Over 130 chemists attended the Bürgenstock resort for the 39th ESF/EUCHEM Conference on Stereochemistry between 17th - 23rd April 2004. This year’s president, Herbert Waldmann (MPI Dortmund), and the Organizing Committee of Hans-Beat Birg (University of Bern), François Diederich (ETH Zürich), E. Peter Kündig (University of Geneva) and Klaus Müller (F. Hoffmann-La Roche, Basel) prepared a spectacular line-up of science. Also, the vice president, Alain Krief (University of Namur), and the Guest of Honor, Ekkehard Winterfeldt (University of Hannover), each played their special responsibilities. The highlights of the conference are described below.

The second day of lectures began with a stunning presentation by Jonathan Ellman (University of California, Berkeley). The first part of his talk detailed the development of a new method for the asymmetric synthesis of amines by the addition of nucleophiles to terminal butyl sulfinyl imines. The sulfinyl group acts both as a chiral auxiliary and a protecting group, with removal from the amine products being readily achieved by treatment with HCl–MeOH. A large number of illustrative examples were presented and the versatility of this new methodology was very clearly demonstrated. Imines derived from ketones could be deprotonated (LDA, MgBr2) and used in a nucleophilic sense in reactions with suitable electrophiles. In addition to the asymmetric synthesis of “simple” amines, this chemistry was applied to the synthesis of more complex targets such as 2,2-disubstituted-3-amino acids and to the solid-phase synthesis of the natural products pavine and isopavine. The second part of the presentation concerned the development and use of novel catalysts in multi-component asymmetric catalysis in multi-component processes being the main focus of attention. The lecture began with the use of transition metal catalysis in multi-component systems that will certainly require a number of textbooks to be rewritten!

The third day of the conference started with a presentation by Roger S. Goody (MPI Dortmund) which began with the use of transition metal catalysis in multi-component systems. The focus of the next presentation by Ekkehard Winterfeldt (University of Bern) was on the structural biology of proteins that use heme as a prosthetic group. Changing tack, the dimeric multidomain nitric oxide synthases were discussed in depth. Again the substrate binding sites explain isoform specificity, for example inducible NOS and neuronal NOS differ in amino acid residues lining the substrate binding channel so that the drug AR-R17477 can bind selectively.

The fourth day of lectures began with a talk by Michel Rohmer (Université Louis Pasteur, Strasbourg) which presented an excellent first day of lectures to a close with a fascinating presentation regarding terpenoid biosynthesis. Until recently it was believed that all isoprenoids were biosynthesised via the mevalonate pathway, and in most cases this could be shown unambiguously via isotope labelling experiments using 13C-acetate as the carbon source. In some cases however, “unusual” labelling patterns and low incorporation levels were observed in bacteria and this was difficult to explain. During work on the hopane family of natural products it was noticed that terpene-derived and sugar-derived fragments were linked in a number of structures and a series of labelling experiments were performed using 13C-glucose as the carbon source. High incorporation levels were achieved and this meant that an alternative non-mevalonate pathway was being used by the bacteria. Following some very elegant and extensive work a completely new isoprenoid biosynthetic pathway was uncovered which uses methyl erythritol phosphate (MEP) as the key 5-carbon building block. This MEP pathway has now been identified in chloroplasts, green algae and eubacteria and this will almost certainly require a number of textbooks to be rewritten!

The first presentation of the conference was given by Eike Schlichting (MPI Heidelberg) as part of a special symposium on carbon fluxes in plastids. Eike started off the Scientific Plenary with a talk focusing on the MEP pathway, which uses methyl erythritol phosphate (MEP) as the key 5-carbon building block. This MEP pathway has now been identified in chloroplasts, green algae and eubacteria and this will almost certainly require a number of textbooks to be rewritten!

The second presentation of the conference was given by Jonathan Ellman (University of California, Berkeley). His talk detailed the development of a new method for the asymmetric synthesis of amines by the addition of nucleophiles to terminal butyl sulfinyl imines. The sulfinyl group acts both as a chiral auxiliary and a protecting group, with removal from the amine products being readily achieved by treatment with HCl–MeOH. A large number of illustrative examples were presented and the versatility of this new methodology was very clearly demonstrated. Imines derived from ketones could be deprotonated (LDA, MgBr2) and used in a nucleophilic sense in reactions with suitable electrophiles. In addition to the asymmetric synthesis of “simple” amines, this chemistry was applied to the synthesis of more complex targets such as 2,2-disubstituted-3-amino acids and to the solid-phase synthesis of the natural products pavine and isopavine. The second part of the presentation concerned the development and use of novel catalysts in multi-component asymmetric catalysis in multi-component processes being the main focus of attention. The lecture began with the use of transition metal catalysis in multi-component systems that will certainly require a number of textbooks to be rewritten!
coupling reactions (MCRs) with amido-carbonylation being an excellent example. This MCR involved the condensation of an aldehyde with an amide, followed by a transition metal-catalysed carbonylation reaction to provide amino acid products. In a related MCR, condensation of \( \alpha,\beta \)-unsaturated aldehydes with alkyne-containing amides produced dienes, which were utilised in a subsequent Diels–Alder cycloaddition. The resulting cyclohexene was used as a substrate for a Pauson–Khand reaction to afford the core structure of dendrobine. A wide range of other catalytic processes were described and these included activation and carbonylation of aromatic and heteroaromatic chlorides using a range of palladium-based catalyst systems. The catalytic conversion of aromatic halides into aromatic nitriles was a particularly fascinating reaction, with non-toxic \( \text{K}_2\text{Fe(CN)}_6 \) acting as the source of cyanide. The use of this reagent overcomes the problem of cyanide anion deactivation of the palladium-based catalyst system.

The lecture ended with an extremely efficient synthesis of l-octene. This catalytic process proceeded with turn over numbers of \( 1 \) 500 000 and this example was a fitting way to demonstrate the power of modern catalytic processes.

**Nicholas E. Leadbeater** (University of Connecticut) gave a very entertaining overview of a range of transition metal-mediated processes that were accelerated by the use of microwave irradiation. The nickel-catalysed Finkelstein reaction for aromatic halides and palladium-catalysed Suzuki reactions were notable highlights. He then went on to describe the discovery of a number of transition metal-catalysed processes that could be performed in the absence of the transition metal! The story behind these unusual and intriguing observations was described and some preliminary ideas about possible mechanisms for these transformations were presented.

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\begin{align*}
\text{B(OH)}_2 + \text{Br} & \rightarrow \text{TBAB} \rightarrow \text{Na}_2\text{CO}_3 \\
\text{H}_2\text{O} & \text{microwave} \rightarrow 98\%
\end{align*}
\]

In the second lecture of the Monday afternoon session, **Milton R. Smith III** (Michigan State University) presented his work on the development of an iridium-based catalytic borylation reaction. This remarkable process involves selective C–H activation of the transition metal! The story behind these unusual and intriguing processes can be used to protect molecular wires and encapsulate dyes. In particular, rotaxanes and polyrotaxanes were used to produce "insulated" materials with the thread being shielded from degradation by the presence of a macrocyclic sheath. Dye-containing threads were protected from chemical and photochemical bleaching thus enhancing the useful lifetime of these materials. In a related study, Suzuki couplings were also used to construct rotaxanes with stilbene-based threads and these materials showed enhanced fluorescence yields. E/Z isomerisation of the stilbene thread was also possible and this resulted in unidirectional shuttling of the cycloextrin macrocycle along the thread. Conjugated polyrotaxanes could also be synthesised using phosphine-free Suzuki couplings and these materials showed significant fluorescence enhancement. Preliminary experiments exploring the behavior of these new materials for use in electroluminescent light-emitting diodes were also described.

The penultimate day of the conference was a rich display of state-of-the-art chemical biology starting off with **Kazunari Taira** (University of Tokyo). The talk began with an enlightening discussion of ribosome technology and the problems with designing intracellularly active ribozymes. Fundamental studies were described of oxygen replacement by sulfur to identify catalytically critical positions in the hammerhead ribozyme. The use of ribozymes in exploring gene function was convincingly conveyed. Since mRNA secondary structure is difficult to predict, because it does not take account of RNA binding proteins, ribozyme activity could be dramatically increased by attaching a RNA helicase to the ribozyme. Gene discovery by these hybrid ribozymes was illustrated by the identification of target genes with a pro-apoptotic function. Combinatorial synthesis of ribozyme sequences generated randomised ribozymes that were screened in a chemotaxis assay.

**Atsushiro Osuka** (Kyoto University) delivered the first lecture on the "materials day" of the conference and he treated the audience to a truly magnificent display of modern porphyrin chemistry. The lecture began in relatively modest style by describing how two porphyrin units could be linked with the use of AgPF$_6$ to generate novel dimeric structures. The steres were raised considerably, however, when it was demonstrated that these dimeric structures could then be linked to generate tetrameric porphyrin, and the resulting tetramers could be linked to generate novel linear octameric porphyrin-based structures. This iterative chain growth could be repeated time and time again and it was possible to generate single oligomeric molecules comprised of 1024 meso–meso linked porphyrins of between 0.1 and 0.8 \mu m in length! These materials could then be oxidised with DDQ to afford extended flat, linear arrays that possessed electronic excitation in the IR region of the electromagnetic spectrum! The synthesis of a range of other porphyrin-based materials was described, but perhaps the most fascinating were the meso-aryl expanded porphyrins. In one case a macrocyclic octaphrin structure displayed "molecular mitosis" and divided to produce two daughter porphyrins as products.

**Matthew D. Shair** (Harvard University) concluded the second day of lectures with a blend of natural product target synthesis and novel synthetic methodology. The first part of the lecture described an elegant total synthesis of the heptacyclic natural product \((-\)\) longithorone A using a strategy that was based around its proposed biosynthesis. The synthesis relied upon the enantioselective construction of two fragments that could then be united in an intermolecular-Diels–Alder reaction. Following the intermolecular cycloaddition, an oxidation and a transannular Diels–Alder reaction afforded the heptacyclic core. This synthesis provided an excellent example of how stereochemistry can be relayed from existing chiral centres to new chiral centres via the intermediacy of atropisomeric intermediates. The second half of the lecture regarded the development of novel methodology for the synthesis of polyketide derived targets. Taking inspiration from polyketide biosynthesis, a new catalytic decarboxylyative aldol reaction was developed using malonic acid half-thioesters as the nascent nucleophiles. The copper (ii)-catalysed process could be run under ambient conditions and was tolerant of exposure to both water and air.
assays revealed that small RNA sequences originating from the so-called “junk” (non-coding) DNA regions were important in gene regulation. siRNA technology could be used to induce gene specific silencing in mammalian cells, and the presentation included a portrayal of advanced vector-based siRNA (small hairpin RNA) interference that have a markedly reduced interferon response. The audience was left convinced of the importance of small RNA technology in many areas of cell biology, such as neurons, tumour genesis, apoptosis, immunity and aging.

After gaining our collective breath again Michael Fumulok (University of Bonn) continued the RNA theme by describing the use of ribozymes for drug screening. Loss of function phenotypic analysis using transgenic knockouts, antisense oligonucleotides, intracellular ribozymes or siRNA can only tell us so much about the function of gene products. Even with these important techniques questions such as “Is the protein gene product druggable?” are still difficult to answer. For example what functional roles do sub-domains and post-translational modification play? A process to rapidly identify ligands to target proteins could be obtained by in vitro selection and delivered into cells with a transgenic virus or lipofectin. The intracellular aptamers (intramers) were illustrated in pathways and disease states as diverse as tumours, memory, apoptosis, cell differentiation, immune response, and hypertension. Rather than using genetics or RNAi technology, the use of small molecules allowed immediate-early effects, rather than steady-state effects, of a kinase to be identified. The major problem with a small molecule approach is that there are not enough specific small molecule kinase inhibitors known. No problem; by changing the highly conserved “gatekeeper” threonine residue in the ATP binding site of a chosen kinase a potent kinase inhibitor can be made specific. The kinase inhibitor was modified to incorporate a bulky group that could only inhibit a kinase without the gatekeeper residue, thereby introducing an analog sensitive allele of any chosen kinase. Over 100 alleles of kinases have been generated and single to multiplex inhibition experiments have been performed, transcriptional profiling was used to make sense of the effects. Pathway mapping with orthogonal, labelled ATP analogues, and post-translational modification mapping was magnificently demonstrated. The piste-de-vanille approach with an innovative approach to identifying the kinase of a given substrate by cross-linking.

With the dawn of a new day came the final series of lectures with the theme being synthesis. Studies toward the synthesis of solanocenein A, a hatching agent of potato cyst nematodes, were presented by Henk Hiemstra (University of Amsterdam). Potato cyst nematodes are parasites that feed solely on the roots of potato plants. By spraying an empty field with the natural chemical signal the nematodes will hatch and die of starvation, thereby reducing the field of the parasite in an environmentally friendly manner. Sounds simple, but unfortunately the compound needs to be synthesised, and that is not a trivial task. Solanocenein A contains 3-, 4-, 5-, 6- and 7- membered rings and is not stable to acid or basic conditions. A beautifully elegant allene photocyclisation approach was illustrated leading to a structurally complex tetracyclic fragment. Rewardingly, simpler analogues of solanocenein A showed significant biological activity. Potatoes are back on the menu.

Continuing the excellence in synthesis tour, Larry Overman (University of California, Irvine) presented solutions to the special challenges in constructing “all-carbon” quaternary stereocentres. In particular, the chiral centre must be made via a C-C bond-forming reaction and be compatible with the inherent steric congestion. The polypropyridinoiodoline (cyclopyrtrimine) and cyclopyrthopan diketopiperazine alkaloids are ideal families of natural products to explore the challenges of any new methodology since they have diverse biological activities, the absolute configuration of many members of the family is unknown, and they incorporate challenging architectures of vicinal and diaryl quaternary centres. The catalytic asymmetric Heck cyclization was spectacularly developed to meet all the challenges required for efficient synthesis. The highlights of the presentation included elegant total syntheses of higher order polypropyridinoiodoline alkaloids, such as Hodgkinsine, Hodgkinsine B, Idiospermuline, by a dissymmetric dienolate dialkylation followed by an asymmetric Heck cyclization. The crescendo was the breath-taking total synthesis of the dodecacyclic alkaloids Quadrigemine C and Psycholeine.

The last lecture of the conference was given by Karl Wieghardt (MPI Mulheim) on the fascinating co-ordination chemistry of life. There are many transition metals essential for life, and they are usually incorporated as metalloproteins enzymes, in fact approximately 40% of all enzymes are metalloproteins. Two enzymes were focussed upon; galactose oxidase and photosystem II (PSII). Galactose oxidase uses a square-based pyramidal Cu(n) ion that is co-ordinated by a modified tyrosyl radical to oxidise galactose with $O_2$. Model phenoxyl radical complexes of Cu(n) mimicking the enzyme have been made in the lab and analysed leading to greater understanding of the enzyme itself. PSII is responsible for the oxidation of water with light into protons (required for ATP synthesis), electrons (required to reduce CO$_2$) and, the by-product of the reaction, $O_2$. A large tree uses photosynthesis to supply enough $O_2$ for five people. The enzyme is remarkable since it catalyses the reaction with charge separation, that is to say it does not produce $H_2$, which is what happens in the lab using electrochemistry. PSII is a metalloenzyme with a tetranuclear Mn complex at the heart of the catalytic machinery. By synthesising model Mn complexes the proposed mechanisms of the reaction were explored. One model catalyst was used as an additive in washing powder as it allowed effective washing at lower temperatures. Unfortunately, it was withdrawn since the catalyst also produced a small amount of $H_2O_2$ that eventually destroyed clothes. Nevertheless, a brilliant functional model for PSII was designed with Ru(n) oxidising centres and phenoxyl radicals.

The last surprise was given in customary fashion by Klaus Müller, who supplied a hilarious, epigrammatic summary of the week’s proceedings. The highly anticipated 40th Bürgenstock meeting was confirmed for the 16th-22nd April 2005 with the president being Alain Krief (University of Namur) and the vice-president revealed as Bernard Krüüter (University of Innsbruck).

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