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Introduction: Organocatalysis

The catalysis with small organic molecules, where an inorganic element is not part of the active principle, has become a highly dynamic area in chemical research. Remarkably though, while several special issues in various journals, book chapters, and even entire monographs have appeared on this topic in recent years, not too long ago the field essentially didn't even exist. For example, in the late 1990s, Sorensen and Nicolaou in their brilliant book *Classics in Total Synthesis* defined asymmetric catalysis by rather accurately (at the time!) stating that "In a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral."

This view has been significantly altered, and it is clear by now that modern asymmetric catalysis is built on three rather than two pillars, namely biocatalysis, metal catalysis, *and* organocatalysis. In light of this, it is quite remarkable that organic chemists had long ignored the fact that the very first catalysts they used in ancient times were purely organic molecules such as acetaldehyde (Liebig in 1859). As organic molecules readily react with each other, why did we disregard these compounds as catalysts and rather relied on the assistance of biologists and inorganic chemists to provide enzymes or explain the foreign world of d-orbitals to us? Why did we not expect catalytic competence from organic molecules—exactly those compounds we can truly design, make, and know most about?

While this thematic issue may not provide an answer to these intriguing questions, it will hopefully give an overview of the area of organocatalysis and provide a more logical structure to the field. There are essentially four types of organocatalysts, Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids. These catalysts initiate their catalytic cycles by either providing or removing electrons or protons from a substrate or a transition state. Organocatalysis is dominated by Lewis base catalysts such as amines and carbenes, while Lewis acids such as carbonyl compounds are rarely used. A relatively new concept is the use of chiral organic Brønsted acid catalysts. This area is likely to grow strongly and is expected (at least by the writer) to ultimately deliver extremely active catalysts that rival the efficiency of enzymes and that of the few superactive chiral transition metal complexes, such as Noyori's hydrogenation catalysts or certain Suzuki reaction catalysts.

Benjamin List was born in 1968 in Frankfurt, Germany. He graduated from Freie University Berlin (1993) and received his Ph.D. (1997) from the University of Frankfurt (Mulzer). After postdoctoral studies (1997–1998) as a Feodor Lynen Fellow of the Alexander von Humboldt foundation at The Scripps Research Institute (Lerner), he became a Tenure Track Assistant Professor there in January 1999. Subsequently, he developed the first proline-catalyzed asymmetric intermolecular aldol, Mannich, Michael, and α-amination reactions and received a grant on *Asymmetric Aminocatalysis* from the National Institutes of Health. He moved to the Max-Planck-Institut für Kohlenforschung in 2003 as an associate professor (2003–2005) and currently is a director (full professor) there and an honorary professor at the University of Cologne. His research interests are new catalysis concepts, bioorganic chemistry, and natural product synthesis. He has received several awards, including the Carl-Duisberg-Memorial Award of the German Chemical Society (2003), the Degussa Prize for Chiral Chemistry (2004), the Lecturer's Award of the Endowment of the Chemical Industry (2004), the Lieseberg-Prize of the University of Heidelberg (2004), The Society of Synthetic Chemistry, Japan Lectureship Award (2005), the Novartis Young Investigator Award (2005), the OBC-Lecture Award (2007), and, most recently, the AstraZeneca Award in Organic Chemistry. He is currently an editor of *Synfacts* and coordinates the DFG-priority program "*Organocatalysis*".

I have the good fortune of being the Guest Editor for this thematic issue, and have organized it into five units, one on each of the four types of catalysis modes above, and a fifth on miscellaneous aspects of organocatalysis. Gratifyingly, several of the leaders within these areas have contributed articles, and I would like to take this opportunity to thank them for their excellent contributions as well as John Gladysz and his reviewers for their heroic efforts of assuring high quality. Less fortunately though, not all key elements of organocatalysis could be included, which is mostly due to an incompatible time schedule of potential authors with the publisher. For example, a treatment of ketone-catalyzed

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epoxidations is missing. This area forms one-half of Lewis acid organocatalysis, which leaves this topic solely (and arguably) to phase transfer catalysis. Also, the reader will notice that some authors have taken the liberty to expand certain areas beyond organocatalysis to include other themes such as biocatalysis and transition metal catalysis, and even noncatalytic reactions. This is certainly not due to an unclear definition of what organocatalysis is, but rather is based on the opinion of these authors that their topics should be viewed from a broader angle.

The first five articles out of the twelve in this issue deal with Lewis base catalysis, once again illustrating the dominance of this area in organocatalysis. Anniina Erkkilä, Inkeri Majander, and Petri Pihko start the issue with a thorough treatise on one of the most powerful and general strategies of organocatalysis, "Iminium Catalysis", introduced by David MacMillan and his group in 2000. This review also includes a highly readable section on the rich history of this interesting activation mode.

Our article (by Santanu Mukherjee, Jung Woon Yang, Sebastian Hoffmann, and Benjamin List) on "Asymmetric Enamine Catalysis" follows. During the preparation of this review, we realized how the enamine catalysis concept that we had originally proposed in 2000 has developed into a powerful strategy that has delivered an impressive amount of highly useful, general, and enantioselective reactions. The development of enamine catalysis, as well as that of iminium catalysis, has not only been inspired by the Hajos−Parrish−Eder−Sauer−Wiechert reaction but has also been "catalyzed" by the creation of aldolase catalytic antibodies in the laboratories of Lerner and his team (Barbas, Reymond).

Continuing with the theme of nitrogen Lewis bases, valuable contributions by Ryan P. Wurz on asymmetric catalysis with DMAP analogues and by Matthew J. Gaunt and Carin C. C. Johansson on organocatalysis via ammonium enolates follow. The fifth article in this series by Dieter Enders, Oliver Niemeier, and Alexander Henseler discusses "Organocatalysis by N-Heterocyclic Carbenes", which for a long period only meant the benzoin condensation and Stetter reaction. This area has grown enormously, not the least with the recent discovery of an a^3−d^3-type *umpolung* introduced independently by Glorius and Bode.

Normally, the next logical article in the unit on Lewis base catalysis would be Varinder Aggarwal and his coauthors' timely discussion on "Chalcogenides as Organocatalysts". However, as this review discusses very little "true" organocatalyis (using the above definition) but is obviously related to the general topic, it has been moved into the fifth unit on miscellaneous organocatalysis aspects.

An article on Lewis acid organocatalysis by Takuya Hashimoto and Keiji Maruoka follows, in which they outline recent developments in phase transfer catalysis (PTC). The authors discuss highly useful and active catalysts based on quaternary ammonium salts. Please note that some organocatalysis purists have argued that as phase transfer catalysis typically involves metal enolates, it should not be considered organocatalysis. Because purely organic examples of PTC have been reported, the area is included here nonetheless.

Another single-article-unit on Brønsted base catalysis follows, in which Iuliana Atodiresei, Ingo Schiffers, and Carsten Bolm discuss "Stereoselective Anhydride Openings". Although this area is clearly dominated by cinchona alkaloid-catalyzed alcoholyses of anhydrides, the authors put the subject into a broader context by including many non-organocatalytic processes.

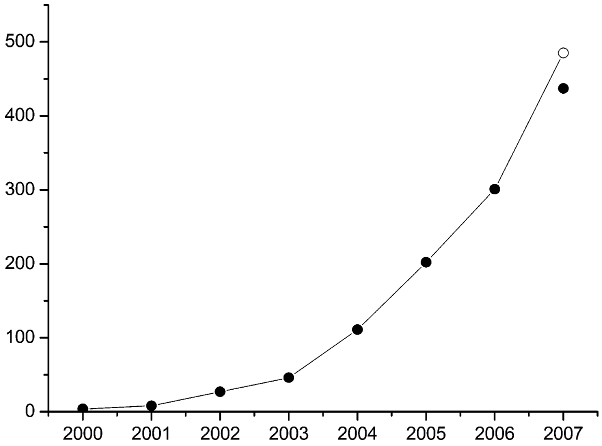

Figure 1. Number of publications using the term "organocatalysis" in the title or abstract since the year 2000: ●, from SciFinder as of November 21, 2007; ○, predicted.

The subsequent two articles deal with Brønsted acid catalysis. This area has grown significantly since the late 1990s, when, by serendipity, Eric Jacobsen and his team identified an exceptionally active and enantioselective H-bonding catalyst of the Strecker reaction. In their review, Abigail G. Doyle and Eric N. Jacobsen have also decided to take a broader approach to the area of "Small-Molecule H-Bond Donors in Asymmetric Catalysis". Some reactions are included that may also be classified differently, such as the proline-catalyzed aldol reaction, and are covered from a different perspective in other articles in this issue.

This seems to point to a general challenge in classifying organocatalysts: Often there is little knowledge of a given reaction mechanism and the exact mode of activation is unknown. Even more complicating is the fact that many organocatalysts are bifunctional. For example, a urea catalyst that incorporates an amine may be described either as an H-bonding donor catalyst or as a Brønsted base catalyst. Accordingly, such catalysts can, in principle, be treated in either of the two units.

Next, Takahiko Akiyama describes the use of "Stronger Brønsted Acids" in asymmetric organocatalysis. In contrast to H-bond donor catalysts, which form hydrogen bonds to a transition state, these are strong enough acids to protonate the substrate of a reaction, forming ion pairs as intermediates. The area has grown quite a bit since its invention by the author as well as independently by Terada and his group in 2004.

The last unit deals with miscellaneous aspects of organocatalysis, such as peptide catalysts. This area is mostly based on the work of Miller et al. Elizabeth A. Colby Davie, Steven M. Mennen, Yingju Xu, and Scott J. Miller, in their review, deal with catalysts that are right in-between the worlds of small organic molecules and proteins.

Nahrain E. Kamber, Wonhee Jeong, Robert M. Waymouth, Russell C. Pratt, Bas G. G. Lohmeijer, and James L. Hedrick describe the increasing use of organocatalysis in polymerization chemistry in their article on "Organocatalytic Ring-Opening Polymerization".

The thematic issue closes with Eoghan M. McGarrigle, Eddie L. Myers, Ona Illa, Michael A. Shaw, Samantha L. Riches, and Varinder K. Aggarwal's treatment of "Chacogenides as Organocatalysts". This article describes several interesting reactions that mostly lead to three-membered rings and that typically combine organocatalysis and metal catalysis.

As illustrated by the citation statistics in the figure, it is obvious that organocatalysis has grown quite dramatically in recent years. Yet, the field should certainly not be considered “mature”, maybe not even “adolescent”. Several areas are yet completely unexplored, and new concepts will surely arise within the more established ones. Also, there are already a number of organocatalytic reactions being used in the pharmaceutical and chemical industries. Yet, the area is clearly not as “mainstream” in industry as it already is in academia. I predict that the coming two decades will bridge the gap between the current academic excitement on the one hand and the industrial realities on the other. I can hardly wait to read the *Chemical Reviews* thematic issue on Organocatalysis to be published in the year 2027, reporting the spectacular advancements that will surely be made by then!

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