidity in a catalyst. Wennemers concluded with the thought-provoking suggestion that perhaps short peptides were the predecessors to the active enzymes we know today.


Ashraf Brik

The second lecture of the day was given by ***Ashraf Brik*** (Technion), who started by demonstrating how organic chemists can support biologists in their quest for comprehension of complex biological pathways. The study of ubiquitination and de-ubiquitination of proteins served as support for his talk, which illustrated how organic chemistry could be applied to the total synthesis of complex proteins. The ubiquitination of proteins, which happens through the successive action of three different enzymes, is known to induce their proteolysis and this discovery led to the 2004 Nobel Prize in Chemistry. However, ubiquitin most probably plays a major role in many other important biological function, such as DNA repair, which is triggered by the ubiquitination of the H2B sub-unit of histone. Brik showed an impressive, convergent total synthesis of ubiquitinated H2B sub-unit of histone, which helped shed light on biologically relevant mechanisms. The chemistry of proteins was expanded through the development of an innovative palladium(II) chemistry toolbox that enables selective deprotection of a variety of sulfur-containing moieties such as thiazolidines *N*-acetylthioaminals or *tert*-butylthioethers. The potential of this chemistry was exemplified through syntheses that required only limited purification, thereby limiting losses of high-value synthetic proteins. Furthermore, this Pd toolbox has the potential to be applied directly in the cell to liberate two or more cross-linked fragments from one molecular entity.

Tuesday evening was devoted to the time-honored tradition of the Bürgenstock Concert. In keeping with previous years' practice, the program was kept secret until the beginning of the concert. However, this year, the attendees enjoyed an additional element of surprise when they discovered that the performers were none other than their fellow chemists. The concert began with pianist ***Nuno Maulide*** (University of Vienna), who charmed the audience with a spellbinding performance of classical pieces by Chopin, Bach, and Debussy, interspersed with stories that highlighted the relationship between music and science. ***Amnon Stanger*** (Technion) then took over the piano and swept the audience in a completely different direction, performing Pink Floyd's *Atom Heart Mother* followed by a jazzy improvisation on the Beatles' *Yesterday*. For a final surprise, Stanger was joined by his former PhD student and soprano singer, ***Renana Gershoni-Poranne*** (ETH Zurich), who sang a few songs and ended the evening by inviting the audience to join in singing Leonard Cohen's *Hallelujah*.


Rubén Martin

The Wednesday morning session was chaired by ***Belen Martín-Matute*** (Stockholm University) and began with a talk by ***Rubén Martin*** (ICIQ Catalonia) dealing with the ability to harness earth-abundant catalysts to build up molecular complexity from very simple precursors (alkenes, alkanes and CO_2). After a brief introduction on the advantages of Nickel for coupling reactions, he presented the use of carbon dioxide as a C1 feedstock to perform the carboxylation of unfunctionalized organic halides using Ni catalysis. This reaction involves halogenated aliphatic hydrocarbons where the migration of the Nickel catalyst along the side chain occurs with complete chemo- and regioselectivity. The beauty of his work relies, among other thing, on the possibility to use a mixture of alkenes converted to a mixture of halogeno-alkanes and converging, through a chain-walking scenario, to the same ω-carboxylated product. Starting from an alkyl bromide, Martin showed also a switchable, temperature-dependent site-selective carboxylation at remote sp^3 C-H sites, suggesting a competition between kinetic and thermodynamic control. Then, the carboxylation of α-olefins promoted by water as hydride source, hydroamination of alkynes with isocyanates or decarboxylation of 1,3 dienes were presented in a very didactic and exciting manner.


Ang Li

The next lecture, given by ***Ang Li*** (SIOC), was dedicated to the art of total synthesis, and an impressive array of polycyclic natural product syntheses were shown. Among them, the total synthesis of the Daphniphyllum alkaloid daphenylline was presented, wherein the 6,6,5-tricycle motif involved a gold calatyzed 6-exo-dig cyclization, followed by an intramolecular Michael addition. A photoinduced olefin isomerization/6π electrocyclization cascade culminating in an oxidative aromatization was performed to construct the heavily substituted aromatic moiety. Then, the synthesis of Daphniyunnine C was described; the latter involved a similar sequence as described before to build the bicycle, followed by a [3+2]-cycloaddition between an allene and an alkene as the key step. In the second part of his talk, Li presented a remarkable Prins-type oxidative cyclization that was applied for hapalonamide H, in a synthetic strategy that was been inspired by a postulated biosynthesis pathway involving the same key reaction.


Odile Eisenstein

The afternoon session on Wednesday was moderated by ***Franziska Schoenebeck*** (Aachen), who gave a very warm introduction to ***Odile Eisenstein*** (Université de Montpellier/University of Oslo). Eisenstein presented the novel concept of using NMR to analyze reaction pathways and made a compelling case for this approach, using the metathesis reaction as a case study. The d^0 Schrock catalysts, the d^6 Grubbs catalysts, and other known metallacyclobutane systems all show similar anomalies in NMR – an unusually high chemical shift for the α-carbon and a near-zero chemical shift for the β-carbon of the trigonal bipyramidal isomer that catalyzes metathesis. This is in stark contrast to the values measured and calculated for inactive species. Thus, understanding the reason for the abnormally high chemical shift is key to understanding the reactivity of these systems. Dissecting the chemical shift tensor shows that there is one component – that in the plane of the alkylidene – that determines the deshielding effect, and within that component, it is the paramagnetic term that is dominant. Eisenstein then presented a simple molecular orbital picture that explains these observations, and concluded by generalizing this analysis to include other observations, such as α-H elimination and spectroscopic data of methyl radical, anion and carbene.

The second poster session was kicked off by another round of flash talks, given by ***Roey J. Amir*** (Tel Aviv University), ***Gabriel N. Lemcoff*** (Ben Gurion University of the Negev), ***Amandine Kolleth Krieger*** (Syngenta), ***Thomas N. Snaddon*** (Indiana University) and ***Christof Sparr*** (University of Basel).


Philippe Renaud

The last talk of the day was presented by ***Philippe Renaud*** (Bern University) was dedicated to radical chain reactions, asking the question "how far can we go?" An efficient method for radical additions to alkenes via desulfitative chlorine atom transfer was presented, followed by an extension to hydrosulfonylation of alkynes, where the solvent is involved in the reaction as a source of hydrogen. In the second part, the design of a new generation of radical fluorinating agents was described to allow the synthesis of fluorinated alkanes *via* hydroboration of alkenes and subsequent radical fluorination. He also demonstrated the usefulness of a radical deuteration process allowing selective incorporation of deuterium atoms into molecules by using D_2O as source of deuterium. Finally, although the notion of repair is known and applied in Nature (such as proteins, DNA, *etc.*) this concept is very new in organic chemistry and Renaud demonstrated such an examplewith a chain repair mechanism that ensures the radical chain processes, especially in the case of highly unreactive species.


Jonathan Nitschke

The final session of the Bürgenstock Conference, chaired by previous president ***Bert Meijer*** (Eindhoven University of Technology) was devoted to the chemistry of supramolecular assemblies. The first talk was given by ***Jonathan Nitschke*** (University of Cambridge), who presented his approach to the formation of self-assembling supramolecular cages, based on the dynamic covalent chemistry of imine bonds. With the aim of making robust and functional capsids, Nitschke outlined rules for building cages that can bind compounds of interest and discussed the mechanism of assembly in terms of stereochemistry. He demonstrated how different architectures can afford varying functionalities, such as binding greenhouse gases or dangerous substances (SF_6 and P_4), affording selectivity in competitive reactions, separation of desired adducts from a reaction mixture, phase transit of cage and cargo, and even signal transduction *via* post-assembly modifications.


Omar M. Yaghi

The closing talk of the conference was delivered by ***Omar M. Yaghi*** (University of California Berkeley), recipient of the 2018 Wolf Prize. Yaghi gave an enthralling account on the field of covalent organic frameworks (COFs), which he fathered a little over a decade ago, and its place within the grand scheme of molecules and atoms. Just as the molecular structure fixes the atom in a certain connectivity and orientation, the framework fixes the molecule in a similar way, providing the space for further manipulations of the molecule. Yaghi's basic approach is to use reticular chemistry, the chemistry of networks, *i.e.*, linking together building blocks with strong bonds. However, issues of solubility and crystallinity are among the many challenges that must be overcome when applying this strategy to the formation of COFs. He identified two major requirements as the key to success: a) microscopic reversibility; and b) fast kinetics – but not too fast, so as to enable time for self-correction. In a lively talk peppered with anecdotes, Yaghi presented the evolution of the field and the rational design of numerous architectures with varying functionalities. He concluded by showing a molecular weave, whose flexibility can be adjusted, depending on the presence or absence of metals, and demonstrating that weaving could be used to form many other types of structures. The elegance of Yaghi's approach, combined with the beauty of the highly symmetric, self-assembled COF structures, was a fitting final note to a conference seeking to bring together science and art.


Organizing committee and speakers of the 53rd Bürgenstock Conference

The 53rd Bürgenstock Conference was concluded with heartfelt closing remarks by president Ilan Marek, who emphasized that the success of such meetings is dependent on the combination of excellent speakers and active participation of the attendees. Undeniably, in these two regards, this year's meeting was a resounding success. The authors thank the organizing committee and the president, as well as the Junior Scientist Participation fellowship (R. G.-P.), for the unique experience that is the hallmark of the Bürgenstock Conference.

We await with anticipation the next meeting, which will be headed by Veronique Gouverneur. It will undoubtedly be another successful edition of the Bürgenstock Conference.