

New Frontiers in Metathesis Chemistry

OLEFIN METATHESIS – TRENDS AND PERSPECTIVES IN ORGANIC SYNTHESIS AND RUTHENIUM CATALYSIS

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A new scientific event in metathesis chemistry, the NATO Advanced Study Institute (NATO ASI) on New Frontiers in Metathesis Chemistry: From Nanostructure Design to Sustainable Technologies for Synthesis of Advanced Materials (1) was held in Antalya, Turkey, from 4th to 16th September 2006 (co-directors: Y. Imamoglu and V. Dragutan). This event is an appropriate sequel to the memorable Nobel Prize awarded to metathesis scientists Yves Chauvin, Robert H. Grubbs and Richard R. Schrock (Stockholm, November 2005) (2–4), and the XVIth International Symposium on Olefin Metathesis (Poznan, Poland, June 2005) (5).

Prominent scientists and young students from twelve NATO countries (Belgium, Bulgaria, Canada, Czech Republic, France, Hungary, Poland, Romania, Spain, Turkey, U.K. and U.S.A.) and six NATO Partner countries (Armenia, Azerbaijan, Kazakhstan, Moldova, Russia and Ukraine), interested in metathesis chemistry convened in Antalya for two weeks under NATO sponsorship. The purpose was to debate on the newest trends in olefin metathesis and identify future perspectives in this fascinating field of synthetic organic and organometallic chemistry, where platinum group metals (pgms), especially ruthenium, are playing a key role.

Olefin metathesis, one of the most efficient transition metal-mediated C–C bond forming reactions, has emerged during the last few years as a powerful synthetic strategy for obtaining fine chemicals, biologically active compounds, architecturally complex assemblies, new materials and functionalised polymers tailored for specific uses, including sensors, semiconductors and microelectronic devices. Metathesis reactions, such as ring-closing metathesis (RCM), enyne metathesis,

cross-metathesis (CM) and ring-opening metathesis polymerisation (ROMP), have moved far beyond their 20th century boundaries. This has resulted in a broad diversification towards sustainable technologies, and in new perspectives for a wide range of industrial applications, from production of smart, nanostructured materials to the manufacture of new pharmaceuticals (6–8).

During the meeting, recent advances in metathesis chemistry were disseminated among a selected audience of distinguished scientists and young researchers. Lectures, discussions and poster presentations, organised by a Scientific Committee (Yavuz Imamoglu (Hacettepe University, Turkey), Valerian Dragutan (Romanian Academy, Romania), Lajos Bencze (University of Veszprém, Hungary), Ezat Khosravi (University of Durham, U.K.) and Kenneth B. Wagener (University of Florida, U.S.A.)) in ten scientific main sessions, dealt primarily with novel metathesis catalysts pertaining to the pgms and several other late transition metals, and their application to key metathesis reactions or tandem metathesis/non-metathesis processes of environmental, industrial and commercial relevance. Such metathesis reactions have profound implications in materials science, nanotechnology, and also in organometallic, organic and polymer chemistry.

Developments in Ruthenium-Based Catalysts

As expected, in lectures on catalyst-related topics emphasis was placed on the newest developments concerning ruthenium-based complexes of high activity, selectivity and robustness, popular for their excellent tolerance toward a variety of functional groups. A whole range of alkylidene ruthenium complexes, both neutral and

ionic, which can be recovered and recycled, were illustrated by Pierre Dixneuf (University of Rennes, France) in his lecture 'Ruthenium Catalysts for Alkene Metathesis'. He included preparation methods and selected applications. In addition to the broad applications of the classical Schrock molybdenum catalysts and the Grubbs (1st and 2nd generation), Nolan or Hoveyda-type ruthenium catalysts, Dixneuf disclosed in a second seminal lecture: 'Recent Applications of Alkene Metathesis for Fine Chemical and Supramolecular System Synthesis', further significant utilizations of other active catalyst precursors, such as the ruthenium allenylidene, **1**, and the indenylidene promoter, **2**, derived from it. These applications refer specifically to the synthesis of new macrocycles *via* RCM, to RCM in the synthesis of new ligands, rotaxanes, catenanes and supramolecular systems, and to CM in organic synthesis and supramolecular system formation.

Elaborating on the essential role played by *N*-heterocyclic carbene (NHC) ligands in creating the most effective ruthenium metathesis catalysts (for example, **4** and **5** *vs.* **3**), Steven P. Nolan (University of Tarragona, Spain) extended the concept of introduction of the valuable NHC moiety to other late transition metal complexes, as outlined in his fascinating talk on 'The Role of NHC

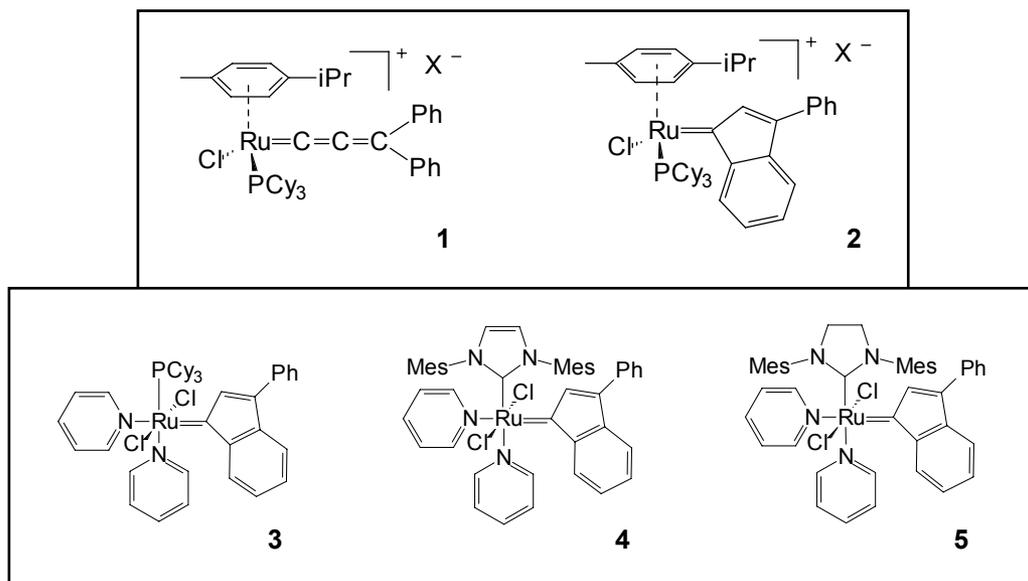
in Late Transition Metal Catalysis'.

As a further topic in this series, the synthesis, catalytic activity and pertinent mechanistic aspects of some recently discovered NHC-endowed late transition metal complexes of palladium, nickel, copper and gold were fully exemplified by Nolan for a set of catalysed transformations other than metathesis (cross-coupling reactions, hydrothiolation of alkynes, 'click chemistry' for rapid synthesis of new compounds and combinatorial libraries, and hydrosilylation of carbonyl compounds, as well as cycloisomerisation of polyunsaturated systems) in his comprehensive and original presentation 'NHC-Metal Complexes of Groups 10 and 11. Recent Developments in Synthesis and Catalysis'.

New Insights into Catalyst Design

New insights into catalyst design were provided by Deryn Fogg (University of Ottawa, Canada) and by Natalia Bespalova (United Research & Development Centre, Russian Academy of Sciences).

In her lecture 'New Insights in Ring-Closing Metathesis: Catalyst Design and MALDI-MS Analysis', Fogg demonstrated that ruthenium catalysts containing electron-deficient aryloxy ('pseudohalide') ligands confer high activity at low



catalyst loadings, while also expanding the structural diversity of the ligand set and the capacity for steric and electronic tuning of activity and selectivity. She pointed out that by using the matrix-assisted laser desorption/ionisation mass spectrometry (MALDI-MS) analysis technique, distinctions in the behaviour of the Grubbs *vs.* pseudohalide catalysts could be revealed. This provides an in-depth understanding of the RCM mechanism, to be exploited in synthesis of large and medium-sized rings.

In addressing ‘Catalyst Design for Functional Olefins Production via Olefin Metathesis Reactions’, Bepalova dwelt on the modification of well-defined ruthenium carbene catalysts through appropriate changing of the carbenoid moiety and the imidazole ligand, which allows a variation in the catalytic properties. A comparison between performances in CM of the new catalysts with those of the ill-defined catalysts based on tungsten was also presented.

Ligands for Catalysis

Following up on the general notion of NHC utilisation in catalysis, Lionel Delaude (University of Liège, Belgium), in his instructive presentations: ‘Olefin Metathesis with Ruthenium-Arene Catalysts Bearing N-Heterocyclic Carbene’ and ‘Studies on N-Heterocyclic Carbene Ligand Precursors’, dealt mainly with the best methods for obtaining symmetrically N,N -disubstituted NHC ruthenium arene complexes and with ROMP of cycloolefins promoted thereby. Karol Grela (Institute of Organic Chemistry, Polish Academy of Sciences), in an interesting and informative exposition on ‘Catalysts for New Tasks: Preparation and Applications of Tunable Ruthenium Catalysts for Olefin Metathesis’, extended the class of Hoveyda catalysts to related ruthenium systems, showing that the catalyst activity can be enhanced by using adequate electron withdrawing groups (EWGs) as substituents on the isopropoxy-benzylidene ligand. Francis Verpoort (Ghent University, Belgium), in his comprehensive accounts ‘Olefin Metathesis Mediated by Schiff Base Ru-alkylidene Complexes’ and ‘Rational Design and Convenient Synthesis of a

Novel Family of Ruthenium Complexes with O,N-Bidentate Ligands’, reported on new strategies in Kharasch addition, enol-ester synthesis and ROMP of dicyclopentadiene (DCPD) using highly efficient Schiff-base ruthenium complexes.

Poster presentations demonstrated additional data in support of the role of NHC ligands in ruthenium-based metathesis precatalysts (Xavier Sauvage, University of Liège, Belgium, and Adriana Tudose, University of Liège and Romanian Academy) and the unexpected activating effect of strong acids on ruthenium complexes incorporating O,N-bidentate ligands (Renate Drozdak and Nele Ledoux, Ghent University, Belgium). Providing interesting information about ruthenium-mediated processes related to metathesis, Chloe Vovard (University of Rennes, France) briefly talked on ‘Ruthenium Catalysed Addition of Diazocompounds to Enynes: Synthesis of Bicyclic Compounds with Vinylcyclopropane Moiety’.

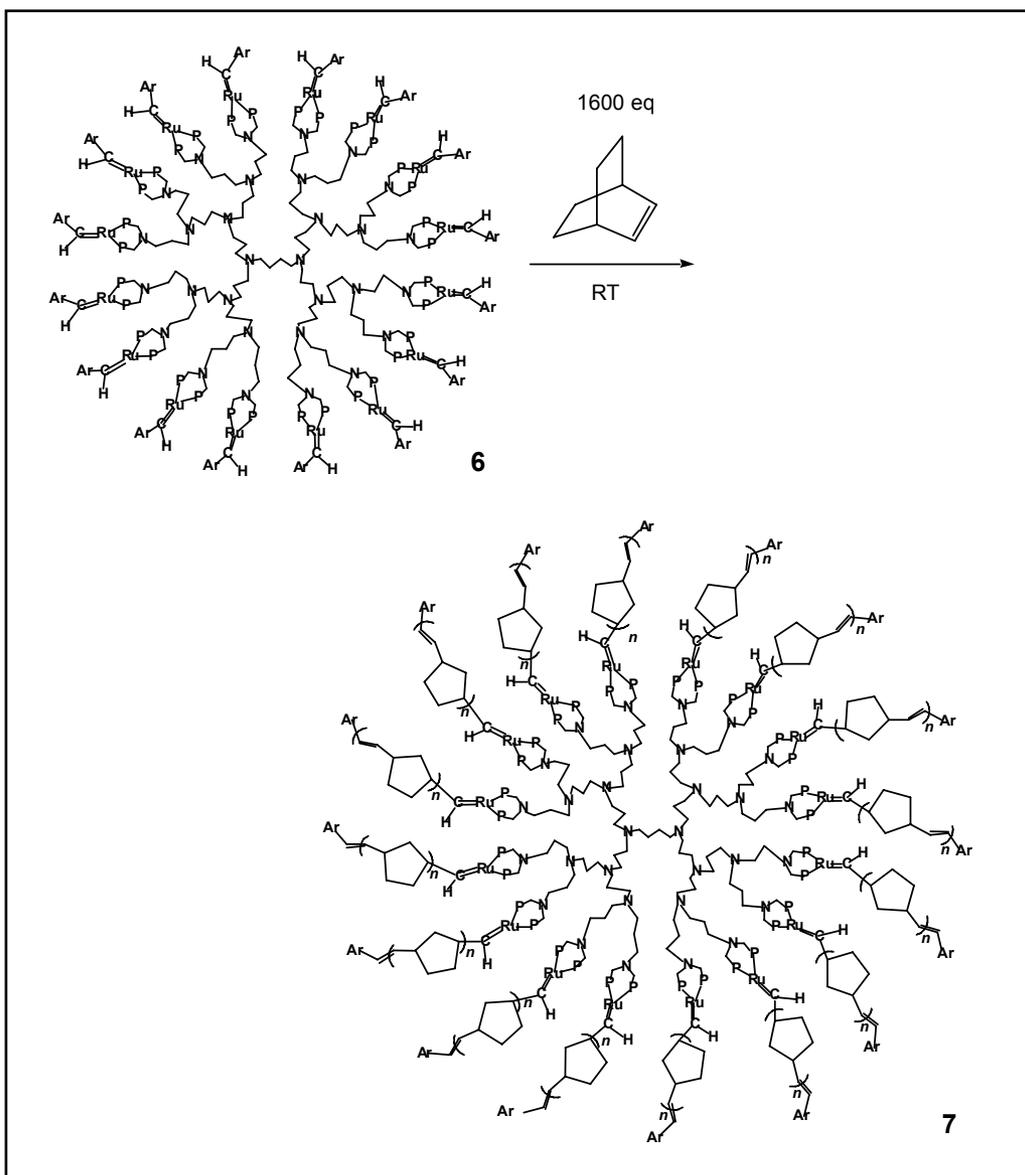
Nanoscience and Materials

In a very attractive lecture, ‘Molecular Nanoscience and Catalysis’, Didier Astruc (University of Bordeaux, France), starting from synthesis of organometallics, catalysts and electron-transfer agents and mechanisms involving electron transfers, dealt eloquently with such hot topics as:

- dendrimers (catalysis, molecular electronics, recognition and transport);
- gold and palladium nanoparticles (sensors and catalysts);
- metathesis reactions with nano-objects;
- ‘click chemistry’.

In another creative subject, ‘Combining Simple Arene Activation with Ru-Catalysed Olefin Metathesis for the Assembly and Functionalization of Nano-Objects’, Astruc revealed convenient routes to desirable supramolecular structures and elaborate synthetic methods. In this extremely broad context, several elegant applications of ruthenium dendritic structures were given (for example, use of **6** in synthesis of polymers, **7**).

New trends presently evolving in metathesis chemistry were critically discussed by Hynek



Balcar (J. Heyrovský Institute of Physical Chemistry, Academy of Sciences of the Czech Republic). The new directions cited were:

- (a) Eco-friendly protocols for metathesis catalysts;
- (b) Supported catalysts and novel techniques for immobilisation;
- (c) Applying to metathesis at room temperature the recognised advantages of ionic liquids through the creation of recyclable imidazolium-tagged catalysts;
- (d) CM, enyne and RCM as key reaction steps in

organic synthesis yielding pharmaceuticals and natural products (sugars, alkaloids, nucleosides, amino acids);

- (e) Chiral catalysts enabling enantioselective metathetical pathways in precision synthesis.

In his talk on 'Molecular Sieves as Supports for Metathesis Catalysts', Balcar described how siliceous sieves (MCM-41 and -48, SBA-15) and organised mesoporous alumina were successfully used in obtaining new catalysts (principally based on molybdenum and rhenium oxides) and in het-

erogenisation of some well-defined homogeneous catalysts for olefin metathesis and metathesis polymerisation.

The details of extending NHC ligands to osmium, with effect on catalyst activity, chemoselectivity and stereoselectivity, have been widely evidenced by Ricardo Castarlenas (University of Zaragoza, Spain) in his talk on 'NHC Osmium-arene Catalysts for Olefin Metathesis Reactions'. Pertinent structural and mechanistic aspects regarding this recently introduced class of metathesis catalysts were also addressed.

New applications of ruthenium-mediated tandem metathesis/non-metathesis processes were fully documented by Deryn Fogg in a presentation on 'Tandem ROMP-Hydrogenation Catalysis in Tissue Engineering Applications'. This drew attention to a potentially important practical application of polymers obtained in this way (galactose-functionalised polynorbornenes), which have so far proved successful in clinical trials for corneal tissue engineering.

The advantages of another tandem combination, RCM-hydrogenation, were presented by Natalia Bepalova in the lecture 'Synthesis of Higher Esters Using Tandem Olefin Metathesis-Hydrogenation Reactions', bringing into prominence the production of valuable highly saturated esters by means of the catalyst pair $\text{Bu}_3\text{SnH}/2\text{nd generation Grubbs}$.

'Catalytic Cycloisomerisation of Enynes Involving Various Activation Processes', presented by Christian Bruneau (University of Rennes, France), extended the scope of ruthenium-based metathesis chemistry to a variety of initiating systems of fundamental relevance in catalysis. Skeleton reorganisations, carried out with catalysts based on palladium, cobalt, rhodium, iridium, platinum, gold and ruthenium and involving electrophilic activation, oxidative coupling and metathesis reactions were described, along with applications of metathesis for the transformation of some natural compounds. 'Cross-metathesis of Vinyl-substituted Organosilicon Derivatives with Olefins in the Presence of Grubbs Catalysts', presented by Cezary Pietraszuk (Adam Mickiewicz

University of Poznan, Poland), evidenced how ruthenium-catalysed metathesis can be fruitfully used in synthesis of novel silicon-containing advanced materials.

Macromolecular Chemistry

Ezat Khosravi (University of Durham, U.K.) illustrated the versatility of ROMP in two complementary lectures on 'Ruthenium Initiators and Oxygen Containing Norbornene Derivatives' and 'Synthesis of Novel Polymers via ROMP'. In the first, he highlighted the importance of both the presence and position of the oxygen substituent in norbornene derivatives subjected to ROMP, while also unambiguously establishing the identity of the propagating alkylidene species. In his second lecture, by discussing two examples taken from their ongoing research: (i) polymers with ball-and-chain sequences synthesised by ROMP of dendronised (polycarbonate) monomers, and (ii) synthesis of polymeric bioresorbable materials based on graft copolymers consisting of polyoxanorbornene backbones with poly(hydroxyacid) side-chains, Khosravi demonstrated that ROMP is a powerful tool in macromolecular engineering, allowing synthesis of polymers with novel topologies.

Moreover, Eugene Finkelshtein (Topchiev Institute of Petrochemical Sciences, Russian Academy of Sciences) in his outstanding lecture on 'ROMP and Other Ring-Opening Processes as an Effective Route to New Carbosilane Membrane Materials', evidenced ways for producing specialty polymers usable as gas-separating membrane materials when a particular combination of high film-forming, permeability and separation properties is met. Debating on the correlation between the polymer structure and the gas transport parameters, he pointed out the role played by the occurrence, number and location of Me_3Si -groups in a variety of copolymers synthesised for this purpose, as further reinforced by Maria Gringolts in a subsequent talk.

The main aspects of the kinetics and mechanism of the carbonyl-olefin exchange reaction, having a formal similarity with olefin metathesis, were elaborated by Christo Jossifov (Institute of Polymers, Bulgarian Academy of Sciences) in his

amply documented presentation 'Carbonyl-olefin Exchange Reaction and Related Chemistry'. This type of reaction could be successfully performed only when the two functional groups (carbonyl group and olefin double bond) are situated in the same molecule and are conjugated as in α,β -unsaturated carbonyl compounds (substituted propenones). Substituted polyacetylenes having valuable conducting and optical properties could also be obtained by this straightforward methodology.

Presentations from Ken Wagener's group (University of Florida, U.S.A.) by two of his students, Emine Boz and Giovanni Rojas, on 'Correlating Precisely Defined Primary Structure with Crystalline Properties in Halogen-Containing Polyolefins' and 'Precision Polyolefin Structures', respectively, showed how acyclic diene metathesis (ADMET) induced by Grubbs ruthenium catalysts can rigorously control the polymer microstructure, and ultimately the product properties.

Special attention was paid to addition polymerisation and copolymerisation of selected monomers (such as silyl-functionalised norbornenes), induced by late transition metal catalysts (nickel and palladium), providing new materials with special properties (high thermal and chemical stability), for applications such as optical components, electrical insulators and photoresists. This was convincingly shown by Eugene Finkelshtein in his lecture on 'Addition Polymerization of Silyl- and Some Other Functionalized Norbornenes'; by Victor Bykov (Topchiev Institute of Petrochemical Sciences, Russian Academy of Sciences) in his communication on 'Copolymerization of Ethylene with Norbornene and Their Functional Derivatives on Nickel-ylide Catalysts'; and by Maria Gringolts (Topchiev Institute of Petrochemical Sciences, Russian Academy of Sciences) in her talk on 'The Influence of Presence, Number and Location of Alk_3Si Groups in Norbornenes and Norbornadienes on Their Polymerisation and Polymer Properties'.

Nanostructured materials and how they could be used in nanomachines and molecular clockworks were attractively described by Lajos Bencze (University of Veszprém, Hungary), in two com-

plementary lectures: 'Long Range Transfer of Chiral Information in Rotalicene Type Nanomachines' and 'Molecular Clockworks as Potential Models for Biological Chirality'. Going beyond metathesis but in close correlation with this reaction, comprehensive and fascinating lectures on 'Smart Nanostructured Materials by Atom Transfer Radical Polymerization' and 'Environmental and Sensors by Atom Transfer Radical Polymerization', delivered by Krzysztof Matyjaszewski (Carnegie Mellon University, U.S.A.), illustrated the great potential of precisely controlled macromolecular structures obtained by atom transfer radical polymerisation (ATRP) to be assembled into smart materials, sensors and various molecular devices. A successful combination of ATRP with ROMP to produce new materials with valuable properties was also discussed. In his turn, Osama Musa (National Starch & Chemical Co, U.S.A.) furnished in his attractive lecture 'Exploration of Novel Thermoset Resins: Faster, Higher and Stronger', a wide range of applications of advanced materials prepared by different polymerisation procedures.

Concluding Remarks

The social programme was organised in a friendly and warm style, facilitating informal scientific discussion among renowned experts and young researchers, and strengthening contacts and the exchange of information between research groups of different nationalities.

At the end of the event, there was a general discussion on perspectives of future NATO ASI meetings on metathesis chemistry. Comments from a number of participants converged to the idea that, in view of the current upward trend in developments in this field, organising further meetings would be both opportune and highly beneficial, especially for the young generation of scientists involved in metathesis research.

A major conclusion emerging from the lectures, posters and discussions at this Institute is that a principal focus in this highly challenging area of research is the advantages of using new ruthenium catalysts for a multitude of chemical transformations. Further exploration of the metathesis

chemistry of other pgms such as osmium is also of great interest. The application profile of the novel metathesis catalysts is expanding rapidly, particularly in RCM, and CM. These methods may be exploited for the synthesis of therapeutic compounds, as well as in ROMP for the production of specialised and highly functionalised polymers.

Following the useful practice of previous NATO ASI meetings (see, for example, (9)), selected contributions including plenary lectures, short communications and posters will be compiled in a special volume dedicated to this outstanding scientific meeting, and will be published by Springer Verlag in 2007 (10).

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