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Organic Chemistry and the Synthesis of Complex Molecules. A tribute to István E. Markó

Thursday 12th and Friday 13th September 2019

Auditoires Croix du Sud 18

Place Croix du Sud – 1348 Louvain-la-Neuve

UCLouvain - Institut IMCN
Place Louis Pasteur, 1 bte L4.01.06
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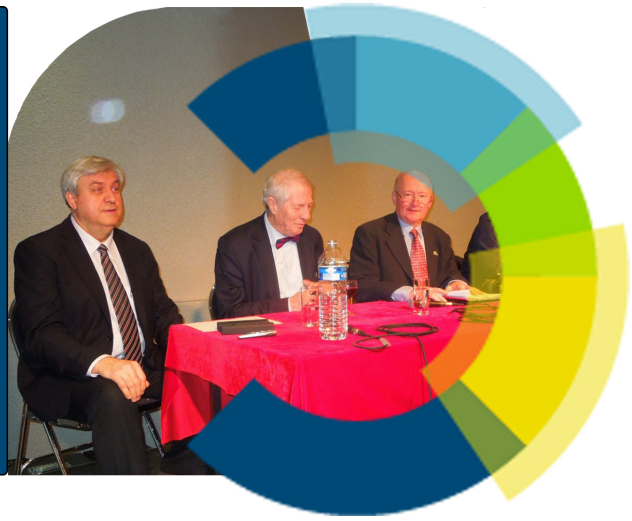
István was a good friend of the section and a frequent contributor to many of our activities from demonstration lectures to our *Café Chimique* debates.

About RSC Belgium

RSC Belgium is part of the UK-based Royal Society of Chemistry (RSC) that boasts over 49 000 members worldwide. RSC Belgium was established in 1989 and has some 120 professional members. The section organises an annual programme of lectures, visits, school activities and social events with the principal objective of promoting the chemical sciences to the public.



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BIOGRAPHY OF

ISTVÁN E. MARKÓ

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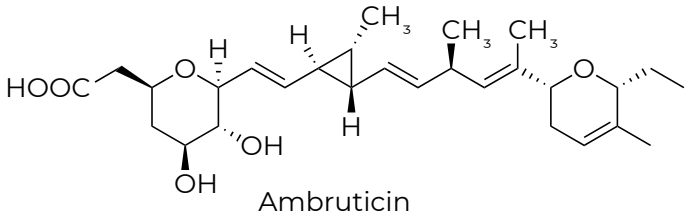
István E. Markó (June 18, 1956 – July 31, 2017) was a **scientist** and **organic chemist**. He was lecturer in the University of Sheffield for 5 years and subsequently for more than twenty years at the Université catholique de Louvain.

He is best known for his numerous contributions to the total synthesis of natural products, including an **unpublished total synthesis of Ambruticin**.



Ambruticin

Professor Markó was also an accomplished mentor of young chemists and many of his students have gone on to make significant contributions in their own right.

István was the eldest of three brothers and was born in Pápa (Hungary) in 1956. His family fled the Soviet repression in 1956 and settled initially in Jemelle, a small village in the Belgian Ardennes when he was only 4 months old. The family subsequently moved to Wavre where he spent his teenage years.

He always had two passions: science and drawing, and although he had a hard time making a choice between the two, happily he finally opted for chemistry, although he always kept alive his passion for comics and drawing. A testament to this are the many drawings found in his notebook in which he would routinely doodle while on the phone. He was happily married to Patricia and had 2 children, Imre and Aurélia.

After his schooling in Wavre, István studied for a "*Licence en Sciences Chimiques*" at the Université catholique de Louvain (Belgium) from 1974 to 1978 (*Summa cum Laude*). He then obtained his PhD in 1983 under the supervision of professor **L. Ghosez**, in collaboration with Union Chimique Belge; the thesis was entitled "*Semi-synthesis of Tricyclic Penicillins*" (*Summa Cum Laude*).

Between 1983 and 1985 he undertook postdoctoral studies in the group of L. Ghosez ("*Intramolecular Keteniminium Cycloadditions. A New Route Towards Prostaglandins*"). Then between 1985 and 1987, he moved to Burlington (University of Vermont, Vermont, USA), working in the group of professor **M.E. Kuehne** ("*Biomimetic Total Synthesis of Monoterpene Indole Alkaloids and Binary Vinca Alkaloids*"). In 1987 he joined the research group of professor **K.B. Sharpless** (MIT, Massachusetts, USA) and worked on the C*atalytic Asymmetric Osmylation of Olefins*.

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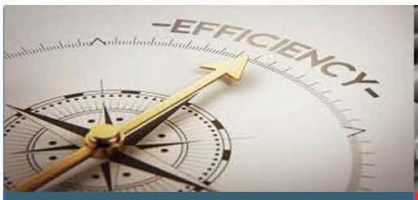

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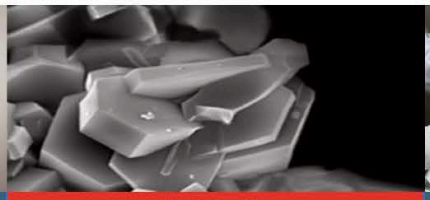

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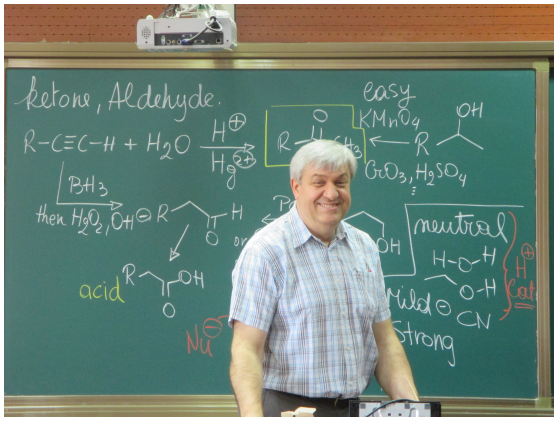
In 1988, he decided to move back to Europe to take up a lecturer position in the University of Sheffield (United Kingdom), where he stayed for 5 years. In 1993 he had the opportunity to come back to his *alma mater*, where he stayed until his death in 2017.



As a professor, he gave courses to bachelor's and master's students of chemistry and bio-engineering (Organic chemistry, Medicinal chemistry, Applied organic chemistry, Biosynthesis and total synthesis of natural products and Industrial chemistry...).

The main **research areas** in his laboratory were: Short, efficient and stereocontrolled total synthesis of natural products - Extraction, purification and structure identification of novel natural products - Development of new methodologies based on multiple bonds and ring formation - Asymmetric catalysis with and without metals - New organometallic reagents -Anionic polycyclisation reactions -Electroorganic synthesis - Development of ecological processes – Botanochemistry - Use of enzymes and microorganisms in organic chemistry - Use of CO_2 as a basic 1-carbon unit...

In the course of his career, Professor Markó supervised 39 post-docs, 66 PhD students, 92 master's students and 58 bachelor's students.

In January 1995, a group of young chemists including István Markó, launched the **European Chemical Society (ECS)**, which at its inception, anticipated working together with the existing national chemical societies to promote chemistry at the European level.

During his career, professor Markó received several **awards**: “Concours Universitaire” (1979), “Prix J. S. Stas” (1983), “Prix P. Bruylants” (1984), R.S.C. Perkin Division Academic Staff Conference Award (1989), Nuffield Foundation Award to Newly Appointed Science Lecturers (1989), Royal Society Parliamentary Grant (1990), Zeneca Fellow (1994 to 1997), Merck Young Investigator Award (1995 - Left picture), Merck Fellow (1996-1997), Prix Triennal de la Société Royale de Chimie (Belgium), Sandoz Chemistry Lectureship (1996), Merck Academic Development Program Award (1996-1999, 2001-2008), Member of the Hungarian Science Academy (2000), Rhodia Oustanding Award and Merck-Froost Lectureship (2002), AstraZeneca European Lectureship (2003), Merck Lectureship Award, Upper Rhine Lectureship Award and Zeneca Foreign Lectureship Award (2005),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Prix Tractebel Environnement (2006), Roche Chemistry Lectureship (2007), Boehringer Ingelheim Distinguished Lectureship (2008), Seasky Award Fellowship (2011-2013), Recipient of the High End Award (2014) among others.

He was scientific **referee** for many journals, including Advanced Synthesis & Catalysis, Angewandte Chemie, Chemical Communications. Chemistry a European Journal, European Journal of Organic Chemistry, Journal of the American Chemistry Society, Journal of Molecular Catalysis, Journal of Organometallic Chemistry, Perkin Transactions, Journal of Organic Chemistry, Synlett, Tetrahedron Asymmetry, Tetrahedron Letters, Tetrahedron.

Professor Markó was **consultant/member of scientific directorate** for a number of companies including Janssen Pharmaceutica, Merck Sharp & Dohme, Rhône-Poulenc, Rhodia, Lytix Biopharma. A.S. (Norway).

During his career he was member of the Advisory Board of Perkin Publication, Chairman of the European Chemical Society, member of the Editorial Board of ARKIVOC, and member of the Editorial Board of Chemistry, a European Journal.

He was the **author** of over 250 publications, more than 200 of them in refereed journals, 19 patents and 16 reviews for books, as well as 38 articles in Belgian newspapers on "*Chemistry in our Society*". He delivered more than 20 general public lectures on "*the key-role of chemistry in our modern society*" and gave more than 350 conferences worldwide.

István regularly took part in **television broadcasts** (RTBF and RTLtvi) to popularize science in order to make it more accessible, notably in collaboration with the Belgium section of the Royal Society of Chemistry, in order to encourage younger pupils to get excited about science, and in particular Chemistry. He was particularly active, together with his faithful technician Fabio Lucaccioni, in performing chemistry shows for schools.

Professor Marko was able to generate the desire to do chemistry among many students, even those outside of organic chemistry.

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Scientific Program

Thursday 12th September 2019

12.45 – 13.45	**Registration**
13.45 – 14.00	**Opening Ceremony**
Session 1	**Chairman – Professor Raphaël Robiette (UCLouvain)**
14.00 – 14.45	*"Unexpected chemistry provides unexpected protein kinase inhibitors", **Professor John Sigurd Svendsen** (The Arctic University of Norway*
14.45 – 15.30	*"Enantiospecific synthesis of 5- and 6-membered nitrogen heterocycles", **Professor Donald Craig** (Imperial College London)*
15.30 -16.00	Coffee Break
16.00 – 16.45	"*Synthesis of complex molecules and development of methods*", **Professor Jeanine Cossy**, (*Ecole Supérieure de Physique et de Chimie Industrielle de la ville de Paris*)
16.45 – 17.30	"*Assembly Line Synthesis*", **Professor Varinder Aggarwal** (*University of Bristol*)
17.30 – 18.15	"*From Molecules to Dynamic Molecular Systems*", **Professor Ben Feringa**, (*University of Groningen*) – *Nobel Prize of Chemistry 2016*

Friday 13th September

Session 2	**Chairman – Professor Jean-François Gohy (UCLouvain)**
09.00 – 09.45	"*Recent advances in enantioselective catalysis*", **Professor Anita Maguire** (*University College Cork*)
09.45 – 10.30	*"Design and synthesis of complex biomolecular constructs for diagnostic devices", **Professor Annemieke Madder** (Ghent University)*
10.30 -11.00	Coffee Break
11.00 – 11.45	"Chemistry and Biology of Sorangicins", **Professor Dieter Schinzer** (*university of Magdeburg)*
11.45 – 12.30	"*August Kekulé : Beyond the Snake Dream*", **Professor Pierre De Clercq** (Ghent *University*)
12.30 -14.00	Lunch in the lobby of the Auditorium Croix du Sud

Session 3	**Chairman – Professor Michael Singleton (UCLouvain)**
14.00 – 14.45	"*Synthetic Access to Metal-NHC complexes for Catalysis*", **Professor Steven Nolan** (*Ghent University*)
14.45 – 15.30	"*Scaling up Organic Chemistry to Kg and Tonne Scale; what goes wrong!!*", **Dr Trevor Laird** (*Trevor Laird Associates*)
15.30 -16.15	Coffee Break
16.15 – 17.00	"*Total synthesis of Natural Products as a Driver for Development of New Methods*", **Professor Ari Koskinen** (*Aalto University*)
17.00 – 17.30	**Closing Ceremony**
18.00	Drink in the Hall Sainte Barbe
19.00	BBQ in the Hall Sainte Barbe

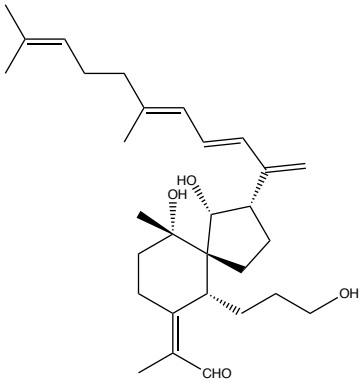
ABSTRACTS

Unexpected chemistry provides unexpected protein kinase inhibitors

Istvan E. Marko[a], Florian Schevenels[a] and **John S. Mjøen Svendsen**[b]

a) Laboratorie Chimie Organique et Médicinale, Université Catholique Louvain
b) Department of chemistry, UiT, The Arctic University of Norway

Istvan had in his whole academic life a strong interest in complex natural products, the more bizarre the molecular framework and unusual the stereochemistry, the more intriguing he found them. Always looking for a novel and efficient synthetic strategy he loved to discuss his ideas with his collogues, standing with a piece of chalk in his hand before the blackboard. If you encountered him in this state of mind, you better not have any other plans for the afternoon.



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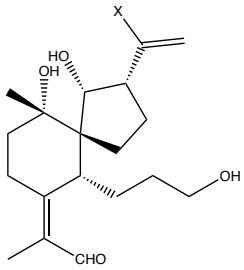
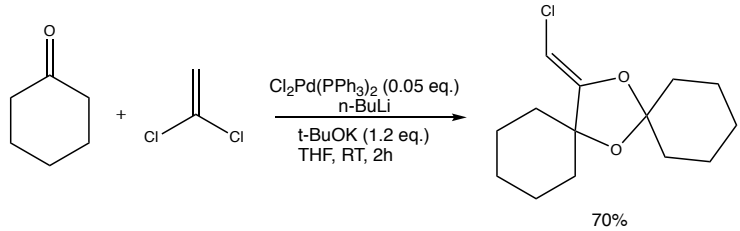


2

Spiroiridal (1) was one of these targets he took a particular interest for, and Istvan convinced a graduate student, Florian Scevenels, to embark on the total synthesis of spiroiridal by first preparing the model compound (**2**). On the route to compound **2**, a palladium catalyzed enolate coupling with a halo-olefin was needed. To save precious starting material, Florian tested the reaction on cyclohexanone. To the great surprise to everyone, none of the expacted vinylcyclohexanone derivative was formed, rather a chloromethylene-ketal was obtained in good yield.



70%

At this point Florian and Istvan abandoned the spiroiridal total synthesis in the pursuit of developing the new-found reaction into a synthetically useful protocol. My lecture will show how this novel chemistry could be used to prepare heterocyclic molecules suitable for the development of protein kinase inhibitors and how synthetic chemists and medicinal chemists must cooperate in order to transform a novel reaction to a useful and practical tool.

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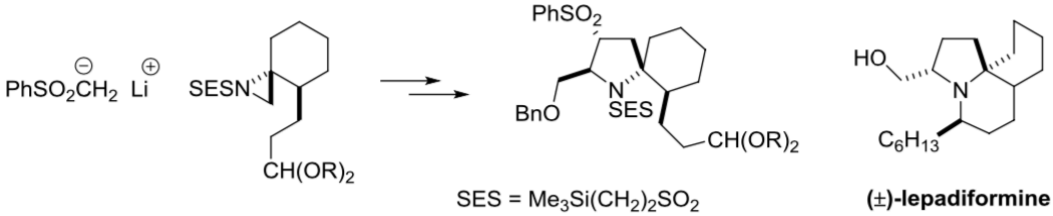
Stereoselective synthesis of 5-, 6- and 7-membered nitrogen heterocycles

Donald Craig

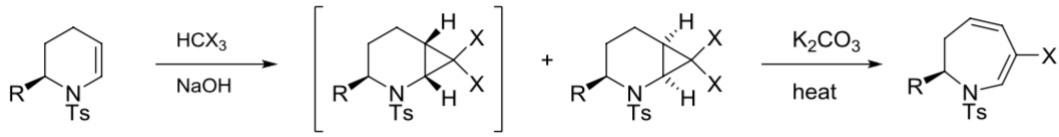
Department of Chemistry, Imperial College London, Molecular Sciences Research Hub White City Campus, 80 Wood Lane, London W12 0BZ, UK d.craig@imperial.ac.uk

This lecture will describe the development of synthesis methods based on ring-opening of activated aziridines by carbon nucleophiles and their application to the synthesis of 5-, 6- and 7-membered nitrogen heterocycles. Simple sulfone-stabilised carbanions enter into ring-opening reactions with a spiroaziridine as part of a sequence culminating in the total synthesis of the marine alkaloid lepadiformine.

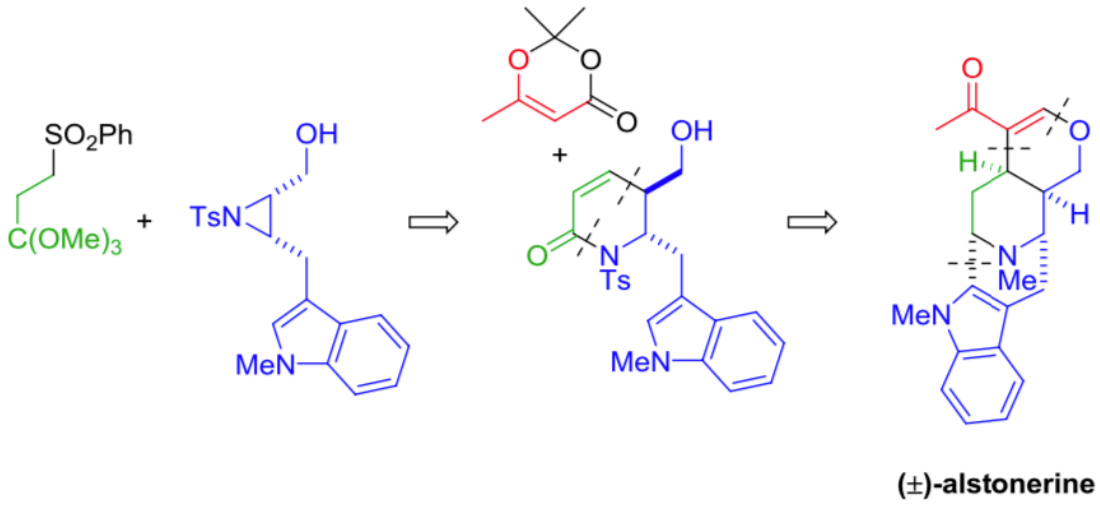


SES = $Me_3Si(CH_2)_2SO_2$ **(±)-lepadiformine**

Sulfone-containing nucleophiles possessing appended acetal groups give bis(sulfonyl)-substituted tetrahydropyridines on acid treatment of disubstituted aziridine ring-opening adducts. These heterocycles enter into highly regio- and stereoselective substitution reactions when combined with soft carbon nucleophiles in the presence of Lewis acids. In combination with dihalocarbenes, simpler monosulfonyltetrahydropyridines provide cyclopropanated 2-azabicyclo[4.1.0] adducts with moderate syn diastereoselectivity. Base-mediated elimination of HX provides halogenated 2,3-dihydro-1H- azepines, which enter into Pd(0)-catalysed C–C bond-forming transformations and highly selective [4+2] cycloaddition reactions in conventional and cascade modes.



Trisubstituted aziridines possessing additional hydroxymethyl or vinyl groups show complete regioselectivity in stereospecific ring-opening reactions, and this reactivity is harnessed in a total synthesis of the naturally-occurring macroline-related indolic alkaloid (±)-alstonerine.



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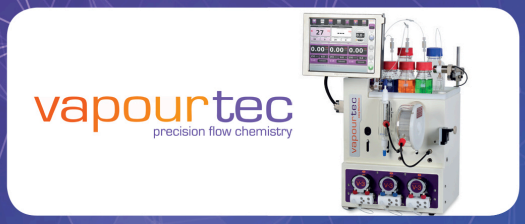

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TRANSITION METAL-CATALYSTS CONSTRUCTION AND FUNCTIONALIZATION OF HETEROCYCLES

Janine COSSY

Molecular, Macromolecular Chemistry and Materials
ESPCI Paris, CNRS, PSL University,
10 Rue Vauquelin, 75231 Paris Cedex 05, France

email: janine.cossy@espci.fr

Complex natural and/or bioactive molecules are a good source of inspiration to develop methods. One major challenge, in synthetic organic chemistry, is the design and execution of concise and efficient approaches to these molecules by generating the minimum of wastes.

Strategies that are using reactions that rapidly lead to the skeleton framework of natural and/or biologically active compounds are attractive. In the context of developing facile entries to oxygen and nitrogen containing heterocycles, present in complex molecules, we have explored their construction and functionalization by tuning up coupling reactions, C-H activation, enantioselective alkylations using transition metal catalysts. These methods and their applications to the synthesis of biologically active complex natural and non-natural heterocycles will be presented.

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Assembly Line Synthesis

Varinder Aggarwal

School of Chemistry, University of Bristol, UK

v.aggarwal@bristol.ac.uk

Nature has evolved highly sophisticated machinery for organic synthesis, many of which resemble molecular assembly-line processes. So far chemists have been able to apply this type of approach in the synthesis of peptides and oligonucleotides but in these reactions, simple amide (C–N) or phosphate (P–O) bonds are created. It is much more difficult to make C–C bonds but this is central to the discipline of organic synthesis. This difficulty is why organic synthesis is challenging and why robust, iterative or automated methodologies have not yet emerged.

Here, we describe the application of iterative homologation of boronic esters using chiral lithiated carbamates and chloromethyllithium enabling us to grow carbon chains with control over both relative and absolute stereochemistry. Applications of this strategy to the synthesis of natural products will be demonstrated. I will show how the methodology can be applied to polydeoxypropionates and to the larger family of polyketides, polyacetates.

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2- J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature*, 2008, **456**, 778.

3- S. Balieu, G. E. Hallett, M. Burns, T. Bootwicha, J. Studley, V. K. Aggarwal, *J. Am. Chem. Soc*. **2015**, *137*, 4398.

4- M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature*, **2014**, *513*, 183.

5- J. Wu, P. Lorenzo, S. Zhong, M. Ali, C. P. Butts, E. L. Myers, V. K. Aggarwal, *Nature*, **2017**, *547*, 436.

6- C. Sandford, V. K. Aggarwal *Chem. Commun*., **2017**, *53*, 5481.

C.G.B. - C.B.B.

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In addition C.G.B-C.B.B. stimulates all initiatives that support young researchers in chemistry at Belgian research laboratories and research laboratories in chemistry at Belgian universities and associations of higher education.

C.G.B.-C.B.B. promotes the European journals of ChemPubSoc, contributes to the establishment of new European research journals and motivates Belgian scientists to publish their research in these European journals and to participate in the activities of C.G.B.-C.B.B.

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From Molecules to Dynamic Molecular Systems

Ben L. Feringa

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Summary. The fascinating molecular motors and machines that sustain life offer a great source of inspiration to the molecular explorer at the nanoscale Among the major challenges ahead in the design of complex artificial molecular systems is the control over dynamic functions and responsive far-from-equilibrium behaviour. Chemical systems ultimately require integration of structure, organization and function of multi-component dynamic molecular assemblies at different hierarchical levels. A major goal is to achieve and exploit translational and rotary motion.

In this presentation the focus is on the dynamics of functional molecular systems as well as triggering and assembly processes. We design switches and motors in which molecular motion is coupled to specific functions. Responsive behaviour will be illustrated in self- assembly and control of biological function. The design, synthesis and functioning of rotary molecular motors will also be presented with a prospect toward future dynamic molecular systems

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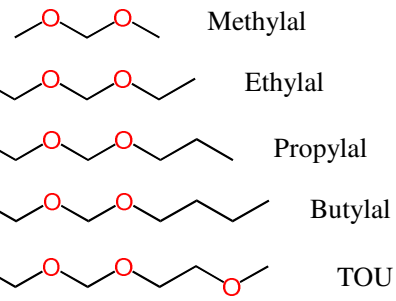
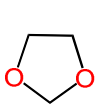
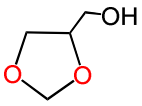
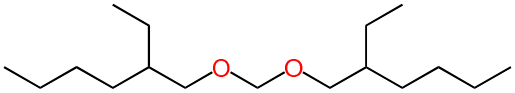




1,3-Dioxolane



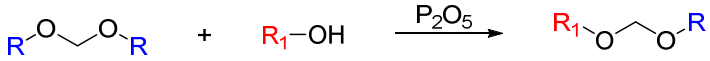
Glycerol Formal



2-EthylHexylal

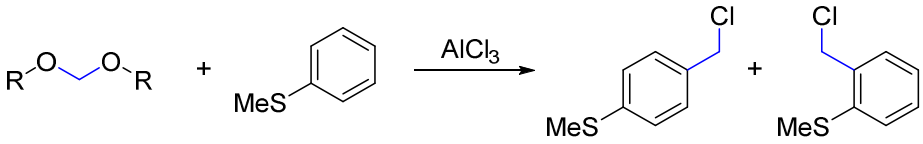
Acetals are not only solvents

Acetal can react with an alcohol to form the protective groups -oxymethyl ethers.



(If R= Me, R_1-OMOM)

In Friedel-Crafts conditions, acetal performs the chloromethylation of aryls.



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Recent advances in enantioselective catalysis

Anita R. Maguire

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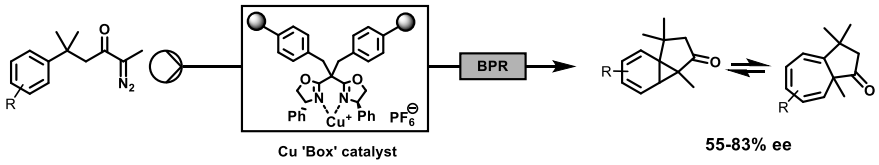
α-Diazocarbonyl compounds are versatile synthetic reagents that can undergo a wide variety of transformations under transition metal catalysis, thermolysis or photochemical conditions. The reactions proceed *via* reactive intermediates such as ketenes, carbenes or carbenoids, and often with excellent selectivity.[1] Over the last decade or so, we have demonstrated highly enantioselective copper–bis(oxazoline) catalysed intramolecular C–H insertion reactions of a-diazo-b-oxo sulfones, generating thiopyrans, sulfolanes, sultones, β-lactams and γ-lactams.[2] This catalyst system has been shown to enable effective desymmetrization of a-diazo-b-oxo sulfone substrates[3] and has also proved useful for intramolecular Buchner addition of a-diazoketones.[4]

To enhance the accessibility of α-diazocarbonyl chemistry at scale,[5] we have established methods for continuous diazo transfer.[6] These methods overcome challenges associated with use of heat and shock sensitive diazo transfer agents,[7] and include the *in situ* generation and use of tosyl azide and mesyl azide, leading directly to the a-diazocarbonyl compounds, without isolation or handling of the hazardous sulfonyl azides.[6] Furthermore, we have demonstrated that the reaction of the a-diazocarbonyl compound can be telescoped in flow with the diazo transfer sequence. Control features including spectroscopic reaction monitoring and an in-line quench system have additionally been incorporated for enhanced process safety. Recently a continuous process has also been developed for the asymmetric Buchner reaction using an immobilised and recoverable copper–bis(oxazoline) catalyst (Scheme 1),[8] enabling potential telescoping of the generation and subsequent reaction of the α-diazocarbonyl substrate *in situ*.



Scheme 1

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Design and synthesis of complex biomolecular constructs for diagnostic devices

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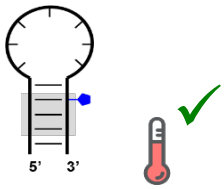
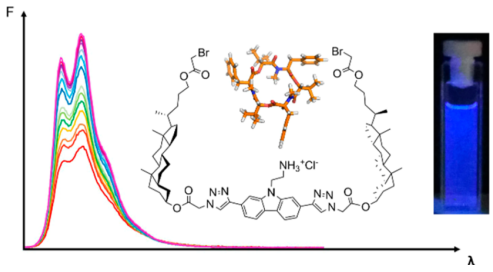
Stable biosensing devices are key in the efficient detection of biomarkers as well as in the monitoring of environmental pollutants. The talk will give an overview of our most recent achievements in the development of methodologies for covalent and non-covalent stabilization of biomolecular constructs for further us in a biosensor context.

DNA directed immobilization allows to precisely position a series of proteins on addressable array surfaces. The development of a furan-oxidation based methodology[1] for the stable covalent linking of oligonucleotide conjugates onto surfaces will be discussed.



Furthermore, the design and synthesis of so-called 'frozen' aptamers as small molecule receptors for immobilization onto electrochemical surfaces will be discussed. Introduction of imidazole modified nucleotide building blocks in a particular sequence context, allows for stabilization of the aptamer fold through non-covalent interstrand interactions.[2] Efforts towards exploitation of our furan-oxidation induced covalent interstrand crosslinking technology[3] for aptamer stabilisation will be discussed.



Finally, the bottom-up design of an artificial receptor for medium-sized cyclodepsipeptide toxins will be highlighted. Through a combination of careful design and modelling with experimental validation of binding affinity, we have developed a series of receptors for the food toxins Beauvericin and Cereulide.[4] Applications in solid phase extraction of the toxins out of complex food matrices as well as the potential use of the artificial receptors as anti-dotes for Cereulide poisoning will be illustrated.

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Recent Progress in Complex Natural Product Synthesis

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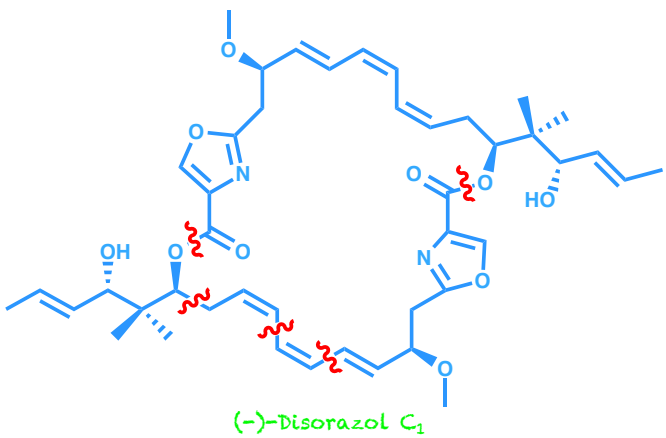
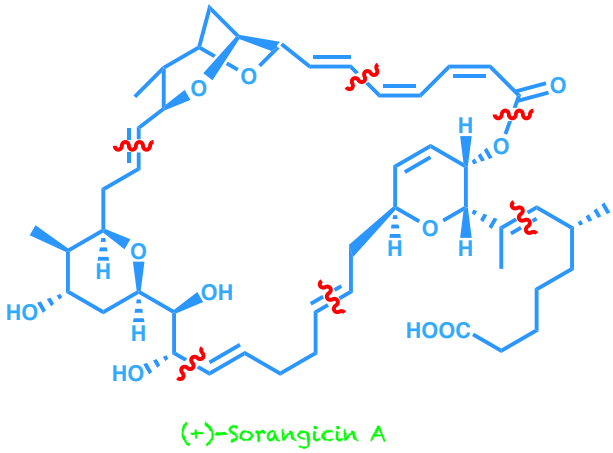
The research groups of G. Höfle and H. Reichenbach at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, Germany, reported the isolation of the novel antibiotic sorangicin A from the gliding myxobacterium *Sorangium cellulosum*. Sorangicins address a validated target in human anti-infective therapy (RNA polymerase) and do apparently not interfere with the CYP enzymes that metabolise drugs in the human body as much as rifampicin (which is presently being administered as component for a combination drug mixture to fight tuberculosis), and finally previous *in vivo* experiments conducted with sorangicin A revealed that the compound is active against bacterial pathogens, but virtually devoid of toxicity at the effective dosages.
At the same time, the cytotoxic natural product disorazol C_1 has been isolated from the fermentation broth of myxobacterium *Sorangium cellulosum*. Disorazol C_1 addresses also a validated drug target interferring with the polymerization dynamics of tubulin a key player in cell division and therefore an interesting compound for potential cancer therapy.
It is synthetically challenging because of its labile polyene structure built-in the pseudo-dimeric macrocyclic-heterocyclic scaffold.





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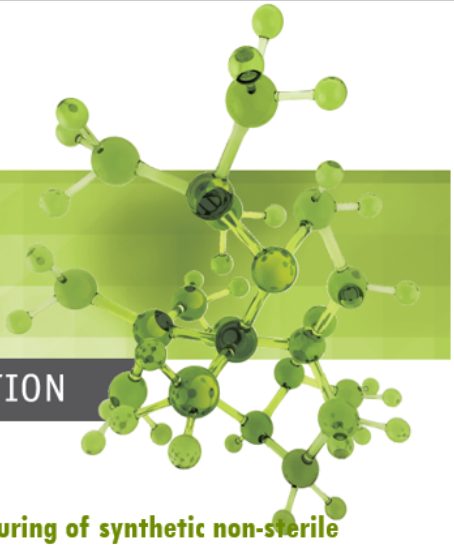

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August Kekulé: Beyond the Snake Dream

Pierre J. De Clercq
(Department of Organic and Macromolecular Chemistry, Ghent University)

The nine years (1858-1867) that professor Kekulé spent in Ghent were without any doubt the most fruitful in his career. In the context of a centennial celebration organized by the ACS (Division History of Chemistry) the following text appeared: “The theory of structural organic chemistry as developed in the 19th century may be the most fruitful conceptual scheme in all the history of science. Central to this scheme is the hexagon structure for benzene, proposed by August Kekulé in 1865.” It is somewhat ironic that Kekulé’s 1865 communications dealing with the structure of benzene contain a correct verbal description of the connectivity in cyclohexatriene according to the Kekulé formula but not the formula itself. Kekulé himself used during that period so-called sausage formulas.

In 1890, 25 years after the formulation of the benzene structure, a great celebration, the so-called “Benzolfeste”, took place in the city hall of Berlin, during which Kekulé held a memorable speech. He entertained his audience by revealing how a dream helped the benzene structure to be solved. The story goes that, while residing in Ghent, supposedly in the winter of 1861-1862, dozing at the fireplace in his appartment, he had a late-night daydream. The view of a snake biting in its tail brought him to the idea of a cyclical molecular structure for benzene. At that time he rented an appartment located in the Veldstraat (Field street), number 72. John Wotiz (1919-2001), among others, has expressed serious doubts about the originality of Kekulé’s benzene theory for in his view the physical chemist Loschmidt deserves the priority.

Another subject of controversy is related to priority claims when in 1858 Kekulé and Couper independently proposed that carbon has the property to bind to itself, hence forming chains. Was the priority debate about the first conception of molecular structure the trigger for another Kekulé dream? In the same Benzolfeste-speech Kekulé recalls that while he was heading home in London in the summer of 1855, he was dreaming about dancing atoms that once in a while would encounter and stick together hence forming living chains.

By claiming to have conceived his theories in dream-like revelations Kekulé avoided crediting his predecessors, is the argument of the non-believers. Whether the dreams actually took place is in fact not relevant. What is relevant is that of all scientists, who in that period had expressed an opinion about structural issues in general and about the structure of benzene in particular, Kekulé was the person who had the most correct view of the nature of benzene, as was corroborated by the results of experimental observations. And so Kekulé probably was the chemist who was the least prone to dreaming.

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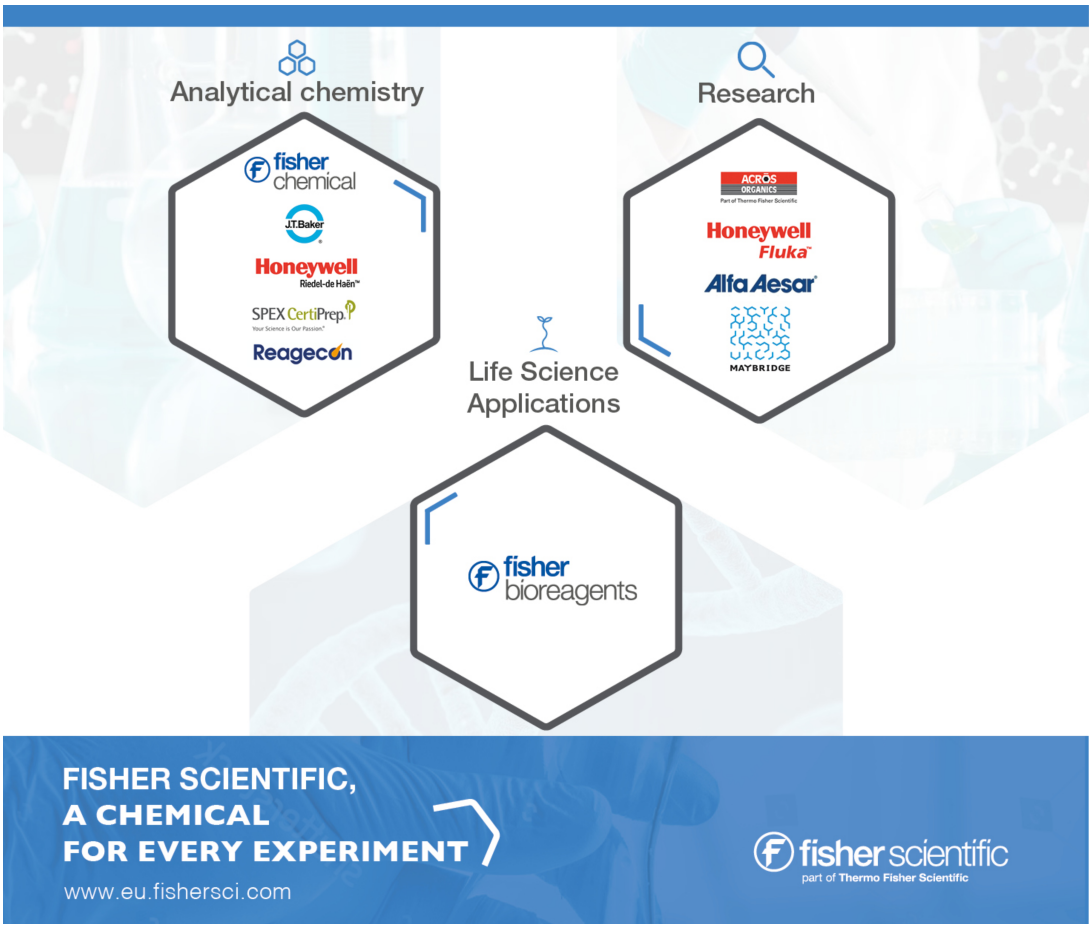

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Easy access to metal-N-heterocyclic carbene catalysts

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Department of Chemistry, Ghent University, Krijgslaan 281 (S3), 9000 Gent, Belgium.

Introduction

Palladium-*N*-heterocyclic carbene (NHC) complexes have been widely studied in the last decade and have been ubiquitously employed in homogeneous catalysis, especially in cross-coupling chemistry.[1] Out of the numerous findings emerging from these studies are the significant advantages associated with metal-ligand stoichiometry control.
Palladium(II) complexes of the type [Pd(NHC)(η^3-R-allyl)Cl] (R-allyl = allyl, metallyl, cinnamyl, indenyl) have shown high catalytic activity in many important C-C and C-heteroatom bond formations.[2] The original synthetic approach made use of a strong base (e.g. KOtBu) to generate the free carbene followed by addition of a suitable palladium precursor such as [Pd(η^3-allyl)(μ-Cl)]$_2$ or [Pd(η^3-cinnamyl)(μ-Cl)]$_2$.[3] The method yielded complexes that are, much to our surprise, air- and moisture-stable, as phosphine congeners had been reported as sensitive. In order to render the synthesis of these pre-catalysts even more facile, cost-effective, sustainable and accessible, we have probed the effect of the nature of the base on numerous metal-centered systems bearing NHC ligands, including the bulky IPr* ligand.[6]

Results and Discussion

Recently, we and others have reported on the use of an external weak base as an effective method to generate Au- and Cu-NHC complexes.[4-5] In the course of our studies, an unusual intermediate was isolated, an "ate" complex, that could be easily observed within minutes of mixing the metal precursor, copper or gold and now palladium, and the imidazolium salt in air. Action of a weak base upon this intermediate led to the well-defined M-NHC complex (M= Au and Cu) (Figure 1). We suspected that such "ate" complexes might be more prevalent than imagined in the context of the organometallic chemistry of M-NHC complexes and might even offer a uniquely simple approach to catalysis. To test this hypothesis, synthetic studies have shown the route to be so far quite general and these studies and the reactivity of the M-NHC family of catalysts will be presented.

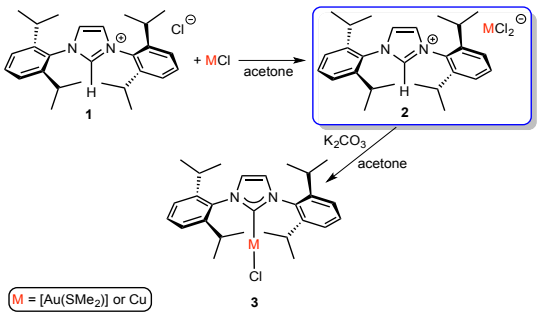

Figure 1 :Synthetic routes leading to well-defined Au-, Cu- and Pd-NHC catalysts

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Scale Up to Kilograms and Tonnes
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Dr Trevor Laird

When a chemical process is scaled up to kilogram quantities and beyond, loss of selectivity is the first difference that the process chemist might notice, or the appearance of new by-products often caused by the desired product remaining in contact with reagents and solvents for a longer time.

With exothermic processes, or those which emit gaseous side-products, loss of control leading to runaway reactions can occur if the correct scale up procedures are not followed.

The talk will examine several case studies where problems have occurred including some from the author's personal experience. Although a mixture of sodium hydride and DMF is a widely used combination in the laboratory and is safe to use on scale, runaway reactions have occurred when these processes are scaled up incorrectly and have led to "rearrangement of the equipment".

In principle, all processes can be scaled and there are many instances – such as the manufacture of diazomethane on 500Kg scale – which have been successfully accomplished without incident.

As more scale ups are contracted out to different companies, the hazards of technical transfer can lead to complications with safety implications.

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Less than two centuries ago, Wöhler's urea synthesis initiated a continuum of developments in chemistry that led to the evolution of organic synthesis to enable chemists to synthesize ever more complex target structures. After Wöhler's seminal work, first the theory of organic chemical structures as well as elementary understandings of chemical reactions had to be discovered. Only after major breakthroughs in the formation of carbon–carbon bonds through what we currently consider classical anion chemistry, the soil was fertile enough at the end of the 19th century to allow chemists to tackle the total synthesis of compounds like sugars, camphor, terpineol and tropinone. More thorough comprehension of chemical structures, mainly the shapes of molecules, 3D structures and still rather elementary aspects of stereochemistry led to the development of strain theories and eventually of conformational analysis. These advances allowed the synthetic chemist to progress towards more complex structures, and soon compounds like morphine, strychnine and reserpine surrendered to synthesis. This trend then culminated in the early 1990's with the total synthesis of palytoxin with 64 chiral centers by Yoshito Kishi and his group. During the decade long charade that eventually culminated in the Mount Everest of synthesis in a single paper in JACS (that has been cited only 60 times!) to announce the feat, several important discoveries were needed both in new bond construction (Nozaki-Hiyama-Kishi coupling), NMR databases for structure elucidation, as well as stereochemical understanding (Kishi rules for allyl alcohol hydroxylations). The value of such massive total synthesis projects is not only in providing the grounds for the invention of new chemistry, but it is also a prolific ground for spin off projects.

This lecture covers a time span of roughly a quarter of century, describing the development of organic synthesis from the perspective of methodology development over the years. The lecture is circled around one target compound, Calyculin C, whose synthesis has provided a versatile playground for developing new chemistry.


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