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The 40th EUCHEM Bürgenstock Conference on Stereochemistry Bürgenstock (Switzerland), April 16–22, 2005

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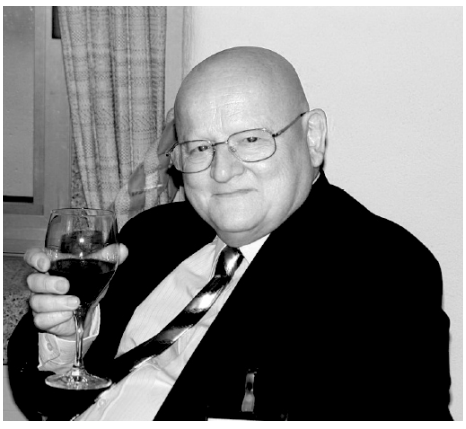
The Bürgenstock resort sits atop a butte overlooking Lake Lucerne, reflecting in its elegant décor the graceful period between the wars. Since 1965 it has played host to the legendary Bürgenstock Conference on Stereochemistry, renowned for its small size, wide-ranging content, and consistently top-notch list of speakers. This year's conference, presided over by ***Alain Krief*** (University of Namur) and having *Sir Jack E. Baldwin* (Oxford University) as the guest of honor, brought together more than 130 chemists from academia and industry to hear 14 talks over five days.

Alain Krief (President)



Sir Jack E. Baldwin (guest of honor)

Each talk was followed by a lively discussion period, and the talks were broken up by a magic show by the masterful Koji Nakanishi, a chamber music recital, and three poster sessions. The attendance of some of the junior poster presenters was generously underwritten by the conference's Junior Scientists Program, with funds generously provided by the European Science Foundation, the Swiss National Science Foundation, and the German Verband Chemischer Industrie.

The theme of this 40th Bürgenstock conference was '1001 Nights', and at the plate of each participant at dinnertime was a small card upon which was written a short chemical fairy tale. The creativity and humor of the conference's organizers, *Hans-Beat Bürgi* (University of Bern), *François Diederich* (ETH Zürich), *E. Peter Kündig* (University of Geneva), and *Klaus Müller* (Hoffman-La Roche, Basel), was clearly well employed in preparing these cards. Upon the first card was written the conference's leitmotiv: "Open Sesame / Where most see a wall / some see a door / and a few go through / to discover a rich new world".

The conference's first talk was given by ***Jonathan Clayden*** (University of Manchester), and was entitled 'Synthesis and Stereocontrol with Lithiated Amides'.

Professor Clayden's approach to stereocontrolled lithiation involves the use of

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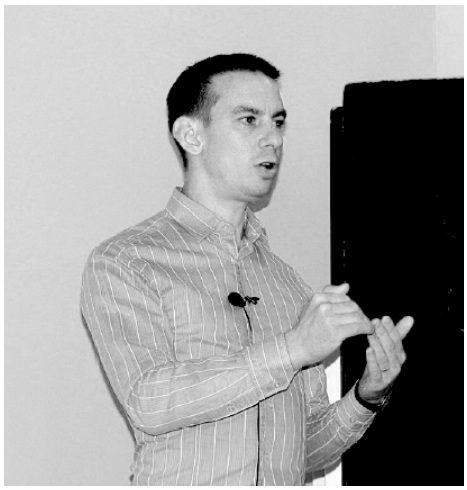


Jonathan Clayden

Charles Mioskowski

phenylamides that do not contain carbon stereocenters, but rather which are chiral as a result of sterically restricted rotation about a single carbon–carbon bond. These atropisomers were shown to direct the lithiation of different substrates in various useful ways. In particular, products containing 5- and 6-membered rings fused together were readily accessible in a single step with a high degree of stereocontrol. The utility of this approach in the synthesis of the natural product Isodomic acid C was demonstrated. The use of chiral amides to prepare chiral sulfoxide reagents was then discussed. In these reactions, the dipole of the amide group orients the dipole of the incoming sulfoxide group to give a single diastereomeric product. This led to the idea that the dipole of one amide group might orient the dipole of another through space, allowing the transfer of stereochemical information from one end of a molecule to another. This concept was tested through the preparation of a series of oligo(xanthene diamides). The covalent attachment of a chiral center to one end of the chain was shown to orient all the dipoles along the length of the oligomer, allowing a reaction at an aldehyde group at the far end of the molecule to proceed stereoselectively 23 bonds away from the initial source of the chiral information. The length of this 'molecular relay' chain for chiral information is unprecedented.

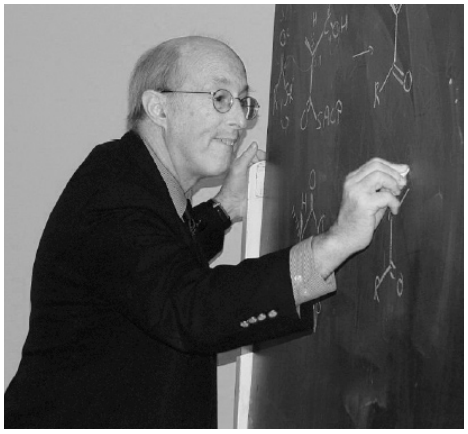
The next talk, entitled 'High-throughput Screening for the Selection of Bioactive Natural Products by Immunoanalysis; Total Synthesis of Norbadione A' was given by ***Charles Mioskowski*** (Université Louis Pasteur, Strasbourg).

This talk was divided into two parts. In the first part, the audience was introduced to the idea of high-throughput screening in general, and its uses in the rapid generation and testing of new molecules and materials in view of a specific purpose. The idea of using monoclonal antibodies to bind specific members of complex mixtures was raised. This led to the notion of using immobilized antibodies bound to haptens that were covalently linked to enzymes in a competitive assay: when competitive haptens are introduced into the system, the relative binding strengths of the two haptens may be determined by measuring the residual enzymatic activity. The proportion of the original (enzyme-linked) hapten remaining is thus directly related to the enzyme activity observed.

The development of a new chemiluminescent probe of enzyme activity, more sensitive than a previous colorimetric test, was then described. A successful example of the use of monoclonal antibodies in high-throughput screening was subsequently discussed, in which a pair of antibodies was employed to screen catalysts for an asymmetric hydrogenation. One of the two antibodies was developed to bind to both enantiomers of the product, and the other to bind specifically to the desired enantiomer. Over 2000 combinations of ligands, metals and hydride sources for the asymmetric reduction of a β-keto acid could thus be rapidly screened, with the yield being determined by first antibody, and the enantiomeric excess by the second.

The use of high-throughput screening to evaluate antioxidants was then discussed, a project of interest to the French Atomic Energy Commission. An antibody was first generated against thymidine, and then mixtures of thymidine and potential antioxidants were stressed through the application of chemical oxidants or radiation in large parallel arrays. The quantity of thymidine left could then be measured using the antibody screen, and the efficacy of the antioxidant thus measured. One of the most effective antioxidants was found to be Norbadione A, isolated from fungi. The total synthesis of this compound was subsequently undertaken using a methodology featuring several palladium-catalyzed cross-coupling reactions.

Following the afternoon poster session and dinner, the evening's lecture was given by ***David E. Cane*** (Brown University), entitled 'The Biochemical and Structural Basis of the Programming of Polyketide Biosynthesis: Destiny or Free Will?'



David E. Cane

The talk described the journey of a series of macrolides, macrocyclic antibiotics that may be considered as modified fatty acids, through an intricate chain of enzymatic reactions. Each enzyme adds a residue derived from proprionic or butyric acid on to the end of a growing chain, stereospecifically reduces a ketone or performs the final cyclization. Individual sub-chains were isolated from the enzymatic chain, and un-natural substrates were fed into these to study the enzymes' selectivities and kinetics. This allowed for the testing of sophisticated hypotheses, which have ramifications for enzymatic systems beyond these specific cases.

The Monday morning session was opened by ***Guy C. Lloyd-Jones*** (University of Bristol), entitled 'Isotopic Desymmetrisation in the Study of Metal-mediated Processes', or 'Reducing Degeneracy by Adding Neutrons'.

Guy C. Lloyd-Jones

The first system described was a derivative of a C_2-symmetric Trost modular backbone palladium catalyst, in which half of the diphosphane ligand's phenyl groups were isotopically labeled with deuterium. This symmetry-breaking enabled one to demonstrate that the catalyst in solution consisted of a monomeric species of lowered symmetry in equilibrium with oligomeric species, which shed light upon the catalytic mechanism. In particular, kinetic resolution between enantiomeric substrates was shown to be very important. Computer models showed how initial enantiomeric excess might be amplified using kinetic resolution, allowing a racemic catalyst to 'paradoxically' amplify enantiomeric excess.

Next to be discussed was an alkene–alkyne metathesis reaction catalyzed by a non-alkylidine ruthenium complex, of interest because most good catalysts for this reaction (such as the Grubbs' catalyst) have alkylidine ligands. Deuterium labeling of this reaction's substrate gave results inconsistent with an yne-then-ene mechanism, strongly suggesting that an alternative ene-then-yne pathway was in fact correct. In addition, when the reaction was run under an atmosphere of ^{13}C-labeled ethylene, the distribution of isotopic label in the product demonstrated the presence of a second, parallel catalytic cycle operating in the presence of ethylene, as well as illuminating its mechanism.

The morning's second speaker was ***Keiji Maruoka*** (Kyoto University), who gave a talk entitled 'Design of C_2-Symmetric Chiral Phase Transfer Catalysts as Truly Efficient Organocatalysts for Practical Asymmetric Synthesis'.

Keiji Maruoka

The basic problem addressed here is the stereospecific synthesis of α-amino acids, an unquestionably important class of compounds. Glycine, protected and made hydrophobic as the *tert*-butyl ester and benzophenone imine, had been demonstrated to react with alkyl halides under basic phase transfer conditions. When chiral phase-transfer catalysts (such as quaternized cinchonine alkaloids) are used, these reactions may proceed enantioselectively. The use of chiral bis(binaphthyl) quaternary ammonium catalysts allows for a dramatic increase in both enantioselectivity and yield, as these catalysts more effectively recognize the enolate intermediate, effectively blocking one face during the formation of a tight ion pair.

Further innovations involved the addition of fluoroalkyl chains to the catalyst, allowing for easy catalyst recovery by simply washing the biphasic reaction mixture with a further fluorous phase, and the introduction of two different groups at the α-carbon of glycine, with either product enantiomer being accessible through a change in the order of addition of the two alkyl bromides. A new generation of catalysts that contain a pair of alkyl chains in place of one of the two binaphthyl groups was then presented, which gave extremely high yields and ee's even at extremely low catalyst loadings.

Following the second set of poster sessions and dinner, the audience was treated to the seminar of ***Paul Knochel*** (University of Munich), entitled 'Functionalized Organometallics for Organic Synthesis'.

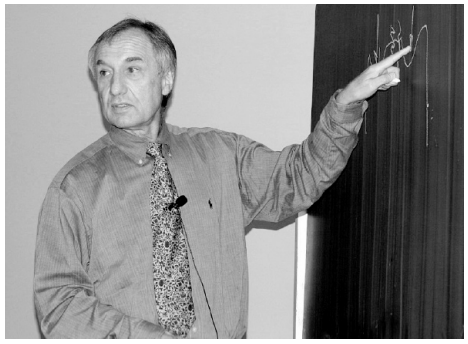
Paul Knochel

This research involved the preparation and reactivity of a set of new Grignard and organozinc reagents. These reagents were generated through halogen–metal exchange starting from simple isopropyl Grignards, as opposed to the traditional synthesis involving magnesium metal. Aryl rings containing groups not generally considered to be compatible with carbanions, such as nitro or ketone, may thus be readily metallated. These reagents are sufficiently stable at moderately low temperatures (0 to –40 °C) to allow for their addition to electrophiles, giving good yields of products.

The preparation of benzynes was shown to be possible through magnesium–iodine exchange with *ortho*-iodophenyltosylates. These benzynes will react with poor nucleophiles, such as magnesium thiolates, to give *ortho*-thioalkyl Grignards, which may then be used for further steps.

The use of lithium salts to push the Schlenk equilibria of organozinc and organomagnesium halides towards the formation of the more electron-rich, nucleophilic species was also discussed. The use of such species allowed for the preparation of previously inaccessible reagents, such as *p*-anisylmagnesiums.

Tuesday's first lecture was given by ***Ian A. Wilson*** (The Scripps Research Institute), entitled 'Chemistry, Biology and Biophysics of Antibody–Antigen Recognition'.



Ian A. Wilson

This highly topical talk delved into crystallographic insights as to the immunology of the HIV-1 and 1918 influenza viruses, discussing their antigenic structure and possible vaccine designs.

The HIV-1 virus has showed itself to be very resistant to vaccine development; it is a major challenge to produce an effective neutralizing antibody response. Its surface proteins are hypervariable and highly glycosylated, rendering them very difficult to recognize. Nonetheless, several broadly neutralizing monoclonal antibodies to HIV-1 do exist, binding to various parts of surface proteins, and offering protection against either infection or disease. In particular, the b12 vaccine, developed from the bone marrow of a long-term asymptomatic patient, was shown to neutralize ~75% of all known HIV-1 isolates. This antibody appears to dock well with the CD4 binding site of the virus, which shows less variability than elsewhere. Docking studies conducted with the help of crystal structures suggested how the recognition process occurred. A second neutralizing antibody, 2G12, binds to a different viral protein, gp120. The surface carbohydrates of this viral protein are strongly implicated in the binding process, the mechanism of which was discussed at length in light of the crystal structure.

The second part of the talk discussed the structural basis of the exceptional virulence of the 1918 'Spanish' flu, with an eye towards the currently brewing bird flu epidemic in Southeast Asia. This influenza strain was not only lethal to the very young and old, but also killed many aged 25–35, who very rarely die in epidemics. Influenza A strains circulate amongst a vast reservoir of bird and mammal hosts, with antigenic drift and point mutations allowing new strains to arise. For a bird strain to adapt to human hosts, a two-residue change is all that is required, suggesting that the virulent avian flu presents a very real and present threat: it is believed that the 1918 strain also started among the bird population, becoming transmissible among humans as a result of such a mutation. The sequencing of the RNA of the 1918 virus was discussed, as well as the mechanism of possible binding to surface viral carbohydrates, in the context of a consortium that has recently been formed to investigate the 1918 flu in light of the current bird flu threat.

The morning's second lecture was given by ***Thomas Carrell*** (University of Munich), entitled 'Replication and Repair of DNA Lesions on an Atomic Level'.

Thomas Carrell

DNA lesions play a central role in carcinogenesis and mutation, and a vast array of enzymatic machinery exists to detect and repair chromosomal damage. The low frequency of lesions within DNA makes them difficult to study, however. The chemical syntheses of several oxidatively degraded nucleosides were thus undertaken to investigate the properties of oligonucleotides into which they were incorporated. Pure oligonucleotides containing a single lesion were investigated in complexes with several proteins that recognize them, allowing the mechanisms of enzymatic action to be elucidated: crystal structures were thus obtained in which the enzyme–DNA complex revealed that the lesions were flipped out of the double helix, providing easy access for repair. Other crystal structures reveal which kinds of mismatches are capable of 'fooling' polymerases, thus potentially leading to genetic mutations.

Tuesday evening's program included a formal dinner followed by a chamber music concert by the *Aura String Quartet* from Basel (Hiroko Suzki, Roger Pyne, Christian Vancher, Conrad Wyss). Pieces by Mozart, Schulhoff, Brahms and Shostakovich rounded out the evening.

The Aura String Quartet

Wednesday morning's program started with a lecture by ***Klaus Müllen*** (MPI for Polymer Research, Mainz) entitled 'From Benzene to Molecular Electronics', a selection of a few ideas from a very extensive research program.

Klaus Müllen

Organic electronic devices are finding an ever-increasing market, necessitating a greater understanding of how they work. For organic light-emitting diodes and solar cells, it is becoming clear that the size, dimensionality, and supramolecular design all play crucial roles in device function. Poly(phenylene) dendrimers are rigid nanoscale objects, possibly of very high molecular weight, that were prepared in monodisperse fashion using an elegant series of Diels-Alder reactions. These dendrimers contain huge voids that may take up solvent molecules, changing the host's conductivity and allowing for an 'electronic nose' function. Perylene diimide dyes may be built into the cores of such dendrimers, completely isolating the dyes from π-stacking and rendering them highly fluorescent. Perylenes of different sizes may be built into the same dendrimer, leading to efficient energy transfer funneled to the largest chromophore upon photoexcitation at different wavelengths, mimicking the function of photosynthetic pigments.

Certain poly(phenylene) dendrimers react with iron trichloride, flattening out into sheets of fused benzene rings, or graphenes, in remarkably high-yielding aromatization reactions. These molecules may be visualized as two-dimensionally crystalline monolayers on surfaces, providing important structural characterization of what are often highly insoluble species. On surfaces these molecules act as diodes, rectifying with current–voltage curves that change as a function of molecular size and shape. When decorated with peripheral alkyl chains, certain graphene molecules organize into columnar liquid crystals, which may be built into solar cells together with perylene derivatives. Finally, a remarkable carbonaceous material results when these liquid crystals are incorporated into porous alumina and then pyrolyzed. When the alumina matrix is subsequently dissolved away, the conductive carbon that is left is capable of binding much greater amounts of lithium than conventional graphitic materials, potentially leading to lithium batteries with improved capacity.

The morning's second talk was given by ***Masahiro Irie*** (Kyushu University), titled 'Photochromism of Diarylethenes: From Single Crystals to Single Molecules'. Many samples were brought along, and the talk was peppered with demonstrations of light-induced color changes. The photochromic materials discussed consist of pairs of molecules which interconvert *via* photochemistry, changing color in the process. The new dia-

Masahiro Irie

rylethene materials discussed show greater thermal stability, fatigue resistance, quantum yields and rapidity of switching than previous materials, opening the door to new applications.

Single crystals of many photochromic molecules, remarkably, may be switched while remaining crystalline. The switching may be spatially localized, allowing only part of a crystal to change color, and a single material can change from colorless to yellow, blue, or red using three different wavelengths of light. Crystallography revealed that during the solid-state photochemical transformation, most atoms stay put, but some move substantially, changing the dimensions of the unit cell and thus the crystal. This deformation may be followed by atomic force microscopy: the surface of a crystal shrinks where photoisomerization has taken place, growing rougher, and grows back to atomic smoothness when the photochemistry is reversed. Finally, experiments were shown wherein the switching of individual molecules, using fluorescent probes, was followed by confocal microscopy, raising the possibility of using single molecules as elements of an optical memory.

Wednesday evening's lecture was given by ***Catherine L. Drennan*** (Massachusetts Institute of Technology), entitled 'Crystallographic Snapshots of Metalloproteins in Action'.

Catherine L. Drennan

The rapid progress made in protein crystallography has allowed one to consider proteins not simply as static entities to be crystallized once and considered 'solved', but rather as dynamic species for which the structure may be solved with a variety of substrates, in different states. The activity of biotin synthase was probed; this enzyme performs a remarkable abstraction of two hydrogen atoms while inserting a single sulfur atom in their place. The structure reveals the presence of iron–sulfur clusters, together with a hydrogen-abstracting group, in close proximity to the enzyme's active site. The proposed mechanism involves the abstraction of a sulfur atom from a Fe_2S_2 cluster, which would be a new mode of reactivity for this kind of cluster.

A second example discussed was carbon monoxide dehydrogenase, an enzyme that enables certain bacteria to use CO as a carbon and energy source. This enzyme is thought to transform CO into one trillion tons of acetate annually, removing this toxic greenhouse gas from the environment, and is implicated in novel bio-organometallic reactions; metal–CO, metal–CO_2H, and metal–CH_3 moieties are all thought to be present in the enzymatic cycle. One active site of this enzyme contains a highly unusual $NiFe_4S_4$ cluster in which one iron atom is displaced from a Fe_4S_4 cluster, with a nickel atom replacing it in the cubic cluster. An additional active site contains nickel, iron, and a third metal, which may be alternatively copper, zinc, or nickel. A long channel was found, just the right diameter for a small molecule of gas (such as CO), which connects the two active sites and prevents the substrate gas from escaping. The enzyme structure must nonetheless have sufficient flexibility to allow gas molecules to enter and exit; this flexibility was demonstrated by the crystallization of the enzyme in a second 'open' conformation. The location of one of the active sites on the boundary of two domains could allow a single methyl group to act as a linchpin, locking the two halves of the enzyme together and keeping the gas within to react.

Thursday morning's session was opened by ***Mikiko Sodeoka*** (Tohoku University), with a talk entitled 'Development of Intracellular Signal Transduction Modulators'.

Mikiko Sodeoka

The phosphorylation state of proteins is strictly controlled by kinases and phosphatases, of which there are many. Within a family of phosphatases, the structure of the active site is generally conserved. Next to the active site is a unique site, which lends selectivity to the enzyme. One approach to developing phosphatase inhibitors thus consists of creating a library of various unique-site binders linked to a single general active-site binder. Docking experiments show how the binding of small-molecule inhibitors might be improved. As an example, binding studies conducted using the small molecule RK-682 as a model tyrosine phosphatase inhibitor show how two molecules are implicated in inhibition, and models suggest how they might bind cooperatively. When two molecules of RK-682 are covalently linked together in such a way as to be preorganized for good binding, the affinity was demonstrated to increase tenfold.

A second example was related to controlling necrosis with respect to apoptosis, two distinct kinds of cell death. Apoptosis is a fairly well-controlled process, whereas necrosis involves membrane rupture and release of cell contents into the environment, whereby neighboring cells may be damaged. It had been previously discovered that BM1, a small bis-indole kinase inhibitor, could indefinitely postpone the necrotic death of ovarian cells. A library of bis-indolylmaleimides with various substitution patterns was thus synthesized and screened as inhibitors of necrosis. An effective inhibitor was found, but it was discovered also to inhibit two essential kinases not implicated in necrosis, leading to general toxicity. Further structural changes eliminated this secondary toxicity, leading to IM-12, a potent blocker of cell death by necrosis. *In vivo* studies showed that damage induced by stopping blood flow to the heart could be significantly reduced by injection of this compound, indicating one path from interesting molecules to compounds of real therapeutic potential.

The morning's second speaker was ***John L. Wood*** (Yale University), who gave a talk entitled 'Bridged Polycyclic Natural Products: Inspirational Targets for Total Synthesis'.

John L. Wood

The theme of this talk was that the most important part of synthesis is often not the final product, but rather the new chemistry that one learns along the way. A challenging synthetic target is the class of Phomoidrides, natural products derived from fungi growing on junipers. Phomoidride D has many synthetically challenging features, including a bicyclo[4.3.1]decadiene skeleton, a bridgehead olefin, a maleic anhydride group, a difficult quaternary center, and a spiroacetal. An initial oxy-Cope rearrangement was investigated in a model system, to see if a key step in the synthesis might work. It did, but then failed when additional steric bulk was introduced. A Wharton fragmentation was then vetted, and worked well, but it required the synthesis of an intermediate that could not be made. An intramolecular Diels-Alder reaction proved more tractable, leading to a precursor of the polycyclic core in excellent yield from readily accessible starting materials, and a subsequent radical cascade reaction created the quaternary carbon center with perfect stereocontrol. A samarium diiodide induced fragmentation gave the required double bond, rearranging the core into its correct configuration. The remaining challenges will involve changing the oxidation state of key carbon atoms, the skeleton being currently complete.

Many different ideas had to be developed and tested to arrive at a feasible pathway. In particular, the SmI_2-mediated radical fragmentation shows a great deal of promise. Samarium diiodide turns out to be a tunable reducing agent – it can give rise to radicals, but also to anionic chemistry, in different solvents. In the fragmentation described above, the chemistry was not purely radical, but had anionic character. Another useful reaction developed during the course of this synthetic effort was the clean reduction of xanthates to the corresponding alkanes using trimethylborane, giving higher yields than tin hydrides and avoiding toxic tin waste. Studies determined that a small amount of water was necessary, and that if D_2O was employed deuterium was incorporated. Calculations showed that the coordination of water to trimethylborane strongly weakens the H–O bond, suggesting that a radical chain mechanism might be responsible.

Just before dinner all were treated to an impromptu magic show by the inimitable ***Koji Nakanishi***. His most remarkable trick was perhaps the transformation of a roomful of serious senior scientists into amazed and laughing children.

The conference's final talk was given by ***David A. Evans*** (Harvard University), entitled 'Asymmetric Synthesis with Chiral Metal Complexes', discussing catalytic

Left to right: Shi-Xia Liu, Koji Nakanishi, Alain Krief

Ian Fleming, Koji Nakanishi

reactions performed with metal complexes of the well-known bis(oxazoline) 'box' and pyridyl-bis(oxazoline) 'pybox' ligands.

David A. Evans

Many chemists investigating catalysis focus upon the properties of the ligands; the focus here was more upon the properties of the metal centers used. The positive charge upon the metal, maintained through the use of a neutral ligand, inhibits aggregation. The electronic structure of the metal ion likewise has subtle effects upon the binding of substrate molecules. Copper(II) complexes are frequently square planar, having a high barrier to the assumption of a tetrahedral geometry but a low barrier to becoming pentacoordinate. The Jahn-Teller effect seen with penta- and hexa-coordinate copper(II) complexes brings axial ligands further out from the metal center than equatorial ligands, whereas tin(II) complexes possess a stereochemically active lone pair, which frequently blocks a coordination site and has the effect of pushing the ligand *trans* to itself further out from the metal center. With tridentate ligands, the substrate is thus strongly coordinated in the plane of the ligand in the case of copper(II), but weakly coordinated in the case of tin(II). Certain cases were discussed in which the stereoselectivity of a given transformation was thus inverted in going from copper to tin, giving the opposite enantiomer of product using the same chirality of ligand. Semi-empirical calculations of substrates complexed to metal box or pybox complexes reflect these metal preferences, as do the crystal structures of certain key intermediates. These structures also suggest the subtle roles played by counterion coordination.

The Lewis acid catalyzed ene reaction was investigated; box catalysts were shown to give products enantioselectively, allowing for a useful synthesis of amino acids from α-hydroxy esters in one step. Pybox-catalyzed aldol reactions were also investigated in depth. This revealed that the use of copper complexes of this 3-coordinate ligand involved 5-coordinate complexes as catalytic intermediates, in which the less basic ether oxygen binds axially, leading to attack on a single face of the substrate. Examples of catalytic scandium(III) pybox complexes were then discussed; calculations show that the metal has the same charge with this 3-coordinate ligand as does a copper(II) center with a 2-coordinate box ligand, leading to similarities in reactivity.

Following the final lecture, *Alain Krief* formally passed the torch, or rather the umbrella, to *Bernhard Kräutler* (University of Innsbruck), the chosen president of the 2006 conference.

Alain Krief, Bernhard Kräutler

Klaus Müller then announced the president of the conference for 2007: *Samir Zard*, professor at the École Polytechnique, Palaiseau. The fairy-tale conference thus dissolved, leaving all to descend back to the day-to-day small triumphs and tragedies of chemistry, leaving this elegant world behind us.

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