Manfred T. Reetz

Date of birth:	13 August, 1943
Nationality:	German
Position:	Director at the Max-Planck-Institut für Kohlenforschung in Mülheim (Germany)
Education:	1961 High school diploma in St. Louis, Missouri (USA) 1965 BA degree, Washington University, St.Louis 1965–1967 MS degree, University of Michigan, Ann Arbor 1967–1969 PhD with U. Schöllkopf, "Synthesis and Photolysis of Bromo- and Iodo-Diazoacetic Acid Esters", Göttingen University (Germany) 1971–1972 Postdoc with R. W. Hoffmann, Marburg University (Germany)
Recent awards:	**2000** Nagoya Gold Medal of Organic Chemistry (Japan); **2001**–Present Member of the Academy of Sciences of the State of NRW; **2003** Hans Herloff Inhoffen Medal (Germany); **2003** Centenary Lecture Award (UK); **2005** Cliff S. Hamilton Award in Organic Chemistry (USA); **2005** Karl–Ziegler Prize (German Chemical Society); **2005** Foreign Member of the Royal Netherlands Academy of Arts and Sciences; **2006** Ernst Hellmut Vits Prize (Germany); **2006** Prelog Medal (Switzerland); **2008** Ruhr Prize (Mülheim); **2009** Arthur C. Cope Award
Current research interests:	Biocatalysis: In the 1990s we proposed a new approach to asymmetric catalysis, namely, the directed evolution of enantioselective enzymes as catalysts in organic chemistry. This Darwinian concept relies on repeating cycles of gene mutagenesis, expression, and high-throughput *ee* screening. Since then, many academic and industrial groups have contributed to this new field. Currently, our focus is on methodology development in the quest to make directed evolution of enantioselectivity and thermostability more reliable and faster than in the past. This requires the creation of advanced methods and strategies for probing protein sequence space with unprecedented efficacy. Moreover, we are learning from directed evolution in two different ways: 1) upon performing mechanistic and structural studies of the evolved mutants, the source of enhanced enantioselectivity, activity, and/or thermostability is unveiled, which also deepens our general understanding of how enzymes function; 2) such studies allow us to make predictions as to the possible substrate scope of a given mutant that was originally evolved for a single substrate, which is important for the future of the field
Hobbies:	Tennis, classical music

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*The author presented on this page has recently published his **25th article** since 2000 in Angewandte Chemie*: "Single-Cell High-Throughput Screening to Identify Enantioselective Hydrolytic Enzymes": S. Becker, H. Höbenreich, A. Vogel, J. Knorr, S. Wilhelm, F. Rosenau, K.-E. Jaeger, M. T. Reetz, H. Kolmar, *Angew. Chem.* **2008**, *120*, 5163–5166; *Angew. Chem. Int. Ed.* **2008**, *47*, 5085–5088.

My favorite subject at school was… tennis.

When I was eighteen I wanted to be… a chemist.

When I wake up I… am happy that a new day starts.

The most significant scientific advance of the last 100 years has been… the development of antibiotics.

The biggest problem that scientists face is… the difficulty in making our mission clear to the public.

My favorite piece of research is… Emil Fischer's paper on the lock-and-key hypothesis regarding enzymes.

If I could have dinner with three famous scientists from history, they would be… Max Planck, Otto Hahn, and Lise Meitner.

I chose chemistry as a career because… it is a wonderful hobby.

The most important future applications of my research are… ecologically and economically viable enzyme-catalyzed organic transformations on a broader basis than practiced today.

My first experiment was… observing the result of exchanging the food bowls of our two dogs at home.

If I wasn't a scientist, I would be… a mediocre tennis player.

My most exciting discovery to date has been… the directed evolution of enantioselective enzymes as catalysts in synthetic organic chemistry.

The most exciting thing about my research is… that it constitutes a new approach to asymmetric catalysis different from all previous ways of thinking about the subject because it relies on properly exerted evolutionary pressure.

In my spare time I… have learned to think about things other than chemistry.

My biggest motivation is… the development of new ideas and concepts.

>>> see next page: *the interview*

How is chemistry research different now than it was at the beginning of your career?

The analytical techniques available to chemists back in the early 1970s have since advanced dramatically, allowing us to work much faster in the laboratory and also to design and implement experiments not readily possible three to four decades ago. NMR spectroscopy and MS are two prominent examples, and modern forms of GC and HPLC spectrometry are likewise taken for granted and used daily as indispensable aids in the laboratory. Without these achievements, many current advances in organic chemistry and chemical biology would not be possible.

Has your approach to chemistry research changed since the start of your career?

Not really, with the exception of the analytical techniques noted above.

Has your approach to publishing your results changed since the start of your career?

No, I still try to be critical and select only the best results for publication in top journals. However, contributions in other journals, including the more specialized ones, are also essential for progress in science. I also believe that full papers with full experimental details fulfill an important function, certainly when new approaches and techniques are reported. Communications accompanied by supplementary material, even if they are groundbreaking, do not always serve as true substitutes for full papers.

What do you think the future holds for your field of research?

I believe that enzyme catalysis as currently applied in synthetic organic chemistry, pathway engineering, biotechnology (including energy problems), bionanotechnology, pollution cleanup, and other areas has a bright future, otherwise I would not be active in the area of directed evolution. Our contributions based on the Darwinian principles inherent in directed evolution help to eliminate some of the traditional limitations of enzyme catalysis, namely, that 1) many substrates are not accepted by the wild-type enzyme; 2) enantioselectivity is unacceptably low; 3) enantioselectivity is high, but the wrong enantiomer is delivered; and 4) the enzyme is active and selective, but not stable enough for real applications. Since our proof-of-principle study regarding directed evolution of enantioselective enzymes, published in *Angewandte Chemie* in 1997, we and many other groups have reported further progress in this form of protein engineering, which includes the above four issues, but also considers further practical parameters such as the elimination of possible product inhibition, reduction of undesired side products, and the enhancement of time/space yields and robustness under operating conditions.

Hopefully, these and future contributions emerging from directed evolution will help to solve some of the challenging problems in current synthetic organic chemistry such as the practical realization of various types of selective partial-oxidation processes, including regio- and stereoselective C–H activation, or catalytic selective glycosylation reactions required for the synthesis of complex oligosaccharides without the necessity to revert to protective-group technology. I expect biocatalysis, transition-metal catalysis, and organocatalysis to continue to thrive in a complementary manner.

Pathway (metabolic) engineering is emerging as a powerful and complementary approach to "natural and unnatural products synthesis". In the future, directed evolution of stereoselectivity may contribute to widening the scope of this intriguing method for harnessing cells as "factories" for the production of simple and complex compounds. An alliance of molecular biologists and synthetic organic chemists is needed in this exciting endeavor. Again, methodology development is crucial, just as it continues to be in the traditional areas of synthetic organic chemistry. Organic chemists need a large toolbox from which to choose from, be it chemical or biocatalytic methods!

Have you changed the main focus of your research throughout your career and if so why?

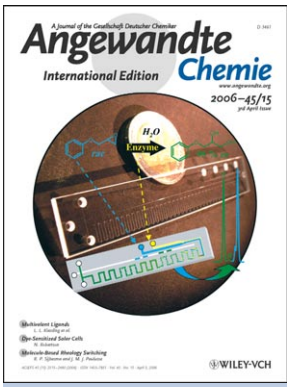
I have changed the direction of my research several times (not always successfully!), typically every eight to ten years with the exception of my present interest in directed evolution, which began in 1995 and continues to this day. These changes were initiated because I find it intellectually appealing to ponder over very different types of chemical problems. However, I do not suggest that this should be construed as a general recommendation, because the history of science has shown that very different approaches can be successful, depending upon the personality of the respective scientist. For example, the exclusive focus on a single, highly important problem for decades, even in the face of seemingly insurmountable difficulties, can lead to true rewards, provided creativity and perseverance characterize the researcher who has chosen this approach.

What has been you biggest influence/motivation?

I guess it is the same with most scientists, the joy of moving into the unknown, hopefully leading to an increase in human knowledge. By definition this means that one needs to be the first.

What advice would you give to up-and-coming scientists?

Keep going!



M. T. Reetz has featured on the cover of Angewandte Chemie:
"Single-Cell High-Throughput Screening to Identify Enantioselective Hydrolytic Enzymes": S. Becker, H. Höbenreich, A. Vogel, J. Knorr, S. Wilhelm, F. Rosenau, K.-E. Jaeger, M. T. Reetz, H. Kolmar, *Angew. Chem.* **2008**, *120*, 5163 – 5166; *Angew. Chem. Int. Ed.* **2008**, *47*, 5085 – 5088.

What is the secret to publishing so many high quality papers?

Why a secret? Obviously, all good scientists not only need to attract excellent co-workers, but they also have to provide and maintain an atmosphere in their groups which maximizes motivation. This can be reached in different ways. I personally believe that having fun when doing research is crucial. High-quality papers, in addition to published or unpublished failures, will surely follow!

My 5 top papers:

1. "Creation of Enantioselective Biocatalyts for Organic Chemistry by In Vitro Evolution": M. T. Reetz, A. Zonta, K. Schimossek, K. Liebeton, K.-E. Jaeger, *Angew. Chem.* **1997**, *109*, 2961 – 2963; *Angew. Chem. Int. Ed.* **1997**, *36*, 2830 – 2832.
   This was our first paper regarding directed evolution of enantioselective enzymes, although only proof-of-principle was demonstrated for a lipase-catalyzed hydrolytic kinetic resolution. We showed, for the first time, that several cycles of mutagenesis/screening exerts evolutionary pressure and, therefore, allows the enantioselectivity of an enzyme to increase in a stepwise manner.
2. "Controlling the Enantioselectivity of Enzymes by Directed Evolution: Practical and Theoretical Ramifications": M. T. Reetz, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5716 – 5722.
   In this paper, we analyzed and evaluated the different methods and strategies known at that time for evolving enantioselective enzymes, hopefully providing a guide for researchers interested in further advances. We also emphasized the crucial role of high-throughput *ee* assays that we had previously developed. Moreover, our earlier concept of directed evolution of hybrid catalysts, that is, laboratory evolution of robust proteins hosting ligand–transition-metal moieties, was highlighted as a novel way to tune conventional transition-metal catalysts.
3. "Directed Evolution of Enantioselective Enzymes: Iterative Cycles of CASTing for Probing Protein-Sequence Space": M. T. Reetz, L.-W. Wang, M. Bocola, *Angew. Chem.* **2006**, *118*, 1258 – 1263; *Angew. Chem. Int. Ed.* **2006**, *45*, 1236 – 1241.
   This contribution introduced the concept of "iterative saturation mutagenesis", specifically for evolving enantioselectivity with unprecedented efficiency, opening a convenient door for fast directed evolution. This approach reduces the screening effort drastically, which is the traditional bottleneck in directed evolution.
4. "Iterative Saturation Mutagenesis on the Basis of B Factors as a Strategy for Increasing Protein Thermostability": M. T. Reetz, J. D. Carballeira, A. Vogel, *Angew. Chem.* **2006**, *45*, 7745 – 7751; *Angew. Chem. Int. Ed.*, **2006**, *45*, 7745 – 7751.
   This paper is important because we showed that iterative saturation mutagenesis can also be used to enhance the thermostability of enzymes with unprecedented degrees of improvement while at the same time minimizing the amount of laboratory work. The two embodiments of iterative saturation mutagenesis are both knowledge driven, which means that the absence of any structural data marks the limitation of this approach to directed evolution.
5. "Addressing the Numbers Problem in Directed Evolution": M. T. Reetz, D. Kahakeaw, R. Lohmer, *ChemBioChem* **2008**, *9*, 1797 – 1804.
   Here we presented yet another technique for increasing the efficiency and speed of directed evolution. Accordingly, the structure- and informatics-guided utilization of reduced amino acid alphabets in saturation mutagenesis provides the researcher with a useful tool in laboratory evolution.

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