15th European Symposium on Organic Chemistry (ESOC 15), Dublin, Ireland

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The 15th conference in the highly successful biennial ESOC series was held in Dublin in July (8th−13th) 2007 under the Chairmanship of Professor P. J. Guiry (University College Dublin) and proved to be an outstanding week, offering some of the very best in organic chemistry from across Europe and further afield. A rather unique characteristic of the ESOC series is the broad range of organic chemistry that is covered, from supramolecular chemistry, through materials, synthesis, synthetic methodology, chirality, biological systems, structural and physical organic chemistry to computation. With a pervading theme of catalysis, in all its manifold guises: enzymic, organo-, organometallic, ionic, Brønsted, this meeting was no exception.

Chirality is ubiquitous in chemistry, but it is most commonly encountered as central chirality, where it is the spatial arrangement about one or more atomic centres that is of interest. Despite numerous advances in asymmetric synthesis, many motifs still present significant challenges. *Eugenijus Butkus* (Vilnius University, Lithuania) described an efficient enzymatic resolution of bicyclo[3.3.1]nonane-2,6-dione with Baker's yeast. The derivatisation of the pure enantiomers gave different bicyclic and polycyclic structures, which were studied by circular dichroism spectroscopy (CD), optical rotation (OR) and computation to determine the absolute configuration. In the second part of his talk, he described the design and synthesis of chiral self-complementary H-bonding molecules based on bicyclo[3.3.1]nonane and 4-oxo-5-azaindole to form channels, helical tubular structures and nanotubes. *Viktor Krasnov* (Ekaterinburg, Russia) discussed kinetic resolution (KR). He described the use of optically active acid chlorides, such as (*S*)-naproxen or *N*-tosyl-(*S*)-proline, and *N*-phthaloyl-(*S*)-alanine for the kinetic resolution of racemic amines. The study of the reaction conditions (solvent, temperature, use of additional bases), the effect of the acylating agent structure and the application of the best conditions to the KR of planar chiral 1-substituted-3-aminocarboranes were reported. Finally, he showed how the dynamic kinetic resolution of 5(4*H*)-oxazolones was a convenient preparative method for the effective antitumor agent Cypheline. The synthetic procedures for the rarer forms of chemical (molecular) chirality are far less well developed. *Ivo Stary* (Prague, Czech Republic) presented a multipronged assault on the demanding synthesis of helically chiral aromatic compounds, many of which display extraordinary optical rotatory powers. Preparative separations of the ra-

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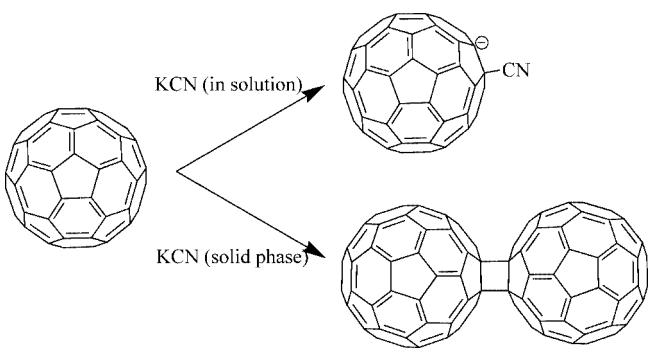
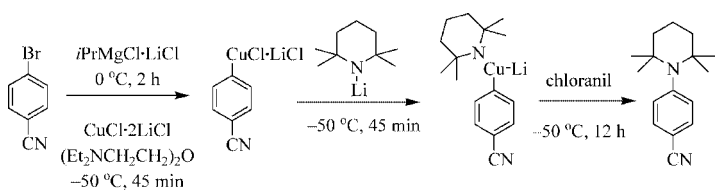
cemates by chromatography on chiral media proved highly efficient, allowing access to essentially enantiopure materials. More challenging is the asymmetric synthesis of helically chiral systems, and two techniques were described: the use of chiral auxiliaries and the use of cobalt catalysis with chiral ligands − both of which have given good results. These helical molecules are not just topologically fascinating species but are also proving of utility in their own right − for example in the generation of novel chiral ligands for asymmetric catalysis (Ir-catalysed amination). A theme of topological complexity was also strong in the lecture given by *Koichi Komatsu* (Kyoto University, Japan), who presented fascinating insights into fullerene chemistry. In particular, solid-state reactions were described, which involved high speed vibration milling. This can overcome solubility issues and produce different reactions as compared with when the chemistry is conducted in solution. For instance, the reaction of C_{60} with KCN in solution yields the green $C_{60}CN$ anion, whereas the same reaction in the solid state yields C_{60} dimers (Scheme 1). Also described was a process dubbed "molecular surgery". This involved modifying C_{60} by making a large opening in the cage wall, so that gas molecules (such as H_2) could be incorporated within. The opening was then closed by further chemical modification to yield a fullerene with H_2 trapped inside. During this process a large upfield shift in the ^1H NMR signal for H_2 was observed, from 4.50 ppm for free H_2 to −1.44 ppm for fullerene-caged H_2.



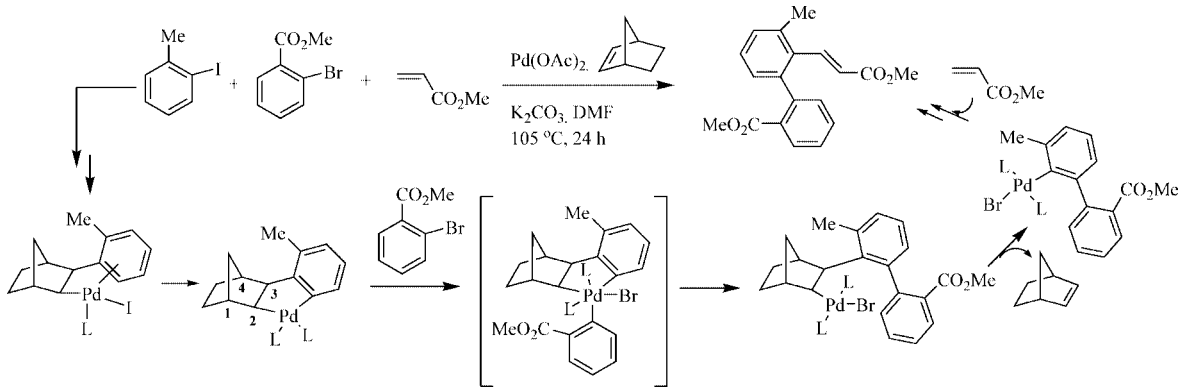
Scheme 1

The application of alternative reaction conditions and technologies was continued in the lecture by *Oliver Kappe* (Graz, Austria), who gave an excellent overview of microwave reactors as heating tools for chemists. We were provided with numerous examples to persuade us that microwave reactors should be "first choice" not "last resort" − they facilitate rapid but controlled superheating, allowing the use of conveniently volatile solvents at abnormally high temperatures and thus providing highly effective thermal acceleration of reactions. For poorly absorbing solvents, doping with ionic liquids or the use of passive silicon carbide heating elements can provide for high-efficiency heating, and the technology for parallel synthesis is rapidly evolving. In addition, the ability to access abnormally high temperatures can change the properties of the reaction medium from one with which we are familiar to one that becomes usefully different; for example, neutral water heated to 270−295°C becomes quite acidic. As chemists continue to tackle synthetic targets of ever-increasing complexity, there will always be a need for new synthetic methodologies. *Paul Knochel* (L.M.U. Munich, Germany) has long been leading the field with his elegant cascades of transmetallation sequences, each metal adding its own particular flavour in terms of selectivity to the synthetic repertoire. More recently he has developed powerfully efficient magnesium halide exchange processes driven by the thermodynamically favourable generation of *i*PrX and ArMgX from ArX and *i*PrMgX, often accelerated by added lithium chloride, via the dihalomagnesiate (Scheme 2). The efficient generation of aryl Grignard reagents at low temperatures allows compatibility with organic functionality not usually associated with such processes (esters, nitriles etc.). A subsequent transmetallation to copper (CuCl·2LiCl) allows the usual cuprate chemistry, but now with a remarkable addition of a new procedure: addition of lithium amides to the aryl cuprate followed by oxidative coupling with chloranil generates anilines. Even examples as hindered as tetramethylpiperidine (TMP) proceed well − thus providing a stoichiometric (Mg, Cu) but cheap alternative to the Pd-catalysed procedure for aniline generation from aryl halides (Hartwig-Buchwald coupling). The aryl halide approach has also been significantly expanded to include the use of a zinc-powder−LiCl combination, which generates aryl zincates within minutes at ambient temperature. A new reagent for aryl metallation was presented: $(TMP)_2NMg{\cdot}2LiCl$, which is readily generated from LiTMP and TMPMgCl·LiCl. This reagent displays high selectivity for deprotonation of aryl and heteroaryl rings at acidic but sterically available sites, with remarkable functional group tolerance. The power of the reagent was elegantly demonstrated in an iterative metallation / electrophilic capture process to generate a hexasubstituted aryl ring.

The pace of development in organometallic catalysis seems to know no end; mid and late transition metals still dominate the scene. *Marta Catellani* (Parma, Italy) reported on her pioneering developments in the use of norbornene as a *participative* catalyst component in palladium-catalysed aryl−aryl coupling and functionalisation (Scheme 3). The intramolecular elimination of hydrogen that is β-related to Pd in σ-alkyl complexes is well known to proceed by a *syn*-agostic interaction. Thus in an *exo*-2-pallada-3-aryl complex, generated by *syn*-[2,3]-carbopalladation of norbornene on the *exo*-face by a pal-



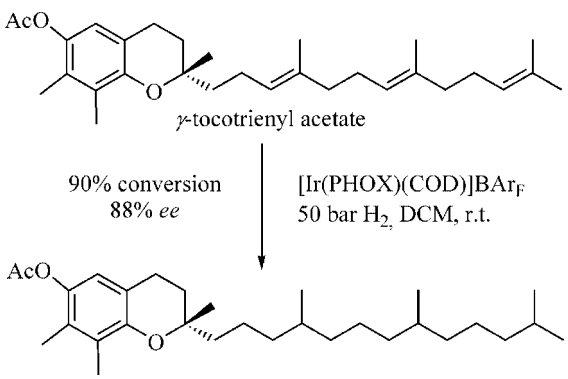
Scheme 2



Scheme 3

ladium aryl species, [2,3]-β-H elimination cannot proceed as the β-H is *anti* related. Moreover, [1,2]-β-H elimination cannot proceed, as this would result in a highly strained bridgehead alkene (Bredt's rule). The presence of the alkyl group on the Pd atom facilitates a curious new manifold of reactivity: a second oxidative addition of Ar−X and then rapid intramolecular arylpalladation of the aryl ring. By careful choice of aryl oxidative addition partners, remarkably high selectivity can be attained for differential participation in the two unique oxidative addition events. A combination of electron-rich aryl iodide with an electron-poor aryl bromide was found to be particularly effective. The catalytic cycle is completed by *syn*-elimination of arylpalladium, whereby the norbornene is released, and final capture of the arylpalladium by terminating agents such as a hydride, an organometallic compound or an alkene is allowed. At every stage of the reaction there is the potential for pitfalls arising from incorporation of one or more of the various components in the incorrect order. And yet, each step proceeds with exquisite selectivity. The wide range of aryl and terminating reactants that have now been successfully employed by Catellani, and by others, is inspirational.

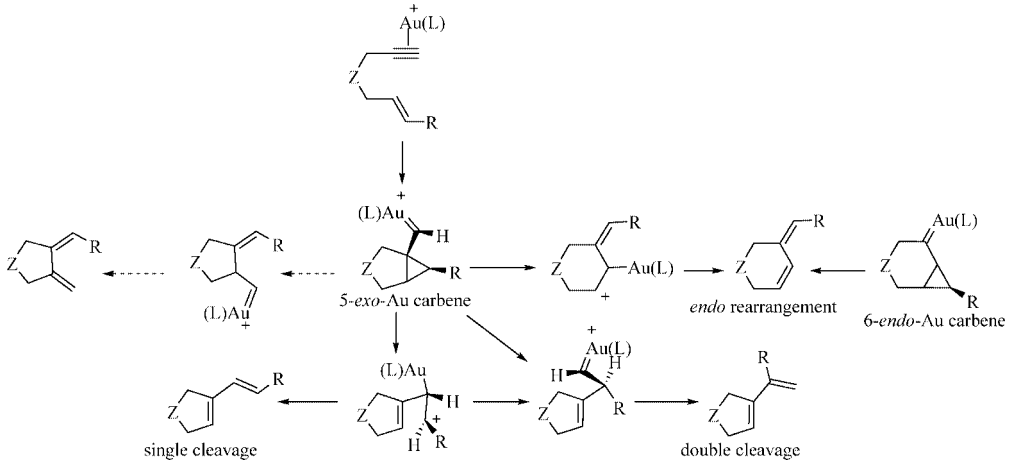
Allylic substitution is an area of palladium catalysis that is still ripe for development, despite its relative maturity in the field. *Andreas Pfaltz* (University of Basel, Switzerland) described a new screening method for chiral catalysis based on electrospray mass spectrometry to detect small concentrations of cationic intermediates, inspired by the work of Peter Chen (ETH, Zurich) in homogeneous polymerisation. His group have used this method in direct enantiomeric determination of the intrinsic enantioselectivity of the cationic Pd-complex intermediates in the allylic alkylation of mixtures of quasienantiomeric allylic substrates in homogeneous solution. This technique allows the comparison of different catalysts at the same time, the use of ligands as quasienantiomers, and it can also be applied to the reaction desymmetrisation of *meso* compounds bearing two enantiotopic leaving groups. Examples of other reactions analysed by this methodology, such us 1,4-additions or retro-Diels−Alder reactions involving cationic Cu species, were also presented. In the second part of his talk, he described the latest results in the Ir-catalysed asymmetric hydrogenation of olefins and furans with chiral phosphinooxazoline (PHOX) ligands for the reaction (Scheme 4). The ultimate goal was to find a catalyst for the reaction of nonactivated tetrasubstituted alkenes, and an example of the application to the synthesis of natural products with a long alkyl chain (tocopherols) was also described.



Scheme 4

In a similar manner to the explosive developments in palladium chemistry two or three decades ago, the chemistry of gold is the new El Dorado of catalysis. One of the contemporary masters in this field, *Antonio Echavarren* (I.C.I.Q., Tarragona, Spain) gave a fascinating lecture about the Au^I chemistry of enynes (Scheme 5). He started by summarising the previous results obtained in his group on the Au^I-catalysed stereoselective alkoxycyclisation of enynes to give 5-, 6- or 7-membered-ring carbocycles, the reaction of enynes containing enol ethers and the skeletal rearrangement of enynes to give products of single or double cleavage and cyclobutenes. A very detailed mechanistic study on the skeletal rearrangement of enynes, showing cyclopropyl Au^I carbenes as the main intermediates of this reaction, was presented.

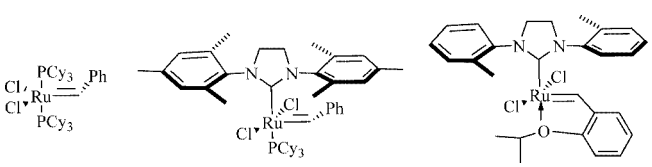
He also described new Au^I complexes with bulky phosphine, phosphite and *N*-heterocyclic carbene ligands that have been demonstrated to be even more reactive and have opened the possibility of new intra- and intermolecular reactions to trap the cyclopropyl Au carbene. Among the intramolecular reactions are the formation of tetracyclic structures by trapping additional olefins present in the molecule, the [4 + 2] cycloadditions of 1,3-enynes with aryl substituents in the alkynyl position and the Prins cyclisation of enynes bearing a carbonyl group at the alkenyl side chain. Olefins and other carbon nucleophiles (aryls, indoles, allyl silanes, 1,3-dicarbonyl com-



Scheme 5

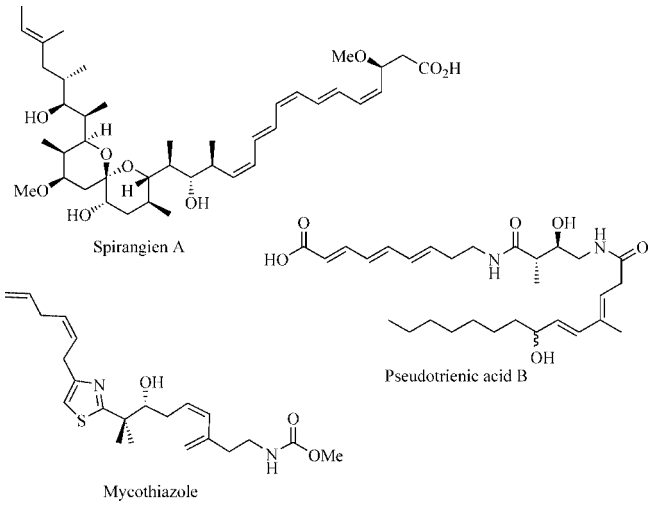
pounds) have also been used to trap the two different 5-*exo*-cyclopropyl Au carbene intermediates in an intermolecular manner, giving two types of products from the reaction at the cyclopropane or the carbene. Finally, some examples of the Au^{I}-catalysed reaction of indoles with alkynes to give eight-membered rings and the intramolecular carbostannylation of alkynes catalysed by Ag^{I} complexes were presented.

The discussion of organometallic catalysis culminated in a magnificent talk from *Robert Grubbs* (California Institute of Technology, Pasadena, CA, USA) about olefin metathesis. The talk started by placing current developments in context, summarising the mechanism, catalysts and variants (CM, ROCM, RCM, ADMET, ROMP). Then, a series of industrial applications of the metathesis reaction were reported. For example, the conversion of low-cost natural oils such as seed oils (highly unsaturated) to value-added, well-defined chemical structures (polyesters or polyolefins) in the absence of solvents, or the transformation of soybean oil through metathesis of oligomers, which after hydrogenation give soy-waxes that can be readily fragranced and machined in the fabrication of aromatic candles and wax blends. The preparation of ^{18}F-labelled nanoparticles, used in the detection of tumours, from block polymers synthesised by olefin metathesis was also described. The pharmaceutical applications of RCM led to the last part of the talk, where the latest improvements on the catalysts and ligands were reported. It was shown that phosphine ligands are involved in catalyst decomposition and that *N*-heterocyclic carbene ligands with different steric hindrance are able to control the geometry of the intermediate carbene and metallacycle complexes, improving the efficiency in the reaction of sterically hindered olefins, the reaction involving vinyl chlorides or vinyl boronic esters (Scheme 6). The difficult problem of *E*/*Z* control was addressed at the end of the talk.



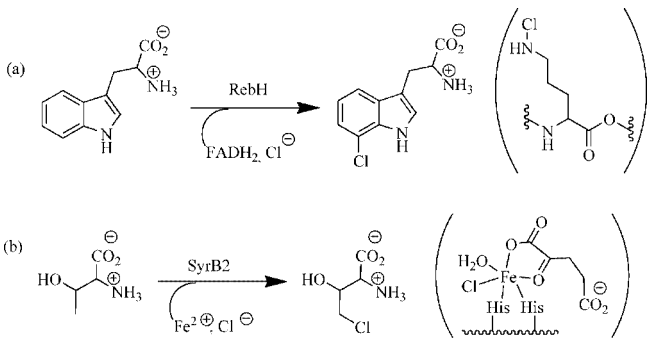
Scheme 6

The zeitgeist in catalysis is of course organocatalysis, and *Petri Pihko* (Helsinki University of Technology, Finland) reported on organocatalysts in organic synthesis, including an enantioselective L-proline-catalysed formation of prelactone B and aqueous pyrrolidine-catalysed aldol condensations as alternatives to the Wittig reaction. Natural products are ever-popular as challenges for synthesis. *Floris Rutjes* (Radboud University, Netherlands) presented his findings from research into glycopeptide synthesis, in which unstable acetal linking groups were replaced with 1,2,3-triazoles using "click" chemistry. *Emmanuel Theodorakis* (San Diego, USA) described the synthesis of norrisolides, a novel family of metabolites from sea slugs, and some analogues with designed properties such as fluorescent probes and recognition elements that facilitate the structural interrogation of cell biology. He then moved on to a lucid discussion of the beguiling chemistry associated with the synthesis of "caged xanthones", which are at the core of a family of compounds isolated from the *Garcinia* plant. A "bio-inspired" synthetic approach led to a remarkable sequential Claisen rearrangement / intramolecular Diels−Alder reaction (CiDA) of *O*,*O*′-diallyl aryl ethers. Differentiation of the two allyl groups in terms of their participation in the CiDA process leads to all four forms of the xanthone cage and neo-cage found in the natural products. An analysis of the selectivity factors yielded "hidden reactivity principles" within these fascinating cage motifs. *Janine Cossy* (CNRS, France) presented research covering chemoselective methods for synthesis of complex natural products (Scheme 7). The first target molecule was spirangien A. A key methodology employed in its synthesis was an iron-catalysed cross coupling of a Grignard reagent with an alkyl halide in the presence of TMEDA. Also described was a synthesis of mycothiazole, which required a method for installing a conjugated *Z* dienol moiety. Under standard olefin metathesis conditions, the *E* isomer was the only product obtained. However, when the two reacting olefins were tethered together by a sulfone ester, the desired *Z* isomer was formed instead. A convergent strategy was used in the synthesis of another target molecule, pseudotrienic acid B, including an enantioselective crotyltitanation to furnish a key chiral centre in the $C_{10}-C_{13}$ fragment.



Scheme 7

Paul V. Murphy (University College Dublin, Ireland) reported on developments in glycosidation chemistry. He described the reaction of glucuronic acids with $TMSN_3$ and $SnCl_4$ to obtain 1,2-*cis*-glycosides, not observed before. Mechanistic studies showed the participation of the acyl group on C_6 to form 1,6-lactones as intermediates (in contrast with the most common participation of the acyl group on C_2 to give 1,2-*trans*-glycosides) and a slow anomerisation reaction during this process. He then talked about some applications of this sugar chemistry in the synthesis of glycosphingolipids and cyclophane−sugar hybrids, including a β-cyclodextrin mimic. To finish his talk, he described the synthesis of novel migrastatin and dorrigocin analogues (important inhibitors of cell migration in metastasis processes) from D-glucal, by a ring-closing metathesis as the key step to assemble the macrocycle. The mechanistic and structural aspects of natural products and their synthesis with enzymes was presented by *Catherine Drennan* (MIT, USA). She elegantly showed how X-ray crystallography can be an extremely powerful tool in the study of enzymes involved in the biosynthesis of halogenated natural products. The first process described was the RebH-catalysed synthesis of 7-chlorotryptophan (Scheme 8). RebH utilises flavin as a coenzyme oxidant, and it was proposed that the chlorine source was a lysine chloramine residue within the enzyme active site and not free HOCl. Studies involving X-ray crystallography, chromatography and enzyme kinetics supported this hypothesis. The second enzyme described was SyrB2, in which a non-heme Fe^{II} coenzyme catalyses the chlorination of threonine in syringomycin biosynthesis. SyrB2 is related to enzymes that catalyse hydroxylation, and it was shown that its chlorination activity stems from an aspartic acid → alanine mutation in the peptide chain. This exposes the Fe^{II} in the active site, so it can form a chloride complex, which then transfers chlorine to threonine by a radical pathway.



Scheme 8

The structural and physical aspects of organic chemistry were well represented at the meeting. *Amnon Stanger* (Israel Institute of Technology) described computational approaches for determining aromaticity and C−H bond dissociation energies. In the former case, an intriguing NICS scan approach was presented as a much more interrogative tool than the classic fixed-distance NICS technique − giving insight into previously ambiguous data and conclusions. *Chris Hunter* (Sheffield, UK) gave a captivating account of his ongoing efforts to deconvolute an aspect of organic chemistry that is omnipresent yet often ignored through lack of understanding: solvation. Most chemists have an intuitive but *qualitative* comprehension of solvation, which is based on "at the bench" experience. However, it is hard to *quantitatively* predict, even for *single*-solvent systems, for example, the effect on simple molecular recognition events (intermolecular binding). We were presented with a striking example: the association constant (K) of $Bu_3P(O)$ and $(CF_3)_3C-OH$, is 2700 M^{-1} in $CHCl_3$, 240 M^{-1} in THF and yet only ca. 10 M^{-1} in a 1:1 mixture of the two! After a holistic treatment of the factors commonly accepted to be important in molecular recognition, it was convincingly demonstrated, by way of cleverly designed molecular probes, that many of these contribute in a rather minor way, often as a result of compensatory effects. However, it emerged that hydrogen bonding, in its manifold forms, between the solvent molecules themselves and between the solvent and the solutes, plays a key role, and an elegant analysis of the thermodynamics of such a solvent competition model was presented. The augmentation of the known solvent descriptors α_S and β_S, through addition of α and β (the hydrogen-bond-donor and -acceptor parameters of the solutes) allowed the development of contour plots of ΔG (z axis) versus $\{\alpha-\alpha_S\}$ (y axis) and $\{\beta-\beta_S\}$ (x axis) for commonly encountered solvents. These plots proved intuitive to use, and the lecture culminated with a simple and utterly convincing explanation for the curious variation in K alluded to above.

