Bürgenstock Conference

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Structures, Reactions, and Mechanisms: Stereochemistry in the Broadest Sense at the 51st Bürgenstock Conference

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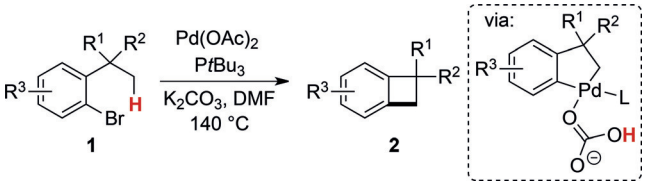
This year's Conference President Paul Knochel (Ludwig-Maximilians-Universität München) put together a highly attractive program for the 51st Bürgenstock Conference. It started with a lecture from Oliver Trapp (Heidelberg), who explained his concept of stereodynamic catalysts based on chirally flexible ligands with biphenyl backbones that were successfully applied to the Rh-catalyzed asymmetric hydrogenation. The modification of ligands with remote auxiliaries allowed access to temperature-dependent bidirectional catalysts. In addition, the speaker made us breathe a sigh of relief by showing proof that the assignment of the absolute configuration of D-glyceraldehyde by Emil Fischer in 1890 was correct. Using Coulomb explosion imaging, the spatial arrangement of atoms in a chiral molecule is preserved in the gas phase and can be detected, thus providing an unambiguous image of the structure.[1]

The Monday morning was dedicated to C–H activation by homogeneous metal catalysts. This field has expanded tremendously over the past 20 years and we had the pleasure to listen to two key experts who developed this topic in different ways. Firstly, Olivier Baudoin (Basel) reported on unactivated C_{sp^3}–H bond functionalization by Pd^0 complexes and its application to the construction of bicyclic compounds, for example benzocyclobutenes (Scheme 1), indanes, or hexahydroindoles. He reported not only on the development of new methods, but also on their application in the synthesis



Scheme 1. Pd-catalyzed activation of a C_{sp^3}–H bond affording benzocyclobutenes **2**.[2a]

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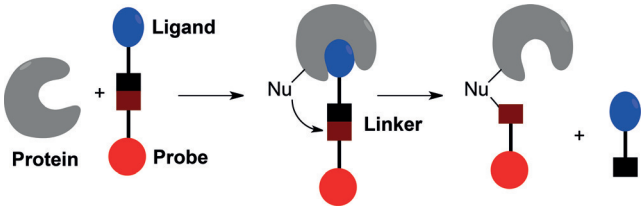
of complex natural products, such as aeruginosins, and investigation of the corresponding reaction mechanisms.[2] Another approach to tackle challenging C–H bonds was presented by Lutz Ackermann (Göttingen). He disclosed his group's achievements in the field of Ru-catalyzed C–H functionalization, for instance the recent development of single-component ruthenium(II) phosphinous acid complexes as highly active and versatile catalysts. Subsequently, he shifted his focus towards the use of cheaper metals and highlighted progress in the use of cobalt, nickel, copper, iron, and manganese complexes as catalysts, thus proving the utility of C–H activation as a synthetic tool.[3]

In the afternoon, the scientific focus moved towards chemistry for understanding proteins. Itaru Hamachi (Kyoto) explained his work on the selective chemical labeling of proteins in living cells. The aim is to develop traceless affinity-based methods in order to target native proteins without disturbing their functions. He described the so-called ligand-directed chemistry method that is based on a reagent in which a cleavable/reactive linker connects the ligand and the probe (Scheme 2). The ligand is released upon the reaction of the linker with a nucleophilic amino acid residue on the surface.



Scheme 2. Protein-labeling method based on ligand-directed chemistry.[4]

The utility of the method was demonstrated multiple times also in endogeneous proteins.[4] The first poster session started with selected short oral presentations given by Jovica D. Badjic, Christopher J. Cordier, Ali Coskun, Bill Morandi, and Yu Zhao. The evening lecture on the totally chemical protein synthesis and its utilization was given by Stephen Kent (Chicago). He and his research group investigate proteins containing only achiral glycine and D-amino acids. Such D-proteins can only be accessed thanks to the native chemical

ligation, which was pioneered and further developed by Kent and his colleagues. These macromolecules are potential human therapeutics, since they are resistant to proteases, are nonimmunogenic, and can be designed to have desired properties. In addition, he highlighted the advantages of the crystallography of racemic and quasi-racemic proteins, such as easier crystallization and structure determination.[5]

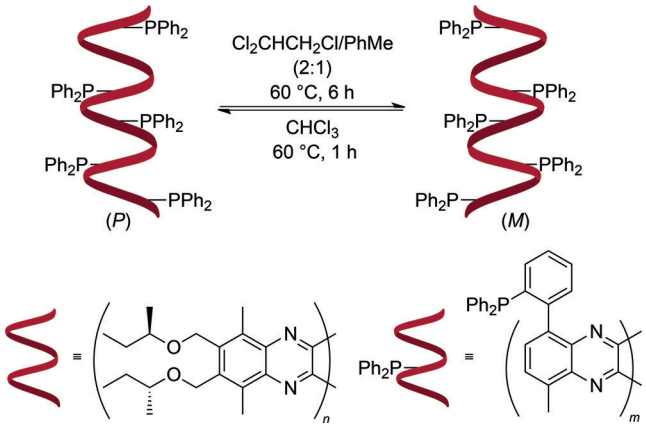
The next day, Giuseppe Resnati (Politecnico di Milano) delivered a fascinating talk on halogen bonding. Halofluorocarbons constitute ideal Lewis acids that bind to electron-donor species such as N and O atoms or halide anions and form self-assembled hybrid materials. Resnati highlighted their various features and applications, for example the formation of one-, two-, and three-dimensional networks, the binding of anions and their active transmembrane transport, or the formation of supramolecular gels and liquid crystals. Recently, they obtained materials with unique properties, where halogen-bonded ionic liquid crystals were formed from ionic liquids.[6] Valery Fokin (University of Southern California) followed with a remarkable demonstration of his ambition to interrogate processes in nature by using chemical reactions that do not occur naturally, and thus study complex catalytic systems, as exemplified on the Cu^{I}-catalyzed azide–alkyne cycloaddition—a widely used transformation to connect two building blocks of all possible kinds. He presented complex mechanistic studies including spectroscopic investigations, in situ reaction calorimetry, and Cu-isotope crossover studies that support a reaction model involving two copper atoms and a stepwise bond formation. Consequently, electron-rich halo- and metallo-acetylides were used as reaction partners in Cu-catalyzed cycloadditions.[7]

The Tuesday afternoon started with a demonstration of the synthetic creativity of Janine Cossy (ESPCI, Paris), who gave a talk on the synthesis of differently sized heterocycles by utilizing multifarious methods, including Fe-catalyzed diastereoselective cyclization of allylic alcohols, Co-catalyzed coupling of Grignard reagents with alkyl halides, and Au-catalyzed cycloisomerization of cyclopropene-enes. Moreover, she showed a remarkable general method to access functionalized [*n*]paracyclophanes by the Diels–Alder reaction of tricyclic 1,3-dienes with activated alkynes and subsequent retro-Diels–Alder reaction of the in situ formed 1,4-dienes.[8] After a poster session that commenced with short oral presentations (Suzanne Blum, Ivana Fleischer, Michal Juríček, Kathrin Lang, and Uday Maitra) and dinner, Jonas Peters (Caltech) introduced us to the world of complex inorganic chemistry and synthetic nitrogenases. His investigations help to understand the role of iron in the natural FeMo nitrogenase cofactor by using defined iron complexes that are able to catalyze the reduction of N_2 to NH_3 by protons and electrons. Peters and his co-workers developed a tris(phosphine)borane-based iron complex that showed a promising catalytic activity, for which the flexible boron–iron interaction seems to play an important role. The suggested mechanistic model is supported by thorough stoichiometric and spectroscopic investigations.[9]

The Wednesday indulged us with two impressive morning lectures. Annette Beck-Sickinger (Leipzig) opened the session with an intriguing talk on the investigation of ligand binding and trafficking of G protein coupled receptors (GPCRs), which constitute important membrane proteins that sense signaling molecules. The understanding of how GPCRs interact with ligands is of great relevance for the development of therapeutics. For example, a new method was developed for breast cancer tumor targeting based on Y_1 receptor ligands derived from neuropeptide Y. In vivo studies showed a selective uptake of a ^{99m}Tc-labeled ligand by the tumor cells.[10] The goal of Judith Klinman (Berkeley) is to understand the physical basis of enzyme catalysis, and she convinced us that she is cracking the code of this topic. She showed that enzymatic C–H cleavage reactions occur by quantum mechanical tunneling, where the H atom moves through the energy barrier; this mechanism results in a large kinetic isotopic effect. Experimental findings support the involvement of protein dynamics in this process. Kinetic, structural, and theoretical studies conducted using soybean lipoxygenase and its mutant showed the dependence of the catalytic performance on protein flexibility, which is needed to ensure close donor–acceptor distances necessary for the tunneling.[11] In the first free afternoon, some of us found that it is much better to climb and not tunnel into the surrounding Swiss mountains.

The topic of the Thursday sessions was synthetic materials for different purposes: nanotechnology, catalysis, and medicine. Hiroyuki Isobe (Tokyo) expressed his love of molecular entities and spoke about carbon-containing molecular bearings. Starting from functionalized [4]phenacene, its cyclic tetramer was prepared by stepwise macrocyclization. This compound is a model for single-wall carbon nanotubes of three variants (helical, zigzag, and armchair) in isomeric forms. All isomers, including enantiomers, were identified and isolated. Subsequently, it was used to produce a stable molecular bearing in a spontaneous supramolecular assembly with a fullerene, which constitutes the pivot. The concept was extended to anthranthrenylene-based macrocycles that encapsulate C_{60} and C_{70} with extremely high affinity.[12] Michinore Suginome (Kyoto) followed with an insightful talk on chirality-switchable dynamic catalysts. The idea is to utilize helical chiral macromolecules as a catalyst backbone that undergoes dynamic helix inversion. The axial chirality is induced by chiral end groups or side chains. One of the presented achievements is the unique phosphine ligand PQXphos that comprises a polyquinoxaline helix decorated with chiral side chains and diarylphosphino units (Scheme 3). A solvent-dependent switch of the helical sense was observed and applied in bidirectional asymmetric Pd-catalyzed hydrosilylation to obtain both product enantiomers separately with high selectivity.[13]

The final stimulating evening lecture was given by Stuart Schreiber (Broad Institute, Massachusetts Institute of Technology and Harvard University), who not only summarized his research activities in the field of application of small molecules in the development of therapeutics, but also



Scheme 3. PQXphos: Structural design and solvent-induced chiral switch.[13a]

provided his vision for the future progress of chemical biology with the aim to shorten the timeline between the synthesis of a compound library and biological test results. One aspect is the investigation of synthetic methods that produce modular collections of compounds, such as the build/couple/pair approach. In addition, Schreiber described multiplexed high-dimensional biological profiling of small molecules by simultaneous measurement of different cellular features.[14]

This interactive and interdisciplinary conference connects various subjects, established and younger scientists, academia, and industry. The idea of André Dreiding, who founded the conference in 1965, lives on!

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