ХИМИЯ ГЕТЕРОЦИКЛИЧЕСКИХ СОЕДИНЕНИЙ. — 2014. — № 10. — С. 1639—1644

ХРОНИКА

TRADITION OF *BALTICUM ORGANICUM SYNTHETICUM*

The biannual scientific meetings known as *Balticum Organicum Syntheticum* (BOS) are among the most highly regarded not only in the Baltics, but throughout Europe. In 2014, BOS took place in Vilnius after previous one held in Tallinn. The original idea has been to share the venue of BOS among the three Baltic States and this year, returning to Vilnius, the conference witnessed the further fulfilment of this vision. BOS conferences are well-known for attracting top speakers from academia and industry who present the most exciting topics of the day and for fostering open discussions. The listing of lecturers features many famous names in organic chemistry, including the total of 6 Nobel Laureates in the eight BOS meetings so far. At the BOS-2014, approximately 250 participants, among them many PhD students, enjoyed high level talks by 18 speakers, viewed poster sessions, and engaged in informal discussions. The posters were evaluated by a scientific committee and awards from Thieme Verlag were presented to the best young authors from each of the Baltic state and the rest of the 109 poster pool. The BOS conference program as usually encompasses mainstream organic synthesis, as well as medicinal chemistry, molecular biology, and also material-science.

Starting off the program and setting the mark was **Michael J. Krische** (University of Texas at Austin, U.S.A.) who spoke about formation of C–C bonds *via* catalytic hydrogenation and transfer hydrogenation. The hydrogen exchange between alcohols and π-unsaturated reactants generates electrophile–nucleophile pairs *en route* to products of carbonyl addition. Direct alcohol C–H functionalization in this manner bypasses discrete alcohol-to-aldehyde redox reactions, use of pre-metallated C-nucleophiles, and the need for the protecting of hydroxyl groups. Many significant examples of total synthesis employing this strategy, such as of trienomycins A and F, were presented. Such general, unique atom-efficient processes of making new C–C bonds, employed in striking ways in the synthesis of complex molecules containing many stereogenic centers, require new thinking in retrosynthetic analysis.

Marek Chmielewski (Institute of Organic Chemistry of Polish Academy of Sciences) discussed novel stereoselective syntheses of ezetimibe, a powerful cholesterol inhibitor. The first synthetic pathway was based on a copper(I) mediated reaction of substituted benzylidene-aniline oxide with terminal acetylene derived from L-glyceraldehyde, which is known as the Kinugasa reaction. The second approach involved 1,3-dipolar cycloaddition between (*R*)-6-(4-fluorophenyl)-5,6-dihydro-2*H*-pyran-2-one and *C*-(4-benzyloxyphenyl)-*N*-(4-fluorophenyl)nitrone. Owing to the rigid transition state of the cycloaddition, the absolute

configuration of the starting lactone controlled the formation of other stereogenic centers of the target molecule.

Lectures from industrial chemists are one of the characteristics of BOS, as significant contributions to process chemistry demonstrate the practical side of organic synthesis. A presentation by **Stefan Abele** (Actelion Pharmaceuticals Ltd., Switzerland) illustrated synthetic route development and pilot plant production of novel bacterial topoisomerase inhibitors. Features of the lecture were production-scale fluorination and a GMP-compliant use OsO_4 for a > 30-step synthesis of the drug. The lecture demonstrated approaches to cut the costs, including novel syntheses of fluoronaphthyridines using either a one-pot diazotation–fluoro-dediazoniation or F_2 gas, and a high-temperature continuous-flow Overman rearrangement on 100 kg scale to access the chiral tetrahydropyran building block, and, finally, to achieve a synthesis of the targeted structure.

A further example of industrial scale synthesis of Simeprevir (TMC435) was presented by **Andras Horvath** (Janssen Pharmaceutical Companies of Johnson & Johnson, Belgium). TMC435 is a synthetic macrocyclic molecule having Hepatitis C virus NS3 protease inhibitor activity, commercially launched in 2013. A ring closing metathesis reaction was used to build the 14-membered macrocyclic core and a *Z*-double bond (key features of the molecule) in a single catalytic step on industrial scale balancing kinetic *vs.* thermodynamic control for the cyclization efficiency.

Herbert Waldmann's (Max Planck Institute for Molecular Physiology and TU Dortmund, Germany) talk focused on biology-oriented synthesis. Waldmann pointed out that relevance to nature is one of the most important criteria to be met by classes of organic compounds for advances in chemical biology and medicinal chemistry. The underlying frameworks of natural products (NPs) provide evolutionary selected chemical structures encoding the properties and their structural scaffolds which represent the biologically relevant and pre-validated portions of chemical space explored by Nature. The presented concept of "Periodic Table of Natural Products" represents the diversity created by Nature in evolution. Biology oriented synthesis (BIOS) is built on these arguments employing core structures de-lineated from NPs as scaffolds of compound collections and creates focussed diversity around a biologically prevalidated starting point in vast structural space. Consequently BIOS offers a conceptual guiding strategy for library design as was exemplified by the synthesis of a series of indolo-quinazolines.

Asko Uri's (Institute of Chemistry, University of Tartu, Estonia) lecture followed the theme of chemistry/biology interface discussing the development of responsive photo-luminescent probes for protein kinases (PK) inhibitors. The latter have become the most important class of target proteins for the development of anticancer drugs. Furthermore, profiling of kinase activity in components of body fluids could be used for diagnosis of cancer and other complex diseases. The development of novel responsive long-lifetime photoluminescent probes ARC-Lum(Fluo) based on conjugates of nucleoside analogs and peptides (ARCs) that can be used for mapping and monitoring of activity of PKs in living cells was presented. The combination of synthetic procedures in solution and on solid phase was used for the construction of these high-affinity probes.

Olivier Dirat (Chemical Research and Development, Pfizer, United Kingdom), gave a talk on genotoxic impurities assessment. This is an area for focus in the pharmaceutical industry since the recent changes in ICH regulatory expectations. A

simple case study of sitaxentan sodium (Thelin®), a drug for treatment for pulmonary arterial hypertension, and also a more complex case study of anticancer drug dacomitinib were presented. A novel risk assessment based on a theoretical purge tool, analytical challenges and a detailed mechanistic understanding of the formation of key genotoxic impurities was introduced.

The Rh catalysis for C–H activation was the topic of the lecture by **Tomislav Rovis** (Colorado State University, U.S.A.). Using common directing groups to selectively activate proximate C–H bonds for the synthesis of nitrogen heterocycles from amide, imine, and oxime precursors based on rational ligand design has been a major factor in achieving high selectivities. Mechanistic considerations contributed to reaction development and applications to synthesis, for example, olefin hydroarylation and aminoarylation. An enantioselective version of the C–H activation process was catalyzed by a bifunctional artificial metalloenzyme in which glutamic acid or aspartic acid residue engineered into streptavidin by site-directed mutagenesis acts in concert with a docked biotinylated rhodium(III) complex $[RhCp^*(biotin)Cl_2]_2$, and its advantages were demonstrated on the coupling of benzamides with alkenes to access dihydroisoquinolones with up to nearly a 100-fold rate acceleration and *ee* over 90%.

The presentation by **Tomas Hudlický** (Brock University, Canada) demonstrated that chemistry is contiguous to biotechnology by the chemoenzymatic synthesis of natural products like *Amaryllidaceae* and morphine alkaloids and their non-natural derivatives. *Amaryllidaceae* alkaloids and several unnatural derivatives, synthesized from diol derived from bromobenzene by enzymatic dihydroxylation with toluene dioxygenase, have shown to have promising anti-tumor activities. The enzymatic dihydroxylation of bromoethyl arenes afforded the corresponding unsaturated cyclohexadiene diols that have been used in several enantiodivergent syntheses of codeine. A short synthesis of *ent*-hydromorphone has been achieved recently. In addition to the details of these endeavours and in the context of overall efficiency, the general and important question of our current appreciation of the term "chemical yield" and the limits of accuracy of reported isolated product yields (*Synlett*, 2701 (2010)) as well as ratios of isomers was addressed.

The selective building up of complex organic molecules by palladium/ norbornene catalysis was described by **Marta Catellani** (Parma University, Italy). The application of this type of catalysis to construct complex molecules from various simple starting materials is impressive considering the necessity a series of bond-forming events according to a well-defined order in spite of numerous competitive reaction pathways. Arylnorbornylpalladacycles are key intermediates for the selective functionalization of the aryl moiety. They are formed *in situ* by reaction of arylpalladium complexes with norbornene and subsequently dismantled by norbornene expulsion to selectively functionalized arylpalladium species. This approach of intermediate scaffold formation was applied to obtain selectively *ortho*-aryl iodopyrroles, vinyl derivatives of unsymmetric biaryls, and other complex molecules.

Edvinas Orentas (Vilnius University, Lithuania) used targeted design of the C_2- and C_1-symmetric bicyclo[3.3.1]nonane derivatives for engineering of supramolecular tubular structures. The complementary hydrogen bonding groups and the directional bonding geometries of the bicyclic monomers lead to controlled spatial aggregation. The unique properties of such assemblies are determined by their cylindrical dimensionality in which information of directionality is encoded.

This approach for the construction of tubular aggregates in which the monomers form cyclic units are able to further aggregate into nanotubular molecular objects and thereby perform a variety of functions without using covalent preorganization seems to provide an attractive alternative to existing methods from both conceptual and synthetic point of view.

The concept of the ideal catalyst was center stage in the lecture by **Eiichi Nakamura** (The University of Tokyo, Japan). The introduction sketched on the need for scientists to concentrate being useful to society, a paradigm shift away from wasting energy and consideration of the imminent danger of losing abundance of certain elements. Then the lecture demonstrated efficient Fe- and Co-catalyzed reactions, and ended with the fascinating display of motion of individual molecules by Single-Molecule Real-Time Transmission Electron Microscope Imaging. Fe(III) and Fe(II) have been widely used as Lewis acids for the generation of carbocations and radicals and the activation of electrophilic substrates. A series of organoiron-catalyzed C–C bond formation reactions were presented including asymmetric carbo-metalation of olefins, cross-coupling of alkyl halides, and activation of sp^2 and sp^3 C–H bonds for amination of aromatics.

Aigars Jirgensons (Latvian Institute of Organic Synthesis) discussed synthetic routes to unsaturated amino alcohols, which are present in pharmacologically active compounds and natural products. New approaches have been developed for the assembly of several types of the unsaturated amino alcohols based on the intramolecular amination reactions of activated intermediates with trichloro-acetimidates (the Overman rearrangement). The allylic substitution involving double bond activation by Pd(II) catalyst provides amino alcohols, i.e. vinyl-glycinols, butadienylglycinol, and C-quaternary vinylglycinols. Allylic and propargylic substitutions obtained by the activation of the leaving group by Lewis acid catalyst could be used to prepare the amino alcohols particularly important given their high derivatization potential leading to relevant unsaturated amino acids. Amination of *in situ* generated cyclopropylcarbinyl/homoallyl cation is key in stereochemical control of the reactions giving enantioenriched products.

William A. Nugent (Vertex Pharmaceuticals, Inc., U.S.A.) talk was based on a recent essay “Black Swan events” by the speaker (*Angew. Chem. Int. Ed*., **51**, 8936 (2012)) including observations from 40 years of reading the chemical literature. As always, the choice of synthetic protocols needs to be guided by the collective experience and inferences that are collectively called "conventional wisdom". Organic chemists have sometimes been guilty of over-generalization, despite the existence in the literature of outliers, which have a tendency to explain away results because they fail to fit the preconceived ideas. It is proposed that the sudden emergence of "hot" research topics typically results from the overturning of unwarranted conventional wisdom. Recent history teaches that conventional wisdom should be regarded as hypothesis rather than dogma. This was demonstrated by several case studies including Au catalysis, asymmetric hydrogenation, Pd-catalyzed cross coupling, olefin metathesis, and enzymatic catalysis in water, tracing the literature to the first inkling which had the chance of triggering the eventual gush of results in the literature for all these areas.

Shū Kobayashi (The University of Tokyo, Japan) presented advances in research on metal nanoparticles as novel heterogeneous catalysts for micro-encapsulated (incarcerated) catalysis which makes more efficient many well-known processes. The lecture focused on the development of so-called "Dream catalysts" that have both merits of homogeneous and heterogeneous catalysts. Several types

of metal nanoparticles as heterogeneous catalysts for reduction, oxidation, and C–C bond-forming reactions including asymmetric catalysis were discussed, for example, heterogeneous polymer-incarcerated nickel nanoparticles that catalyze cross-coupling reactions. The matrix structure of these catalysts incorporates both *N*-heterocycle carbenes (NHCs) as ligands and nickel nanoparticles, thanks to a new design of cross-linking agents in polymer supports. These embedded NHCs were detected by Field Gradient Swollen-Resin Magic Angle Spinning (FG-SRMAS) NMR analysis. They were successfully applied to Corriu–Kumada–Tamao reactions with a broad substrate scope, functional group tolerance, and possibility to recover and reuse the catalyst several times without loss of activity.

All-carbon quaternary stereogenic centers present synthetic challenges, and this important area was addressed by a contribution from **Ilan Marek** (Technion – Israel Institute of Technology). In his lecture he presented a new strategy that exploits multifold reactivity of easily accessible substrates with a single organometallic species so as to furnish advanced molecular scaffolds through a unique allylic C–H and selective C–C bond activations. Thus $C_4H_8ZrCp_2$ reacts with the remote double bond of 2-(alk-ω-en-1-yl)cyclopropyl methyl ether to induce an allylic C–H activation followed by a fragmentation of the three-membered ring. The resulting bifunctional nucleophilic species, possessing an all-carbon quaternary stereogenic center, can further be selectively derivatized by an addition of two different electrophiles to give more complex molecular architecture from these easily available starting materials. The synthesis of challenging molecular skeletons could be therefore designed not through the construction of carbon–carbon bonds, but rather through selective activation of bonds with high regio-, diastereo- and enantioselectivity.

Mats Larhed (Uppsala Biomedical Center, Uppsala University, Sweden) presented continuous flow (CF) organic synthesis using a novel non-resonant microwave reactor. The prospect of a microwave applicator fully dedicated to CF applications offers many advantages over traditional heating methods, such as fast and controlled heating at high temperatures and a higher level of safety regarding explosive reagents and pressure-producing reactions. In the lecture, synthetic protocols were presented that were developed with unique equipment. It features a non-resonant microwave heating applicator, purpose-built for CF that heats the entire reactor tube without pronounced hot and cold spots allowing method development in small scale and subsequent scale-out without scale-up translation. With a pressure resistance of 100 bars and volumes between 160 μL and 6 mL, the borosilicate reactor tubes allow a variety of flow regimes as well as superheating of solvents. The technology was demonstrated with method development and subsequent scale-out of classic organic reactions including heterocycle synthesis, palladium-catalyzed organic transformations, as well as the synthesis of a bioactive *M. tuberculosis* proteasome inhibitor.

The climax of the conference was a lecture by **Ei-ichi Negishi** (Purdue University, U.S.A.) on recent advances in catalytic asymmetric carbon–carbon bond forming reactions. Negishi began his lecture by recalling the discovery of his name reaction, among other metal-catalyzed processes. The expansion of the scope of the Zr-catalyzed reaction was sought in order to develop its alkene version for catalytic asymmetric C–C bond formation, namely the ZACA (Zr-catalyzed asymmetric carboalumination of alkenes). Three mutually complementary procedures for the enantioselective synthesis of methyl-substituted 1-alkanols have been developed, which allow highly flexible designs for the syntheses of chiral

organic compounds of biological and medicinal interest. A new widely applicable and highly satisfactory protocol for synthesis of a wide range of chiral alkanols of *ee* ≥99% by ZACA–Cu- or Pd-catalyzed cross-coupling was presented. These functionally rich intermediates of high enantiopurity serve as very useful synthons for the construction of a broad array of chiral compounds without epimerization. The title of the lecture, *"Conquering one of the last bastions in organic syntheses"* begs the question whether this is truly "the last bastion" in organic synthesis.

In general, BOS 214 in Vilnius was not only a conference of listeners, as discussions inspired by the conference founder V. A. Snieckus were evident in coffee breaks, lunches, evening gatherings at dinners and bars, and hotels. Without consistent and generous support from companies and institutions worldwide, BOS would have remained a dream in the year 2000. We thank most sincerely all that supported the conference.

E. Butkus,
Vilnius University, Lithuania