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Conference Report

The 45th EUCHEM Conference on Stereochemistry (Bürgenstock Conference 2010)

Brunnen, May 2–5, 2010

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Peter Kündig

Hisashi Yamamoto

For the second consecutive year, the EuCheMS Conference on Stereochemistry, better known as the Bürgenstock Conference – was held in the Seehotel Waldstätterhof Hotel in Brunnen situated directly on the bucolic shores of the Luzern Lake, 30 km away from the historical venue. As the night and the rainy clouds were progressively covering the magnificent mountains surrounding the lake, the program of the 45th edition of the Bürgenstock Conference was revealed to the 128 participants gathering in the Fronalp-Saal for an enjoyable reception dinner. From the balcony overlooking the room, the president, Professor ***Peter Kündig*** (University of Geneva), warmly welcomed all the attendees, with particular attention to this year's guest of honor: ***Hisashi Yamamoto*** (University of Chicago), a former lecturer of the conference in 1985. Peter Kündig also emphasized the outstanding scientific program put together by the organizing committee *Don Hilvert* (ETH Zürich)*, Jerôme Lacour* (University of Geneva)*, Reto Naef* (Novartis Pharma AG)*, Philippe Renaud* (University of Bern)*, Jay Siegel* (University of Zurich) and *Helma Wennemers* (University of Basel), with the continued and generous financial support of the Swiss Chemical Society, the Chemistry Platform of the Swiss Academy of Science and 19 chemical and pharmaceutical companies from Europe, Switzerland and the USA. With his characteristic sense of humor, Peter Kündig pointed out to the audience that, as a long-standing tradition of the Bürgenstock Conference, the weather was the responsibility of the vice-president… and maliciously highlighted the British nationality of *Jeremy Sanders* (University of Cambridge).

As may soon become a new tradition in the long history of the Bürgenstock conference, the spectacular scientific program started with the opening lecture on Sunday evening, right after the reception dinner. As chairman of the first session, *Alexandre Alexakis* (University of Geneva) introduced the speaker, ***Andreas Pfaltz*** (University of Basel) who reported on the most recent achievements reached by his group in the design of new catalysts for asymmetric catalysis. In a convincing manner he presented a time-saving screening method for the identification of lead catalyst structures in diverse asymmetric transformations as a promising alternative to existing high-throughput and systematic ligand screening methods. The approach relies on a measure of the enantiomeric ratio by mass spectrometric analysis of mixtures of reactive intermediates (catalyst-bound substrates) rather than on final product analysis. The benchmark Pd-catalyzed allylic alkylation, a convergent kinetic resolution with a favorable kinetic profile, served to establish the validity of the method. On the basis of the microscopic-reversibility principle, the approach was successfully extended to transition metal catalyzed and organocatalyzed retro-Diels Alder reactions. In the second part of his talk, over 15 years of intense research in the elaboration of iridium complexes for the asymmetric hydrogenation of unfunctionalized olefins were summarized, culminating in the identification of a uniquely selective catalyst for the hydrogenation of the unsaturated side chain of tocopherol derivatives relevant in the synthesis of Vitamin E.

Andreas Pfaltz

Dan Yang

The scientific program on Monday morning also started off on a rather 'historical note' featuring, for the first time in the Bürgenstock conference, Chinese and Dutch speakers with an Austrian moderator within the same session, as cheerfully pointed out by chairman *Dirk Trauner* (University of Munich). On the Chinese side, ***Dan Yang*** (Hong Kong University) delivered a spectacular talk on aminoxy acids as building blocks for the efficient construction of artificial ion channels. The rigidity introduced by the N–O bond both in α- and β-aminoxy acids compared to natural amino acids allowed the Yang group to achieve novel secondary structures independent of the side-chains such as turns and helices. Yang presented successful examples of the use of such motifs in the formation of chloride channels not only in liposomes but also in cellular settings. Even if still far from having a clinical application, the potential of these artificial channels to modify the membrane potential and regulate the Ca^{2+} intake promises interesting discoveries in the near future.

Following the coffee break, ***Wilfred van der Donk*** (University of Illinois) gave an insightful presentation on genome-assisted methods for natural product synthesis. His group is one of the pioneers in the use of gene-based techniques to access larger and more diverse natural products libraries, in contrast to the classical natural product isolation campaigns. Two successful examples were disclosed dealing with lantibiotics and phosphonate antibiotics respectively. Lantibiotics are structurally challenging polypeptide molecules, which are synthesized by the ribosome in a

Wilfred van der Donk

linear form and then extensively post-translationally modified to their active forms. These modifications introduce a thioether-containing cross-linked amino acid called lanthionine (Lan). His group has recently succeeded in the first *in vitro* biosynthesis of a member of the lantibiotic family, lacticin 481 and 11 non-natural analogues using an *in vitro*-reconstituted lacticin 481 synthetase in conjunction with synthetic peptide substrates containing nonproteinogenic amino acids. Interestingly, two of these synthetic analogues surpassed the activity of the natural product.

Among the 15 posters of the first session, five were selected for short oral presentations. Thanks to the generous support of the Swiss Chemical Society and the Chemistry Platform of the Swiss Academy of Science in Switzerland, this gave the opportunity to some of the most promising European young scientists to give a taste of the most recent developments achieved in their respective laboratories on various topics such as molecular recognition to direct functional materials along DNA scaffolds (*Glenn Burley*, University of Leicester); iridium catalyzed asymmetric isomerization of primary allylic alcohols (*Clément Mazet*, University of Geneva); total synthesis and biological evaluation of iriomotelide-3a and analogues (*Cristina Nevado*, University of Zürich); natural products and their biological targets (*Stephan Sieber*, Technische Universität München) and residual dipolar couplings as novel NMR parameters for structure determination (*Christina Thiele*, Technische Universität Darmstadt). The short oral communications were followed by a lively and relaxed two-hour poster session involving all participants along with the appropriate beverages.

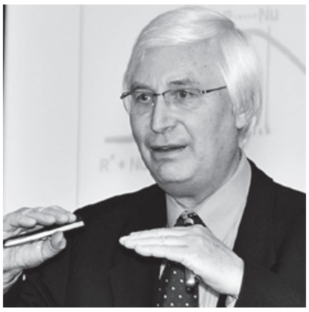
Viresh H. Rawal

Moving back to synthetic organic chemistry, moderator *Shun-Ichi Muarashi* (Okayama University of Science) introduced ***Viresh H. Rawal*** as the speaker of the second evening session. Rawal described how his group systematically utilizes hydrogen bonding as a design element for the elaboration of new organocatalysts for various classes of asymmetric transformations. Rawal summarized a long journey in this field which started with the initial observation that protic solvents in general and alcohols in particular have an accelerating effect on challenging hetero Diels-Alder reactions between Kozmin's diene and notoriously unactivated ketones. This led to the development of a first family of H-bond donor catalysts designed around a privileged one-point binding Taddol structure and later around two-point binding catalysts articulated on a modular squaramide backbone. The desymmetrization of the latter also allowed the installation of pendant amine functionalities for dual activation catalysis. Benchmark Diels-Alder reactions, challenging hetero-Diels-Alder reactions and several variants of Mukayama aldol additions served to validate the design elements and rationales based on X-ray crystallography for both families of catalysts. In all cases, impressive reactivity, diastereoselectivity and enantioselectivity were consistently attained.

The morning session on Tuesday was chaired by this year's vice-president, *Jeremy Sanders*. In both a scholarly and enthusiastic manner, ***Eric Anslyn*** (University of Texas) described a fascinating strategy to develop high-throughput screening methods for asymmetric catalytic reactions that rely on supramolecular analytical chemistry and, in an echo to Andreas Pfaltz's lecture, may offer attractive alternatives to the widespread HPLC and GC techniques. The Anslyn group has developed a user-friendly microwell plate format kit using enantioselective indicator displacement assays to determine the *ee* of diols and α–amino acids. A related technique relying on MLCT transitions in CD spectroscopy was also developed to fingerprint the chemical identity, the concentration and the *ee* of various chiral 1,2-diamines upon interaction with either enantiomer of $[Cu(BINAP)(CH_3CN)_2]^+$. To showcase supramolecular chemistry as a mimic taste or olfaction, application in real-life samples led to the creation of a training set for the identification of saccharides in beverages using tea sweetened with Splenda®. Similarly, displacement based assay arrays can be used to 'fingerprint' tannins in wine and serum albumin arrays can be used to characterize complex fragrance mixtures.

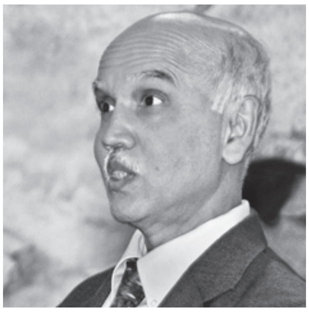
Eric Anslyn

The second part of the session featured the outstanding talk from ***Herbert Mayr*** (Ludwig Maximilian University Munich). Over the past 30 years, the Mayr group has devoted its efforts to the development of semi-quantitative approaches to polar organic reactivity scales. The first steps in the elaboration of such scales involved the recognition of the reaction intermediates. His group focused on benzhydrylium cations generated during the Lewis acid addition of benzylic halides to alkenes. In an effort to make the information accessible and useful to the community of synthetic chemists, a single scale has been constructed by applying parametrization for both nucleophiles and electrophiles, and correlation analyses. After presenting several applications of such scales (*e.g.* nucleophilic reactivities of phosphorous ylides and phosphoryl-stabilized carbanions, electrophilicity of iminium ions in organocatalyzed processes), Mayr focused on the analysis of substitution reactions where the nucleophilic attack does not necessarily take place at sp^2 hybridized carbon atoms. His work has been able to reconcile both the Ritchie and Swain-Scott equations, which now can then be seen as particular cases of the Mayr equation.



Herbert Mayr

Following an afternoon reserved for work, recreation or sightseeing, last year's president, *Ben L. Feringa*, had the privilege to chair Tuesday's evening session and to introduce ***G. K. Surya Prakash*** (University of Southern California). Professor Prakash gave an impressive overview of the research activity in his laboratory and presented the development of new reactions utilizing fluorinated reagents. In the presence of a catalytic amount of an initiator (a fluorine anion donor such as TBAF or TBAT), $TMS-CF_3$ was used for the nucleophilic addition of trifluoromethyl anion to various ketones and imines. The very same electrophiles were employed to demonstrate the transferability of $-CF_3$ and $-CF_2CF_3$ fluoroalkyl chains using sul-



G. K. Surya Prakash

fur-based reagents. Equally impressive was the stereoselective monofluoromethylation of primary and secondary alcohols by using a monofluro-bis(phenylsulfonyl) derivative as fluorocarbon nucleophile in a Mitsunobu-type reaction. A detour in asymmetric catalysis led to the development of a highly enantioselective organocatalytic hydroxyalkylation of indoles with ethyl trifluoropyruvate using either cinchonine or cinchonidine as chiral catalyst. Professor Prakash also presented new electrophilic monofluoro- and difluoromethylating reagents that were successfully applied to a variety of carbon, sulfur, oxygen, nitrogen and phosphorus nucleophiles.


Matthew Gaunt

Per-Ola Norrby (University of Gothenburg), one of the most active discussion participants of the conference, was delighted to moderate the morning session on Wednesday. The first speaker, ***Matthew Gaunt*** (University of Cambridge), not only presented some of his most recent results on site-specific aromatic and heteroaromatic C–H bond activation, but – much in the spirit of the Bürgenstock conference – he shared with a captivated audience an incredible amount of unpublished and unexpected exciting results. For instance, the challenge to sequentially and specifically activate all positions of an indole was used to illustrate the general philosophy of the Gaunt group who stated that "as chemists we have the capacity to design reactions that go beyond Nature's ability'. Most of the directed C–H activation reactions presented were run under relatively mild conditions and relied on the use of hypervalent iodine reagents in conjunction with the appropriate palladium or copper sources. More unexpectedly perhaps, it was found in certain cases that meta-selective C–H activation could also be performed without copper or any other Lewis acid present.


Tamejiro Hiyama

The second morning speaker, ***Tamejiro Hiyama***(Chuo University, Tokyo) delivered a fabulous talk focused on the development of new synthetic strategies for C–C bond formation. First, he disclosed the new optimization of the already 'classic' Hiyama Pd-catalyzed cross coupling reaction of halides with novel silicon derivatives, named HOMSi in honor of the French post-doc who developed them within his group. These novel silicon species can efficiently transfer alkenyl and aromatic groups to α,β-unsatured ketones using rhodium catalysis, also in an enantioselective manner. In the second part of his talk, Hiyama presented the use of nitriles in carbocyanation reactions mediated by nickel. A broad array of transformations was shown dealing with the oxidative addition of nickel to C-CN bonds, followed by the insertion of alkenes and alkynes, highlighting the synthetic potential of nitriles and nickel catalysis.

The second poster session gathered 22 posters. This was an opportunity for five more established scientists to share their most recent results: *Sofia Barluenga* (University of Strasbourg; 'Resorcylic acid lactones: a pluripotent scaffold with therapeutic potential'), *Maurizio Benaglia* (University of Milano; 'Stereoselective direct Aldol-type reaction catalyzed by chiral biheteroaromatic diphosphine oxides'), *Krishna Kaliappan* (IIT Bombay; 'A formal total synthesis of Palmerolide A'), *Yixin Lu* (National University of Singapore; 'Development of primary amino acid-based enantioselective organocatalytic synthetic methods') and *Per-Ola Norrby* (University of Gothenburg; '18e R.I.P'). All the participants then joined the poster session in the Rütli-Saal of the Waldstätterhof Hotel, prolonging the lively discussions for more than two hours.


Laura Kiessling

The evening session, moderated by *Kai Johnsson* (EPF Lausanne) featured the stunning lecture from ***Laura Kiessling*** (University of Wisconsin – Madison) on carbohydrate polymer assembly. Carbohydrate polymers are the most abundant organic compounds and intriguingly enough they are composed of a distinct number of monomeric residues. How these polymers are assembled, why each has a particular length and whether this can be used to attack the highly resistant cell-wall of mycobacteria was the major focus of Kiessling's talk. First, she presented studies on a key isomerization step performed by the UGM flavoenzyme. For the first time, her group has confirmed that the enzyme uses a reduced version of the flavone, which reacts as a nucleophile capturing sugar and liberating UDP via a flavine-iminium intermediate, implying an unprecedented nucleophilic character of the flavone at N5. Her group has also shown that this enzyme is a valid target in trying to inhibit the mycobateria growth, which guarantees further interesting developments in this field.


Ronald Raines

Mikiko Sodeoka (RIKEN Advanced Science Institute) introduced both speakers on Thursday morning, a session centered on structural chemical biology. The first speaker, ***Ronald Raines*** (University of Wisconsin – Madison) explained how his group is interested in identifying unappreciated inductive effects that are responsible for a protein's stability rather than more classical interactions (Coulombic interaction, covalent bonding, H-bonding…). The triple helix of the most abundant protein in animals – collagen – was used as a fundamental platform for their systematic investigations. In particular, the Raines group explored in detail the salient stereochemical features responsible for the high prevalence of (2*S*)-proline (Pro) and (2*S*,4*R*)-4-hydroxyproline (4*R*-Hyp) in each strand of the helix. On the basis of NMR measurements, density functional calculations and CD spectroscopy, they disclosed that the ring pucker of a pyrrolidine ring can be influenced by electronegative substituents. In particular, the gauche effect stabilizes the C^{γ}-*exo* pucker form. Similarly, an additional $n\ \pi^*$ interaction enhances collagen stability by favoring the requisite *trans* conformation of the hydroxyprolyl peptide bond. Not only is this subtle stabilizing interaction reconciling calculations and experiment, but it is also expected to have implications in the initial folding of helices, in the increased cooperativity in helix formation, in conduit formation for faster tunneling and in enhanced protein formation.

The second speaker, ***Raymond Stevens*** (Scripps Research Institute) delivered a vibrant lecture outlining some of the major challenges faced in structural biology. Over the past twenty years, his group has focused on the largest family of transmembrane proteins, the G-protein coupled receptors. GPCRs are major contributors to the information flow into cells, but have been so far elusive to crystallographic structure determination. His talk showcased how long-term scientific commitment is often crucial for success: after almost two decades without results, in the past five years his group has been able to solve several key GPCRs structures such as Human B2 adrenergic and the A2a adenosine receptor. Interestingly, cholesterol molecules are consistently present in the *trans*-membrane region of these proteins. As a take-home message, Raymond highlighted how the knowledge acquired over the past years will now streamline not only the resolution of new members of this family, but also the design of molecules for interacting with these relevant biological targets.


Raymond Stevens

On Thursday evening the participants had the privilege to attend to a wonderful chamber music concert by the *Asasello Quartet*. *Rostislav Kojevnikov* (violin), *Barbara Kuster* (violin), *Justina Śliva* (viola) and *Wolfgang Zamastil* (cello) performed a subtle selection of compositions from Karol Szymanowski (String Quartet Nr. 1 C-Dur, Op. 37), Alexander Borodin (Notturno from the 2nd String Quartet) and Ludwig van Beethoven (String Quartet F-Dur, Op. 59/1 'Rasumowski'). This enjoyable moment was followed by a post-concert get-together with the musicians in the Fronalp-Saal.


Jeffrey Bode

With *Jérôme Lacour* chairing the first morning session on Friday, and the presentation of ***Jeffrey Bode*** (ETH Zürich) the organizers expected to revitalize some of the audience after the extended get-together from the preceding night. As many other speakers in this 45th Burgenstock conference, Bode shared a rather recent and exploratory project. Inspired by mythology, where creatures could mutate their appearance (but also by more modern mutation examples, as the Barbapapa cartoons), his group has been trying to develop new chemistry and applications for shape-shifting molecules. Using bulvallene as primary scaffold, Bode showed how dynamic libraries can be implemented and potentially used as temperature, solvent or even C_{60} sensors. Beyond the applications, his group is also exploring the stereochemical features in such dynamic systems: his results, even if preliminary, present a rather complex energetic panorama for the racemization of enantiomerically enriched species, since some pathways are energetically accessible but many others are not.


Peter Wipf

The honor to close the scientific sessions was awarded to a Swiss chemist, ***Peter Wipf*** (Pittsburg University). Following the introduction by *Emmanuel Theodorakis*, Wipf presented numerous examples of his group's efforts towards the total synthesis of complex natural products. He showed how target-oriented synthesis reaches its best when applied to highly potent biologically active molecules, as in the Disorazole family of natural products. Disorazoles are recognized nM or even pM antimitotic agents and their synthesis and biological evaluation have fostered his group's efforts over the past ten years. In the second part of his talk, inspired by Greek mythology and the chimeras, Wipf presented the design and synthesis of hemigramicidin-TEMPO conjugates featuring segments of the antibiotic gramicidin S as inhibitors of oxidation processes that occur at the mitochondria. The direct tethering of 4-amino-TEMPO to a shortened peptide isostere sequence provided a lead that can serve as potent radioprotector and radiation injury mitigator.

On the behalf of the organizing committee*, Philippe Renaud* warmly thanked all the speakers, chairmen and participants for their presentations and fruitful discussions. A special mention – along with a gift – was given to the six assistants: *Rebecca*, *Simon*, *Martina*, *Carsten*, *Ajoy* and *Audrey* who managed to set up the presentations, take pictures, coordinate the names and interventions of the participants with discretion and professionalism. This year guest of honor, *Hisashi Yamamoto*, received a special bottle of white wine, containing the sun that had been missing during the conference. The vice-president *Jeremy Sanders* took over the stage to receive not only another bottle of sunny-wine but also an umbrella commemorating his efforts to control the rain during the time of the conference. The president, *Peter Kündig* acknowledged in his final remarks the other members of the organizing committee for their devoted efforts, which made his presidency fully enjoyable. Finally, it was announced that Professor *Andreas Pfaltz* will be the next vice-president for the Bürgenstock conference to be held again in Brunnen in May 2011.

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