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Conference Report

The 54th Conference on Stereochemistry: Bürgenstock Conference 2019, Brunnen, May 5–9, 2019

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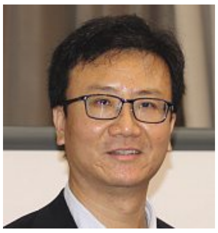
It was snowing on the Bürgenstock summit and the surrounding countryside when the participants of the 54th Conference on Stereochemistry reached Brunnen on Sunday May 5th, 2019. The organizing committee (Christian Bochet, Alain De Mesmaeker, Fabrice Gallou, Cristina Nevado, Thomas Ward and Jérôme Waser) warmly greeted each newcomer and disclosed the confidential program of the prestigious conference before all the participants gathered for dinner in the beautiful dining hall of the Seehotel Waldstätterhof. This year President, ***Véronique Gouverneur*** (University of Oxford), welcomed the guest of honor ***John Brown*** (University of Oxford) and all of the attendees during the dinner, and officially opened the conference with a few words of introduction.


Hagan Bayley

The first speaker of the conference, ***Hagan Bayley*** (University of Oxford), was introduced the same evening by the Vice-President, ***Janine Cossy*** (ESPCI Paris). With his team, Bayley uses the ionic current flowing through a single protein nanopore to observe individual binding interactions. This methodology was used to examine different classes of reactions, ranging from seemingly simple reactions to extremely complex network of up to 38 possible interconversions, and allowed for the determination of the rate constants of every mechanistic step and the observation of short-lived (and otherwise elusive) reactive intermediates. After discussing the strengths and limitations of this method, Bayley showed that the nanopores can also bear a cysteine-track on which a molecule carrying a cargo such as DNA can walk through disulfide exchange reactions in a simple, autonomous and directional way. The molecule is pulled along the track by voltage in one direction, and can even walk back if the voltage is reversed.


Peng Chen

On the following day, the morning session was moderated by ***Jean-Louis Reymond*** (University of Bern) and focused on chemistry at the interface between medicine and biology. The first lecture was given by ***Peng Chen*** (Peking University), who showed how proteins can be manipulated through biorthogonal chemistry to control their activity in space and time. Proteins can be genetically encoded to incorporate artificial amino acids at specific positions, allowing for the introduction of moieties such as alkynes, azides, or strained alkenes. Chen explained how it is possible to take advantage of inverse electron-demand Diels-Alder reactions to decage a *trans*-cyclooctene-modified lysine residue with a tetrazine derivative. Following this strategy, he showed that it is possible to inactivate enzymes that rely on a catalytic lysine residue by mutating it with the *trans*-cyclooctene-caged lysine and restore its activity, both in living cells and animals, after the addition of tetrazine. Chen also demonstrated that this decaging strategy can be extended to activate a *trans*-cyclooctene-modified doxorubicin prodrug, with spatiotemporal control in cancer cells. *In vivo* studies with a xenografted cancer model in mice show an effective tumor inhibition as well as good biocompatibility and safety.


Dario Neri

Dario Neri (ETH Zurich) then presented his approach to simplify drug discovery using DNA-encoded chemical libraries. The use of DNA as a barcode to screen large libraries of small molecules speeds up the process of drug discovery, but Neri emphasized that many chemotherapeutics remain unable to specifically target the site affected by the disease. Specific targeting represents one of the main challenges currently faced in the field. In that regard, armed antibodies hold a great potential. Neri notably described early stage successes in the treatment hematological malignancies using radiolabeled antibodies. The effect of drugs already sold on the market, such as cytokines IL-2 or TNF-α, can be significantly improved by conjugation with an antibody. Antibody-cytokines fusion allows both a targeted delivery and a strong synergy effect between IL-2 and TNF-α, and can be used as an efficient complement to the surgical removal of melanoma tumors.


Yasutero Urano

The afternoon session, chaired by ***Francesca Paradisi*** (University of Nottingham), started with the talk of ***Yasutero Urano*** (University of Tokyo). Continuing on the topic initiated in the morning session, Urano showed novel imaging approaches for precision medicine. The first part of his talk focused on the development of activatable probes, whose photophysical properties change after recognition. In this regard, Urano discussed how spirocyclization of tetramethylrhodamine or rhodol-based probes can be exploited to obtain environment-sensitive fluorophores that detect changes in pH or small molecules such as hypochlorous acid or α-galactosidase. The second part of Urano's talk was focused on the application of specific probes in medicine. He showed that activatable fluorescent probes can be topically applied during surgery to differentiate healthy tissues from cancer lesions. He also demonstrated how a photo-inactive selenorhodamine derivative can turn into a potent photosensitizer after being specifically cleaved by tumor-associated enzymes. Photoirradiation in a tumor model resulted in the ablation of the tumor without damaging the healthy tissue. Urano concluded his talk with an attempt to elucidate the mechanisms of spirocyclization and to predict the fluorescence properties of activatable probes.

This session continued with flash talks given by five junior faculty – ***Josep Cornella*** (Max-Planck-Institut für Kohlenforschung, JSP Fellow), ***Todd Hyster*** (Princeton University), ***Jeremy Luterbacher*** (EPFL, JSP Fellow), ***Elena Pazos*** (Universidade da Coruña, JSP Fellow), and ***Joanna Wencel-Delord*** (Université de Strasbourg, JSP Fellow) – and a very interactive poster session.


Eric Jacobsen

In the evening session, moderated by ***Edward Anderson*** (University of Oxford), ***Eric Jacobsen*** (Harvard University) discussed the concept of 'privileged' chiral catalysts. Schreiner-type catalysts modified with arylpyrrolidines are 'privileged' because of their ability to catalyze efficiently a wide range of asymmetric reactions such as the allylation of chloroglycine, oxetane ring opening or glycosylation. These catalysts can be easily optimized for each reaction. In particular, the choice of the arylpyrrolidine moiety proved to have the most dramatic effect on the enantioselectivity of the catalyzed reactions. The exploration of the mechanisms underlying the observed high enantioselectivity revealed important factors that affect the outcome of these reactions. In one example, trace amounts of water were sufficient to generate equally enantioselective, but competing, reaction pathways. Finally, dimeric catalysts act as highly stereoselective glycosyltransferase mimics and catalyze reactions as challenging as β-mannosylation.


Jonathan Clayden

Tuesday morning session was moderated by ***Joëlle Prunet*** (University of Glasgow) and the first talk was given by ***Jonathan Clayden*** (University of Bristol). Clayden started his talk explaining that nature can be used as an inspiration source to drive advances in synthetic chemistry. During this part of his talk, he demonstrated how induced-conformational changes in foldamers can be used to mimic the way that cells communicate information through distance, and showed several examples resembling the cellular signal transduction through G-protein-coupled receptors. The design of these molecular structures relies on a modified helical foldamer inserted in a lipid bilayer that transduces a specific input by changing its conformation. The second part of Clayden's talk was devoted to reactivity. He discussed new strategies to obtain asymmetric quaternary amino acids, which are important precursors of bioactive molecules. Following his methodology, it is possible to obtain asymmetric α-arylated and alkenylated (and double bond geometry-selective) amino acids, starting from the same amino acid precursor and by selecting the reaction conditions. Clayden ended his talk giving some insights into artificial translation. He showed how oligourea foldamers can change the directionality of the intramolecular hydrogen-bonding network after the intermolecular association with an anionic guest.


Darren Dixon

On a different note, ***Darren Dixon*** (University of Oxford) described how the key step of the total synthesis of Manzamine A triggered his interest in the development of reductive nitro-Mannich cyclizations. The use of Vaska's complex proved particularly powerful in this context, allowing his team to complete an elegant synthesis, and inspiring new chemistry. Indeed, Vaska's complex could be used to obtain bicyclic amines and indole monoterpene alkaloids, opening up a new synthetic route for a wide range of natural products. The development of this chemistry also provided a strategy to late stage functionalization of lactams and amides. Dixon ended his talk with another total synthesis, that of Himalensine A. This synthesis required the development of a novel enantioselective prototropic shift/furan Diels-Alder (IMDAF) cascade, and allowed him to introduce BIMP, a Schreiner-type urea catalyst connected to an iminophosphorane that plays the role of a super-base.

After a short break during the afternoon, the evening was reserved for the long-established Bürgenstock Concert. Continuing the tradition, the concert program was kept a secret until the president Véronique Gouverneur introduced us to a group of young jazz musicians. ***Pierre Gillet*** (7-string guitar), ***Benoît Minon*** (7-string guitar), ***Thibault Dille*** (accordion) and ***Marcos Della Rocha*** (percussions), who knew each other but had not given a concert together before, delighted the public with jazz pieces influenced by Brazilian music. Most of the pieces of the performance, such as '*noites cariocas*' (Brazilian nights) or '*simplicidade*' (simplicity), were written more than fifty years ago by Jacob Bittencourt. A new piece, recently composed by Thibault Dille, was humorously entitled for the occasion '*Bürgenstock stereo-something*'.


Tobias Ritter

Wednesday morning session was moderated by ***Christof Sparr*** (University of Basel). The first lecture was given by ***Tobias Ritter*** (Max-Planck-Institut für Kohlenforschung), who explained the importance of developing methodologies for late-stage functionalizations that can be applied to synthesize new fluorine-18 labelled PET (positron emission tomography) tracers for diagnosis. Ritter showed different strategies for the effective fluorine-labelling of many substrates. The first one was focused on the use of metal-catalyzed cross coupling reactions to obtain fluorinated arenes in a variety of substrates with different functional groups. Then, Ritter continued his talk explaining the interest in developing new fluorinating reagents that allow effective transformations. In this regard, he showed examples ranging from the use of a palladium-based electrophilic fluorination reagent that yields aryl fluorides, to deoxyfluorinating reagents that give access to fluorinated compounds starting from both aromatic and aliphatic alcohols. The implementation of a ruthenium-mediated deoxyfluorination affords previously inaccessible electron-rich aryl fluorides, which allows the incorporation of a 4-fluoro-phenylalanine residue in peptides, opening the door for the development of highly specific peptide-based PET probes. In the last part, Ritter described an approach for direct aromatic carbon–hydrogen (C–H) fluorination using a square planar Pd(II) catalyst and mild electrophilic fluorinating reagents.


Paolo Melchiorre

Maintaining a high level of stereocontrol in reactions driven by visible light is challenging. Nevertheless, ***Paolo Melchiorre*** (Italian Institute of Technology and ICIQ) explained how the ability of a molecule to be both a better oxidant and a better reductant in the excited state than in the ground state can be exploited to perform metal-free organocatalysis. Chiral enamines, for example, act as photosensitizers upon excitation by light irradiation. In the excited state, enamines become strong reductants able to generate radicals from alkyl bromides and to initiate radical reactions under mild conditions. More recently, his team reported the development of chiral carbazole-based catalysts that form iminium intermediates with α,β-unsaturated ketone substrates. In this case, the catalyst induces the transient formation of a visible-light-absorbing intramolecular electron donor-acceptor complex and triggers a photochemical asymmetric radical process.


Abigail Doyle

The afternoon session was moderated by ***Edward Anderson*** (University of Oxford) and started with a talk given by ***Abigail Doyle*** (Princeton University). During her talk, Doyle illustrated the current directions of Ni-catalyzed cross-coupling reactions. The first part of her lecture was focused on recent advances exploiting the combination of photoredox and nickel catalysis. Using this approach, it is possible to perform decarboxylative sp^3–sp^2 cross coupling reactions of amino acids or phenyl-substituted carboxylic acids with aryl halides. The second part of her talk was focused on the identification of ligands for Ni-catalyzed cross-coupling reactions. Doyle explained how electron-deficient olefins, known to accelerate reductive amination in cross-coupling reactions, can be used and tuned to promote Ni-catalyzed Negishi alkylations of mono- and disubstituted aziridines. Finally, she showed a new class of effective phosphine ligands for Ni-catalyzed C-sp^3 Suzuki cross coupling reactions. She demonstrated that the effectiveness of these developed phosphines is related with the remote steric hindrance that they exert in the metal. These studies can ease the design of new nickel ligands.

This session continued with five more flash presentations by: ***Edward Anderson*** (University of Oxford), ***Yimon Aye*** (EPFL), ***Rene Koenigs*** (RWTH Aachen University), ***Francesca Paradisi*** (University of Nottingham), and ***Simon Duttwyler*** (Zhejiang University, JSP Fellow).


Marc Fontecave

Following a second poster session, ***Francesca Paradisi*** (University of Nottingham) moderated the evening session. Hydrocarbons, CO, H_2 or O_2 constitute a form of energy storage (or fuel) usable for the production of heat by combustion, electricity and for organic synthesis. ***Marc Fontecave*** (Collège de France) exposed his strategy to develop methods that mimic natural photosynthesis and use solar energy to generate these products from CO_2 and H_2O. Fontecave first presented the design of multifunctional porous hybrid solids that bring together catalysis, light harvesting and porosity. The incorporation of both a photosensitizer and a catalyst into a solid MOF enables water oxidation in aqueous solution without using any noble metal. He then further elaborated on the conversion of CO_2 into hydrocarbons. CO_2 reduction to ethylene and ethane was achieved with a 2% energy efficiency using a low-cost system coupling a photovoltaic and an electrochemical cell, and optimized to minimize energy losses. Finally, he reported an ongoing study on a heterogeneous catalyst able to achieve CO_2 reduction into ethanol. The mechanism of this reaction raised a particular interest in the audience during the discussion.


Miquel Costas

Thursday's session was chaired by ***Ilan Marek*** (Technion-Israel Institute of Technology) and the first lecture was given by ***Miquel Costas*** (Universitat de Girona), who described the design of iron and manganese complexes, inspired in non-heme oxygenases, which effectively catalyze the oxidation of C–H and C=C bonds. During the first part of his talk, focused on asymmetric epoxidations, Costas discussed how tuning the electronic effects of the ligands on the metal center and the catalytic addition of carboxylic acids influence the selectivity of these reactions. In the second part he showed iron and manganese complexes that successfully catalyze selective C–H bond oxidations in a broad range of substrates. In one example, supramolecular recognition was exploited to achieve a site-selective oxidation of primary aliphatic amines if the manganese complex is appended to 18-benzocrown-6 ether receptors. Continuing with aliphatic C–H bond oxidation, Costas demonstrated that fluorinated alcohols promote a polarity reversal on electron rich functional groups, deactivating proximal C–H bonds towards oxidation and directing iron and manganese catalyzed oxidation towards remote positions. The last part was focused on the use of an iron catalyst for the selective *syn*-dihydroxylation of alkenes and the identification of the species responsible for the catalysis. Importantly, the catalytic cycle for these transformations involves Fe(V) species that mimic the reactivity of Rieske oxygenase.


Shannon Stahl

As an inexpensive and environmentally benign oxidant, molecular oxygen is 'the' quintessential oxidant. ***Shannon Stahl*** (University of Wisconsin-Madison) demonstrated that the oxidizing power of O_2 could be captured and channeled to perform alcohol oxidation with remarkable chemoselectivity. He outlined the development of practical methods to perform the aerobic oxidation of alcohols into aldehydes without over-oxidation. In this context, Pd(II) can be used in flow chemistry for kg-scale syntheses, but is not tolerant to many functional groups. On the other hand, Cu(I)/TEMPO constitutes a user-friendly system to catalyze alcohol oxidation at room temperature in a reactor as simple as an open beaker. The substrate scope of this system, highly selective for primary alcohols, is much broader. The substrate scope of the closely-related Cu(I)/ABNO system is even broader and allows the oxidation of both primary and secondary alcohols. On a different note, he showed that the combination of TEMPO and soluble mediators (NO_x) could be used to perform electrochemical oxygen reduction reactions at high potentials.

In the closing remarks, President Véronique Gouverneur warmly thanked all the contributors and concluded that the event had been a great success. Once more, the organizing committee has fulfilled everyone's expectations by maintaining the traditional diversity and the high-quality level of the conference. The 55th edition of the conference will be held next year under the presidency of Janine Cossy.

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The attendees of the 54th Bürgenstock conference.