Thematic Variations on Stereochemistry: Bürgenstock, the 45th!**

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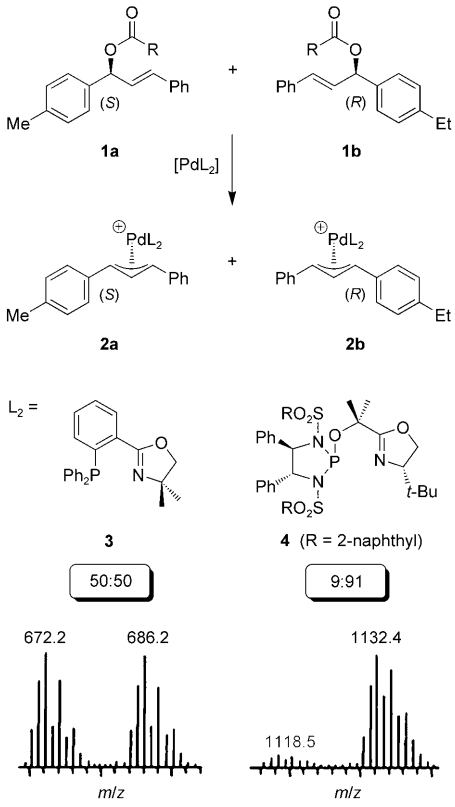
Who would still buy the proverbial pig in a poke these days?

This question could be asked considering the rules of this world-renowned EUCHEM Conference on Stereochemistry, which has not changed in the last 45 years. Both the identity of the lecturers and their topics remain a tightly kept secret until the start of the conference. Only one thing is almost certain: No scientist gets the chance to lecture more than once at this symposium in his or her lifetime. But it is precisely rules like these which make the Bürgenstock Conference so attractive; add to the thrill of attending it and guarantee that its high scientific standards never wane from year to year. The conference's rules also discourage certain deplorable customs, such as attending symposia lasting several days for a single day only or purely to give one's own presentation: All of the around 120 participants, a potpourri of young and old hailing from both academia and industry had been asked to be present for the entire duration.

President E. Peter Kündig (University of Geneva) and his organizing committee, consisting of Don Hilvert, Jérôme Lacour, Reto Naef, Philippe Renaud, Jay S. Siegel, and Helma Wennemers, had compiled a program comprising 14 presentations and two poster sessions, which interpreted the general theme of the conference in different ways. At the beginning of the conference, the President welcomed the participants and especially the guest of honor Hisashi Yamamoto (University of Chicago).

The scientific presentations commenced that first evening with a lecture by Andreas Pfaltz (University of Basel), who presented studies on asymmetric catalysis. He dealt with both a screening of catalyst mixtures and highly selective hydrogenation reactions on unfunctionalized olefins with cationic iridium complexes.[1] The first part of the lecture in particular was greeted with enthusiasm. A lively discussion followed, as the catalyst screening utilizing ESI-MS gives way to unforeseen possibilities. For the screening, Pfaltz uses quasi-enantiomeric substrates (for example **1a**/**1b**). The catalytic intermediates **2a**/**2b** can easily be distinguished by MS to determine the intrinsic enantioselectivity of chiral catalysts (Scheme 1).[2]



Scheme 1. Determination of the intrinsic enantioselectivity of chiral catalysts by ESI-MS screening.

Hydrogen Bonds as cantus firmus...

During the first morning lecture, Dan Yang (University of Hong Kong) demonstrated the use of aminoxy acids for the construction of new peptidomimetic foldamers. The conformational rigidity of the N–O bond and the excellent stability towards proteases play decisive roles. Unusual motifs of hydrogen bonds lead to hybrids of α helices and β sheets that enable access to astonishing molecular architectures of artificial self-assembling ion channels.[3] Immediately afterwards, Wilfried A. van der Donk (University of Illinois) spoke about his genome-supported research for the biosynthesis of natural products. Using the lantibiotics, a class of polycyclic, strongly post-translational modified

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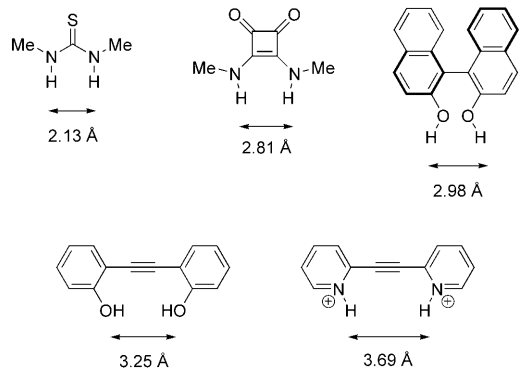
peptides with anti-microbiotic activity as an example, he discussed the role of leader peptides and natural combinatorial biosynthesis.[4] Viresh H. Rawal (University of Chicago) also talked about hydrogen bonds in the later evening lecture. He sought to convince the auditorium that such interactions, despite being quite weak, have become a crucial instrument for asymmetric catalysis. Rawal has succeeded in producing astounding reactivities and selectivities in a number of reactions, such as Mukaiyama aldol, Hetero Diels–Alder, or Friedel–Crafts reactions by making use of intelligent hydrogen bond motifs.[5] Therein organocatalysts derived from taddol and thiourea and also squaric acid amides and other more unconventional motifs, with which the distance between hydrogen atoms can be easily varied, play a prominent part (Scheme 2). In the subsequent discussion, the idea to utilize protonated binap in the place of protonated pyridine derivates was brought up.



Scheme 2. Several organocatalysts as two-point hydrogen donors and corresponding distances between the respective hydrogen atoms.

Physical Organic Chemistry

Physical organic chemistry was a core area dealt with at the conference. Eric V. Anslyn (University of Texas at Austin) pursued the question of what sensors actually are. He elucidated a great number of differential sensing methods, some of which being based on a variation of fluorescence and the circular dichroism. The audience was particularly fascinated by his research on terpenes in perfumes and on tannins in various red wines. Instead of undertaking the extremely difficult and time-consuming task of synthesizing specific receptors, Anslyn uses proteins such as BSA and a binding fluorescence indicator for his terpene analysis. The varying behavior exhibited by the terpenes as they bind to BSA along with a corresponding analysis of the fluorescence responses permits an unambiguous assignment of various terpenes even in complex mixtures.[6]

In the following presentation, Herbert Mayr (LMU Munich) highlighted basic questions of polar organic reactivity. Ever since the 1980s, Mayr has been involved with semi-quantitative predictions of rate constants in polar organic reactions. His comprehensive model uses only two parameters, namely a nucleophilicity and an electrophilicity parameter.[7] In this way Mayr has shown that even reactions that do not occur and diffusion-controlled reactions which proceed very rapidly can be explained through a combination of these two parameters. Deviations from this correlation can indicate an alternative reaction mechanism.

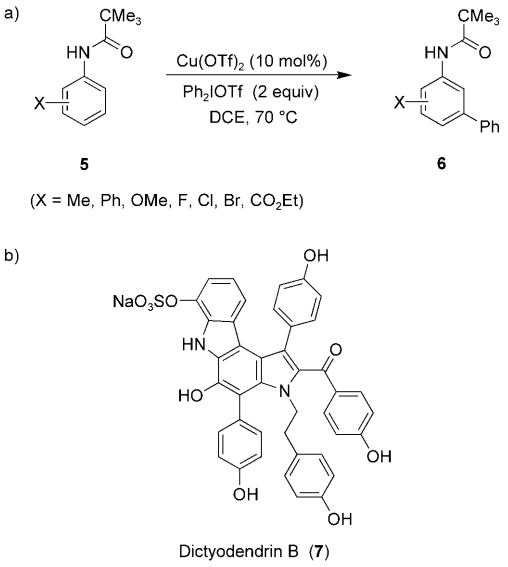
The fact that fluorination methods are not just a recent trend but have been developed for decades was made clear in the presentation by G. K. Surya Prakash (Loker Hydrocarbon Research Institute) entitled "*Fluorine, a Small Atom with a Big Ego*". Starting from physical organic problems concerning non-classical carbocations, a large number of new fluoroalkylation methods have been developed.[8] Here, too, the physical organic portion was in no way cut short, as structural peculiarities of an α-fluoro carbanion were dealt with in ample measure.[9]

Organic Synthesis and Catalysis

New catalytic strategies for chemical synthesis were implemented by Matthew Gaunt (University of Cambridge). Inspired by the electronic similarity between palladium(II) and copper(III), he has developed a wide range of impressive copper-mediated C–H bond activations, such as selective arylations of indols[10] and a *meta*-selective arylation of anilides **5** utilizing Ar_2IOTf as arylating agent (Scheme 3a).[11] These and related metal-catalyzed C–H bond activations are also applied on the way towards the total synthesis of dicytodendrine B (**7**), a persubstituted indole derivative (Scheme 3b).

Innovative reactions for the formation of C–C bonds were the main topic of the talk by Tamejiro Hiyama (Kyoto University). Having initially dwelt on the palladium-catalyzed Hiyama coupling, the speaker soon turned towards the use of nickel-derived catalysts. In this area, he presented his recent results on carbocyanation reactions[12] of alkenes and alkynes and C–H bond activations of pyridines.[13]

The question of how mycobacteria provide the synthesis of a carbohydrate polymer was addressed by Laura L. Kiessling (University of Wisconsin) in the evening lecture on this rather synthetically oriented day. The focus was on two problems: In the first, Kiessling has looked into how galactopyranose is isomerized into the galactofuranose that is essential for mycobateria. In this process, a flavine next to the active center in the corresponding



Scheme 3. a) *Meta*-selective C–H bond activation of anilides (DCE = 1,2-dichloroethane, OTf^- = trifluoromethanesulfonate); b) persubstituted indol derivative dictyodendrin B.

UDP–galactopyranose mutase is mandatory.[14] On the other hand, the question of how the length of carbohydrate polymers can be biochemically controlled was investigated.[15] The postulated increase of conformational entropy in the polymer chain was discussed as a cause of the dissociation and the termination of the polymerization.

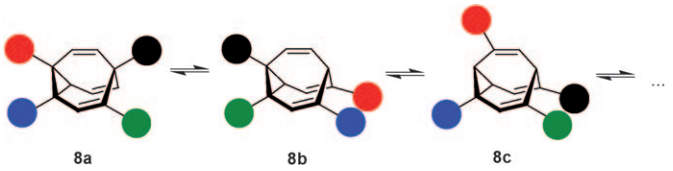
From Stereoelectronics via Structural Biology and Back to Synthesis

The second-to-last day was marked by biochemical matters. Ronald T. Raines (University of Wisconsin) revealed that thorough stereoelectronic knowledge is a must for biochemical understanding. Gauche effects in hydroxyproline and $n \rightarrow \pi^*$ interactions between lone pairs of oxygen with amide functionalities permit a high pre-organization of collagen strands.[16] In inserting isosteric moieties in peptides, a high degree of caution is necessary; secondary structures may change substantially.

In a lecture strongly oriented towards structural biology, Raymond C. Stevens (Scripps Research Institute) spoke about the structure and function of receptors of the GPCR superfamily. These receptors appear in multiple conformational states. Biologically, this is an advantage, but it turns out that their examination is highly challenging. Despite this, Stevens was able to perform striking studies towards structural determination.[17] The significance of this work was made apparent to the audience when it was pointed out that approximately half of all current therapeutics interact with GPCR proteins.

On the final day, Jeffrey W. Bode (ETH Zurich) talked about stereochemistry of organic molecules that are able to shift their shape. The issue of shape-shifting—even on a non-molecular level—has fascinated mankind since antiquity and has frequently found its way into mythology, as Bode pointed out at the beginning of his talk. Multisubstitution of bullvalene **8**, which undergoes Cope rearrangement, provides access to molecules with varying shapes (Scheme 4).[18] Four different substituents enable the generation of approximately 800 different isomers, whereas eight different substituents produce as many as 1.2 million compounds. Therefore, the potential of the bullvalene scaffold for pharmaceutical research was also debated.

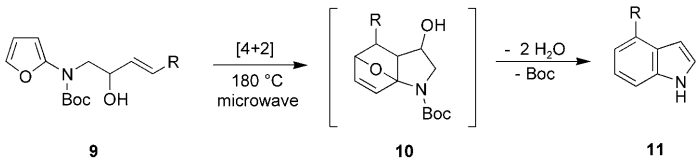
The final lecture was delivered by Peter Wipf (University of Pittsburgh); he presented highlights



Scheme 4. Dynamic combinatorial library of shape-shifting bullvalene derivatives.

of his total syntheses. To build up indol moieties **11**, he makes use of a highly elegant intramolecular Diels–Alder reaction with furan (Scheme 5).[19] He also stirred the listeners' imaginations by presenting peptides that are conjugated to the stable nitroxide radical TEMPO and demonstrate great affinity to the membrane of mitochondria.[20] At least as far as the mouse model is concerned, these substances are able to decrease the speed of the aging process significantly.

Stereochemistry—and this was shown yet again most illuminatingly during the conference—is the basis of the entirety of organic and bioorganic chemistry. What began with the extraordinary simple model of tetrahedral carbon, which is still displayed on the conference logo today, has grown



Scheme 5. Diels–Alder approach to 4-substituted indoles. Boc = *tert*-butoxycarbonyl.

up to be more complicated and far less easily graspable. But it is precisely in this that the fascination lies—not just the fascination of chemistry in general, but also the fascination of this conference in particular. I am convinced that the president in 2011, Jeremy K. Sanders (University of Cambridge), and his organizing committee will reinterpret stereochemistry—the most basic subject of organic chemistry—in new and interesting ways. That the contributions will be of the highest quality is already a given.

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