Highlights from the 43rd EUCHEM Conference on Stereochemistry, Buergenstock, Switzerland, April 2008

Post-print of a peer-reviewed article published by the Royal Society of Chemistry.
Published article available at: http://dx.doi.org/10.1039/B816863F

Cite as:
Cockroft, S. L., & Lindsay, D. M. (2008). Highlights from the 43rd EUCHEM Conference on Stereochemistry, Buergenstock, Switzerland, April 2008. *Chemical Communications*, (48), 6441-6445.

Article published: 10/11/2008

Highlights from the 43rd EUCHEM Conference on Stereochemistry, Bürgenstock, Switzerland, April 2008**

Scott L. Cockroft[1,*] and David M. Lindsay[2,*]

[1]EaStCHEM, School of Chemistry, Joseph Black Building, University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK.

[2]Department of Chemistry, The University of Reading, Whiteknights, Reading, UK.

[*]Corresponding authors; S.L.C. e-mail: scott.cockroft@ed.ac.uk, tel: +44 (0)131 650 4758, D.M.L. e-mail: d.lindsay@reading.ac.uk, tel: +44 (0)118 378 4707

[**]The authors thank the conference organising committee, the Royal Society and the Swiss Chemical Society for generous financial support to attend this meeting.

The scientific programme began with a lecture by **Jérôme Lacour** (University of Geneva) on chiral anions and their use in asymmetric catalysis. Much of the lecture was centred around TRISPHAT, a chiral, hexa-co-ordinate phosphate anion, where three molecules of tetrachlorocatechol are bonded to the phosphorus. In terms of metal catalysis, Lacour reasoned that the chirality of the anion might better impart asymmetry into a catalytic process if it could be covalently bound to the metal catalyst, rather than relying on an ion-pair interaction. To this end, he described the derivative TRISPHAT-N, wherein one of the tetrachlorocatechol ligands was replaced by a pyridyl-containing diol. Resolution of the racemate was readily achieved *via* the benzylcinchonidinium salt. Thus, TRISPHAT-N is able to bind to metals *via* the pyridyl nitrogen, and a range of metal complexes were prepared, including cyclopentadienyl ruthenium complexes. An application of the TRISPHAT-N ruthenium complex to the Carroll rearrangement of allyl β-ketoesters was reported. Complexaton with TRISPHAT-N rendered the ruthenium catalyst much more thermally stable, leading to a microwave acceleration of the reaction, and appreciable levels of enantioselectivity were observed with chiral catalysts. The enantoselective [1,2]-Stevens rearrangement of quaternary ammonium salts was shown to be possible when the ammonium salt substrate was paired with a chiral TRISPHAT counterion.

ChemComm editor Sarah Thomas and next year's conference president Ben Feringa tackle the path leading from Hotel Fürigen

The second lecture of the morning was delivered by **Benjamin List** (Max-Planck-Institut für Kohlenforschung, Mülheim), detailing his impressive contributions to the burgeoning field of asymmetric organocatalysis. In particular, List described his group's work on the asymmetric

enamine organocatalysis of a range of organic reactions, including the Mannich-, Michael-, α-amination-, intramolecular aldol- and aldehyde α-alkylation reactions. In many of these transformations, proline and its derivatives are found to be highly effective catalysts. Indeed, List presented an elegant synthesis of the linearly-fused triquinane (+)-hirsutene using a fluorinated proline derivative as catalyst in the key asymmetric transannular aldol cyclisation. Dominated for a long time by iminium- and enamine catalysis, the last few years have seen the emergence of Brønsted acid organocatalysts. One of the most notable advances in this area has been the development of chiral, BINOL-dervied phosphoric acids. List's group have made extensive use of a bis(tri-*iso*-propylphenyl) derivative given the acronym TRIP. In tandem with a Hantzsch ester derivative, TRIP is able to promote the asymmetric reduction of PMP-protected imines with high levels of enantioselectivity. The reaction was also successful in reductive amination mode, removing the need to perform the imine from the corresponding ketone and amine. TRIP has also been applied successfully to asymmetric Friedel-Crafts reactions and asymmetric aza-Diels-Alder reactions. Finally, ammonium salts, obtained by mixing a variety of secondary amines with TRIP, were shown to be even more enantioselective than TRIP itself in many reactions. This approach has been termed asymmetric counterion directed catalysis (ACDC).

Fragrance connoisseur, botanist and adventurer **Roman Kaiser** (Givaudan, Switzerland) brought the first day to a close with an especially (olfactory) stimulating lecture. Whilst the extraction of natural scents for use as perfumes dates back thousands of years, modern fragrances are the result of detailed scientific analyses of natural scents followed by the chemical synthesis of molecules that match or improve upon the sensory properties of the target fragrance. Thus, the discovery of new inspirational scents is of great benefit to the perfumery industry. Kaiser gave a fascinating account of his globe-trotting adventures in search of scents in some of the most endangered environments on Earth; from the rainforests of South America, Madagascar, the Seychelles, and the Hawaiian islands, to the deserts of Death Valley and South Africa. Kaiser described how he and his colleagues used non-destructive methods to collect scents from over 9,000 botanical species. 2,500 of these scents were subjected to full olfactory investigations, with GC/MS analysis allowing individual chemical constituents to be identified. This facilitated the reconstitution of 530 of the natural scents, in addition to guiding the synthesis of new analogues for use in the fragrances and flavour industry. Some of the exotic flora encountered during these adventures was highlighted, including astonishing examples of plant-animal co-evolution. The audience had the delight of being able to sample countless floral scents from around the world; of particular note were those from the Black Vanilla Orchid (*Nigritella nigra*), which grows less than 2 hours hike away from Bürgenstock, and the delightful fragrance of *Coryanthes kaiseriana* G. Gerlach, an orchid named in honour of Kaiser's outstanding research in the field of orchid scents.

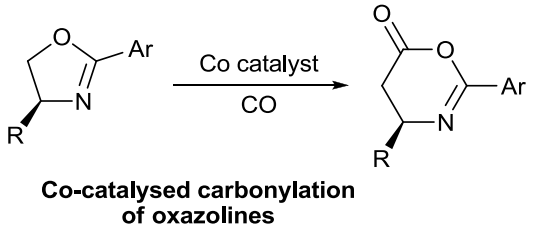
The second day of the conference was opened by **Lorena S. Beese** (Duke University), who enlightened the audience with structural and mechanistic insights gained from crystallographic studies of DNA replication and repair machinery. Particularly memorable was an animation generated from high-resolution crystal structures showing the conformational transitions in *Bacillus* DNA polymerase I as it replicated and translocated a DNA template sequence. Extensive systematic studies of mismatch tolerance and replication across carcinogenic legions, such as those caused by O^6-methylguanine DNA, revealed the structural bases of the replication fidelities of these fantastic enzymes. Encouraged by their successful observation of multiple successive nucleotide incorporation steps in single DNA polymerase crystals, the Beese group continue to make important steps towards obtaining high resolution structural data on increasingly short time-scales. The challenges faced when attempting to synchronise events throughout an entire crystal were described, and the tantalising prospect that the structures of transient intermediates might soon be captured by 'time-resolved crystallography' was raised.

Continuing in the biochemical theme, **Mohamed A. Marahiel** (Philipps-Universität Marburg) gave a tour of the molecular machinery involved in non-ribsomal peptide biosynthesis. Non-ribosomally synthesised peptides display great structural diversity and often contain unusual building blocks such as D-amino acids, fatty acids, and sugars. These incredible natural products are synthesised by non-ribosomal peptide synthetases; modular multi-enzyme assembly-lines that parallel those involved in fatty acid and polyketide synthesis. Each module is made up of specialised subdomains that perform each of the steps involved in a single substrate incorporation cycle; *i.e.* substrate recognition, activation, fixation of the intermediate enzyme-bound thioester, and peptide bond formation. This essential set of subdomains are supplemented by additional substrate modifying domains that perform additional biochemical manipulations such as heterocyclic ring formation, product cyclisation, epimerisation, C*β*–hydroxylation, *N*-methylation, which serve to further boost the structural diversity of non-ribosomally synthesised peptides. Substrate fidelity, intermodule recognition and the orchestration of substrate transfer between modules featured in the discussion following the lecture.

In the Monday evening session, **Ben Davis** (University of Oxford) delivered a lecture on various aspects of glycoprotein synthesis and their chemical modification. Davis described several methods for the site-selective functionalisation of proteins, with the common goal of developing a set of synthetic equivalents that mimic post-translational modification. Davis described the use of *O*-mesitylenesulfonylhydroxylamine (MSH) to effect the conversion of cysteine side-chains to dehydroalanine under mild conditions. Conjugate addition of allyl thiol to the dehydroalanine provided a reactive olefinic handle for functionalisation by cross-metathesis – the first time this metathesis process had been carried out on a protein. Both α- and β-allyl glycosides could be

attached to proteins in this manner. A second method employed two chemically orthogonal methods to allow more complex protein modifications. Firstly, glycosylation of cysteine residues using glycomethanthiosulfonate allowed the formation of disulfide linked glycosides. Secondly, by site-directed mutagenesis of methionine residues to the unnatural amino acid derivatives azidohomoalanine, propargyl glycosides could be attached using the Cu(I) mediated Huisgen cycloaddition reaction. These mimics of post-translationally modified proteins could then be used as *in vivo* probes to investigate complex multi-component binding domains involving a variety of post-translational modifications.

The third morning of the conference had both organometallic- and polymer chemistry as its themes. **Geoff Coates** (Cornell University, New York) delivered a lucid narrative of a metal-catalysed journey from the synthesis of stereodefined polymers through to the application of similar catalyst systems to the efficient synthesis of small organic molecules. Synthetic organic chemists usually deal with molecules containing a relatively small number of stereogenic centres; those engaged in the synthesis of chiral polymers have to ensure that hundreds, or even thousands, of stereocentres are correctly installed in their macromolecules. Coates highlighted his group's work in developing a range of transition metal-based catalysts for the production of stereodefined polymers. Of particular note was the system based on $NiBr_2$ and a chiral diimine ligand, which catalyses a 'living' polymerisation of propylene to give highly isotactic poly(propylene) with narrow molecular weight distribution at low temperature. At room temperature, the same catalyst system produces amorphous and regioirregular poly(propylene) and thus by varying the temperature during the polymerisation, block co-polymers with interesting physical properties could be produced. Coates then described a system for the co-polymerisation of propylene oxide and carbon dioxide, to give poly(propylene carbonate). In a conceptual extension to small molecule organic synthesis, this work led on to the development of cobalt-based catalysts for the carbonylation of epoxides and oxazolines. In particular, the carbonylation of oxazolines provides an elegant catalytic method for the overall conversion of α-amino acids to the corresponding β-amino acids, effectively employing carbon monoxide as the one-carbon homologating agent. The lecture concluded with a very interesting and detailed overview of the stereospecific double carbonylation of epoxides to give succinic anhydrides.



Co-catalysed carbonylation of oxazolines

Figure 1. Co-catalysed carbonylation of oxazolines.

Lecturing at Bürgenstock 29 years after her father had the same honour, **Kyoko Nozaki** (University of Tokyo) expanded on the theme of organometallic chemistry in the synthesis of polymers. In particular, the use of Pd-BINAPHOS complexes to effect the co-polymerisation of mono-substituted alkenes with carbon monoxide, to give chiral poly(ketones) was presented. Real mechanistic insight into the process was achieved through both experimental mechanistic studies as well as theoretical calculations. As well as being interesting and useful materials in their own right, the rich chemistry of the carbonyl group in the poly(ketones) was then exploited to deliver a range of new materials after, *e.g.* reduction, olefination, Baeyer-Villiger rearrangement or acetal formation. Recent achievements in the Nozaki group on the olefin/CO copolymerization were also presented. A catalyst system comprised of a mono-sulfonated triarylphosphine and $Pd(dba)_2$ was shown to be competent in the co-polymerisation of vinyl acetate/CO and methyl acrylate/CO, giving some of the first examples of alternating copolymerizations which directly utilise functionalised alkenes in the copolymerization. Professor Nozaki conlcuded her lecture with a digression into main group organometallic chemistry by describing her group's work in the synthesis of anionic boryl compounds. The synthesis and isolation of a boryllithium compound, isoelectronic with an *N*-heterocyclic carbene, was described. Undoubtedly, future studies of these exciting, nucleophilic boryl compounds will reveal a rich and abundant chemistry.

Wednesday brought a return to more biological themes. **Frances H. Arnold** (California Institute of Technology) described her tales of reengineering cytochrome P450 enzymes through directed evolution. P450 enzymes are remarkable proteins that catalyse the regio- and stereoselective insertion of oxygen into inactivated R-H bonds in mild physiological conditions. Different classes of P450 enzymes that act upon an array of different substrates have emerged through millions of years of natural selection. Although these enzymes only share 15% sequence identity, the fold has been retained over long periods of evolution. Thus, P450 enzymes provide a superb test-bed for pushing evolution to its limits to reveal novel catalytic activities and provide fundamental insights into evolutionary mechanisms. Since there are thousands of possible single-residue enzyme mutations that retain at least some catalytic activity, extensive exploration of functional space is possible using *in vitro* evolution experiments that free the protein from the constraints of biological function. By using a high-throughput directed 'breeding' programme involving repeated cycles of screening, selection and mutation, the Arnold group have successfully generated P450 enzymes with non-native activities. For example, P450 enzymes that catalyse reactions normally performed in nature by structurally and mechanistically unrelated gaseous alkane monooxygenases have been evolved. Strikingly, the evolutionary paths to such enzymes were seen to pass through promiscuous intermediates with broad substrate specificity, with further cycles of selection leading to the spontaneous re-emergence of substrate specificity, even though it was never explicitly selected for.

Shifting towards a more bottom-up approach to synthetic biology, **Homme W. Hellinga** (Duke University) spoke about computational and experimental approaches to redesigning proteins and biological pathways. The central aim of these studies is the *de novo* genesis of function through structural adaption of natural protein scaffolds. Maltose binding protein, thioredoxin and F_1-ATPase have all been re-engineered to contain metal binding sites *via* this approach. Single-molecule studies of the re-engineered ATPase enzyme established that rotation of the motor could be reversibly switched on or off in response to Zn^{2+}. Other proteins have been re-engineered to bind a wide range of non-native substrates including drugs, metabolites, explosives, pollutants, sugars, amino acids, and chemical agents. Re-engineered maltose binding proteins can serve as sensors for non-native substrates since binding events often induce conformational changes that can be detected electrochemically or *via* fluorescent tags. If an appropriately engineered protein involved in a biological signal transduction pathway is genetically encoded within the DNA sequence of a living organism, then transcription of another protein can be triggered in response to a target substrate of the re-engineered protein. The successful rewiring of biological pathways has been demonstrated in bacteria that have been 'tricked' into synthesising green fluorescent protein by artificial stimuli.

After filling our bellies with melted cheese from either fondue or raclette, conference participants returned to the lecture theatre to enjoy a lecture by **Kai Johnsson** (Ecole Polytechnique Fédérale de Lausanne) who spoke about methods for observing and manipulating proteins inside living cells. Fittingly, the talk began with a review of the seminal work of **Roger Y. Tsien** (University of California, San Diego) who was originally scheduled to give a lecture during this session. Johnsson went on to speak about fusion proteins; recombinant proteins that can be expressed with additional polypeptide tags that allow a protein of interest to be labelled and visualised within living cells. The polypeptide tag itself may be autofluorescent as exemplified by green fluorescent protein, or serve as a specific site for the attachment of a fluorescent small molecule. Small chemical tags provide properties that cannot be genetically encoded and are often less biologically intrusive than bulky protein tags. Numerous acronym-laden tagging strategies compatible with physiological conditions were outlined (SNAP, FLASH, Halo and CP-tagging), in addition to cunning approaches that highjack biological DNA repair and post-translational machinery for labelling proteins. Armed with this array of techniques, Johnsson showed that it was possible to identify the localisation of proteins within cells, and to study dynamic biological processes such as protein synthesis and translocation during complicated cellular events such as mitosis and cell wall budding. Variations of these approaches have also been used to covalently trap transient protein-protein interactions and to monitor substrate-induced conformational changes in proteins.

Thursday morning saw a shift back towards organic synthesis as **Goverdhan Mehta** (Indian Institute of Science, Bangalore) delivered a breathtaking *tour de force* of the total synthesis of an astonishing range of bioactive natural products. Recurring themes in this lecture were the use of practical, scalable chemistry whenever possible, and the design of synthetic routes towards challenging targets with the goal of flexibility always foremost, to allow not only the synthesis of the natural products themselves, but also to enable access to analogues. The lecture focussed on a range of natural products possessing biological activity which identified them as potential neurotrophic agents. Professor Mehta began by discussing the polyprenylated acylphloroglucins (PPAPs), of which Garsubellin A and Hyperflorin are examples. These targets were assembled in an efficient manner, at one stage making use of the rare Effenberger cyclisation to rapidly construct complex polycyclic systems from relatively simple starting materials. Next, the audience were guided through the synthesis of several members of the seco-prezizaane family, including Merrilactone A and Minwanenone. Of particular note was the elegant use of cyclopentadiene-quinone Diels-Alder adducts, wherein the bicyclo[2.2.1]heptene moiety serves not only as a stereodirecting unit, but also as a double bond protecting group. Following the lecture, a lively discussion took place concerning the role of natural products research in the pharmaceutical industry, and the potential implications for the industry, should there be any decline in natural products research.

Staying with organic synthesis, but changing theme from natural products as targets to natural products as engines for new reaction development, **Justin Du Bois** (Stanford University) presented some of his work in the emerging area of C-H activation, and in particular the oxidative insertion of nitrogen into unactivated C-H bonds. Du Bois presented the rhodium-catalysed C-H insertion of primary carbamates and –sulfamates *via* hypervalent iodine nitrenoid intermediates. The cyclic carbamate and –sulfamidate products can be further manipulated to give a range or 1,2- and 1,3-diamines and amino-alcohols as well as many other functional motifs. However, the majority of the lecture was concerned with the rigorous and exquisite mechanistic studies the Du Bois group have performed in order to understand the system and hence enable them to design more effective catalysts. By employing a combination of substrate probes and kinetics analysis, Du Bois has obtained compelling support for the generation of a Rh-nitrene as the active oxidant in this amination process. Furthermore, the investigations provided evidence for the rapid modification of the catalyst structure upon reaction initiation. In turn, these insights led to the preparation of tethered dicarboxylate Rh dimers, based on the hypothesis that such complexes would display enhanced kinetic stability under the reaction conditions. Indeed, remarkable catalyst turnover numbers were observed for intramolecular C–H amination reactions using these new tethered catalysts. Additionally, the new catalysts have allowed the extension of this methodology to encompass previously recalcitrant C–H insertion substrates such as ureas, guanidines, and sulfamides.

The final talk of the conference was given by **David R. Liu** (Harvard University) who dazzled the audience with both his blue laser pointer, and his masterful exploitation of biological evolutionary principles in organic synthesis and reaction discovery. Liu described how the molecular recognition properties of DNA can be harnessed to control the relative positions between functional groups in small molecule-DNA conjugates. By controlling the effective molarities of reactive groups in this manner, reactivity and the order of multi-step reactions can be programmed by the templating DNA sequences. This methodology has been used for many different reactions (including Diels Alder, C-C bond formation, epoxide opening and nitro-aldol reactions) in the synthesis of a wide range of molecules including macrocyclic and polymeric products. DNA sequences can also serve as useful identifying tags that can be used to evaluate molecules in ways not accessible by conventional synthesis and screening methods. In the case of reaction discovery, small molecules tagged with DNA sequences can be flowed over an array of immobilised candidate co-reagents. When a DNA-labelled reagent reacts with an immobilised reagent it will become covalently attached to the array, whereas unreacted reagents can be easily washed away. The DNA sequence of the reagents that have reacted with the array can then be amplified by PCR, and the identity of the reactive small molecule can be revealed by conventional DNA sequencing. Such an approach allows reaction discovery screens to be performed on unprecedented femtomole scales.

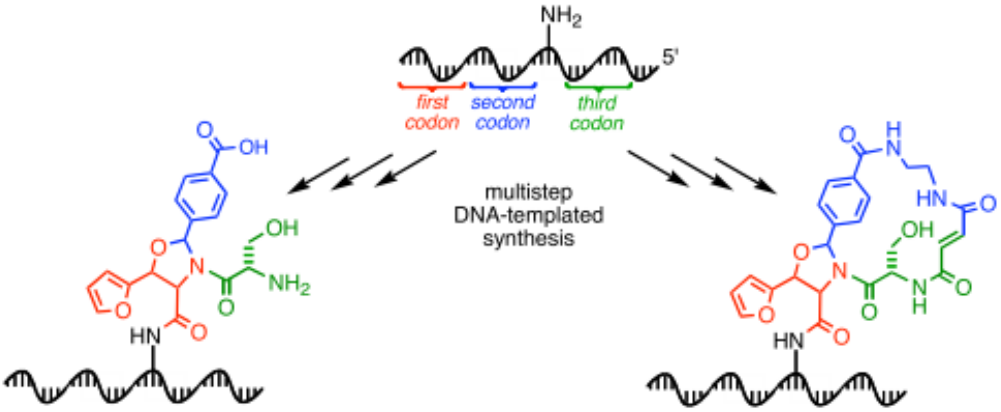


Figure 2. DNA-templated organic synthesis pioneered by Lui.

As is now traditional, the close of the scientific programme was followed by a light-hearted review of the meeting, presided over by **Klaus Müller**. Among many observations which ensured the delegates left smiling, was a suggestion to mirror the Swiss rural speed limit with a Bürgenstock 'slide limit'.

The 44th EUCHEM conference will take place on the 17th-22nd May 2009. Next year's conference

will bring a series of changes. Firstly, François Diederich, E. Peter Kündig and Klaus Müller will step down from 10, 12 and 26 respective years of committee service, with **Don Hilvert** (ETH Zürich), **Jérôme Lacour** (Université de Genève), **Helma Wennemers** (Universität Basel) and **Reto Näf** (Novartis Pharma AG) stepping to the helm. Nobody could argue that Bürgenstock would be the same without Klaus Müller (who undoubtedly holds the All-time World Record for the highest number of Bürgenstock questions asked), thus he was rightfully announced as the guest of honour for next year's conference. The second major change affects the conference venue, which since 1965, has been held at the Bürgenstock resort above lake Lucerne. However, under the presidency **Ben Feringa** (University of Groningen) the conference will head downhill to Lucernes's very own 'low country', the Seehotel Waldstätterhof, Brunnen, which lies on the shore of Lake Lucerne.