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Prelog Lecture 2006

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Abstract: On Monday, November 6, 2006, the rector Prof. Dr. K. Osterwalder presented the Prelog Medal 2006 to Prof. Dr. Manfred T. Reetz, Max-Planck-Institut für Kohleforschung, Mülheim an der Ruhr, Germany. The title of the lecture that followed was 'Evolution in the Test-Tube as a Means to Create Selective Biocatalysts'.

Keywords: Reetz, M.T. · Prelog Lecture

Photo R. Häfliger

Konrad Osterwalder and Manfred T. Reetz

The recipient of the 2006 Prelog Medal, Prof. Manfred T. Reetz, was born in 1943 in Hirschberg Germany. He received his BA degree from Washington University in St Louis in 1965 and his MS degree from the University of Michigan in Ann Arbor in 1967. He subsequently joined the group of Prof. U. Schöllkopf at the University of Göttingen for his doctoral dissertation which he completed in 1969. Following a postdoctoral stay with Prof. R.W. Hoffmann at the University of Marburg from 1971–72, he was appointed as an Assistant Professor in Marburg from 1973–78. He subsequently moved as an Associate Professor to the University of Bonn (1978–80) before becoming Full Professor at the University of Marburg where he stayed from 1980–91. In 1991, he was appointed as the successor of Prof. G. Wilke and became Director of the Max-Planck-Institute für Kohleforschung in Mülheim/Ruhr. He profoundly changed the Institute, substituting a pyramidal structure to a structure of equal colleagues with rotating directorship, which subsequently enabled the hiring/retaining of some of the finest chemists worldwide. Manfred T. Reetz has published more than 450 papers, many of which are very highly cited. He has been awarded several honors for his original, innovative research, among others the Otto-Bayer Prize in 1986, the Leibniz-Prize of the Deutsche Forschungsgemeinschaft in 1989, the Fluka Prize 'Reagent of the Year 1997', the Nagoya Gold Medal in Organic Chemistry, and the Karl-Ziegler Prize in 2005. He is also a member of several scientific academies including the Deutsche Akademie der Naturforscher Leopoldina and the Royal Netherlands Academy of Arts and Sciences.

Manfred T. Reetz is a synthetic organic chemist with a broad range of interests focusing on methodology development. His chemistry has been exploited by numerous academic and industrial groups. Early in his career, he solved the long-standing problem of α-*tert*-alkylation of carbonyl compounds by reacting the corresponding enolsilanes with a wide variety of tertiary alkyl halides in the presence of a Lewis acid. In fact he demonstrated that all S_N1 active substrates undergo this kind of C–C bond formation, which means that the general concept is complementary to classical S_N2 reactions of primary alkyl halides with lithium enolates. It is used by Merck/USA in the production of the antibiotic Thienamycin. Reetz then turned to organotitanium chemistry and developed the idea of adjusting chemo-, enantio-, and diastereoselectivity of carbanions by titanation using transmetallating agents which contain halo, alkoxy, or amino ligands. His book entitled 'Organotitanium Reagents in Organic Chemistry' not only summarizes these developments up to 1986, it also inspired many other groups to study trans-metallation using other metals and ligands. Parallel to these achievements, Reetz developed a new and general method for diastereoselective chelation-controlled Grignard-type processes, Mukaiyama aldol additions, and cyanohydrin-forming reactions. The concept is based on the simple idea of chelating chiral α- or β-alkoxy aldehydes or ketones with Lewis acids such as $TiCl_4$ and then to react them with appropriate reagents such as organozinc compounds, allylsilanes, enolsilanes, or silylcyanides. This method has found wide acceptance in organic synthesis.

In the late 1980s and early 1990s, Reetz described the racemization-free transformation of α-amino acids into the corresponding N,N-dibenzylamino aldehydes which opened new avenues for synthetic applications, including non-chelation-controlled addition reactions of organolithium and magnesium reagents, lithium enolates, cyanide ions, carbenoids, or nitronates. The Reetz N,N-dibenzylamino aldehydes and ketones turned out to be key compounds in other reactions as well.

In the 1990s, Reetz pioneered a completely new approach to asymmetric catalysis. It concerns the use of directed evolution as a means to create enantioselective enzymes for application in organic synthesis. This novel idea is based on the proper combination of molecular biological methods for random mutagenesis and gene expression as well as high-throughput screening for the determination of enantiopurity. For example, the enantioselectivity in the lipase-catalyzed kinetic resolution of a certain chiral ester was increased dramatically without any knowledge of the 3D-structure of the enzyme. The theoretical analysis of the best mutant, characterized by remote mutations, revealed a novel relay mechanism, which demonstrates that important lessons can be learned from directed evolution. Moreover, high-throughput analytical screens for enantiopurity were developed and are now also being used by industrial groups. Thus, the use of isotopically labeled compounds in the determination of enantioselectivity of enzymes by mass spectrometry allowed more than 7000 exact ee-determinations per day. The Reetz group has extended the research to include the directed evolution of monooxygenases as catalysts in enantioselective Baeyer-Villiger reactions and sulfoxidation of prochiral thio-ethers (ee = 90–99%). Most recently the group has introduced the concept of combinatorial active-site saturation test (CAST) which is a milestone in directed evolution, making the search in protein sequence space unusually efficient. Highly enantioselective epoxide hydrolases were evolved using iterative CASTing, which is a crucial follow-up development of the original concept. Among the other challenges being addressed successfully is the classical problem of extending the substrate scope of enzymes and increasing their thermostability.

Parallel to these efforts, Reetz has recently pioneered the use of chiral monodentate P-ligands in efficient asymmetric transition metal catalysis, which constitutes a change in paradigm. He has extended their application by using mixtures, which is a novel combinatorial approach allowing for high catalyst diversity without the need to prepare new ligands. Like directed evolution, it holds great promise for truly practical applications.

Former Prelog Lecturers

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1988 K. Barry Sharpless
1989 Jeremy R. Knowles
1990 Henri B. Kagan
1991 Clayton H. Heathcock
1992 J. Michael McBride
1993 Hisashi Yamamoto
1994 Jean-Pierre Sauvage
1995 Yoshito Kishi
1996 David M.J. Lilley
1997 Günter Helmchen
1998 Lia Addadi
1999 David Evans
2000 Helmut Schwarz
2001 Robert H. Grubbs
2002 David E. Cane
2003 Andreas Pfaltz
2004 Marvin H. Caruthers
2005 Ben L. Feringa