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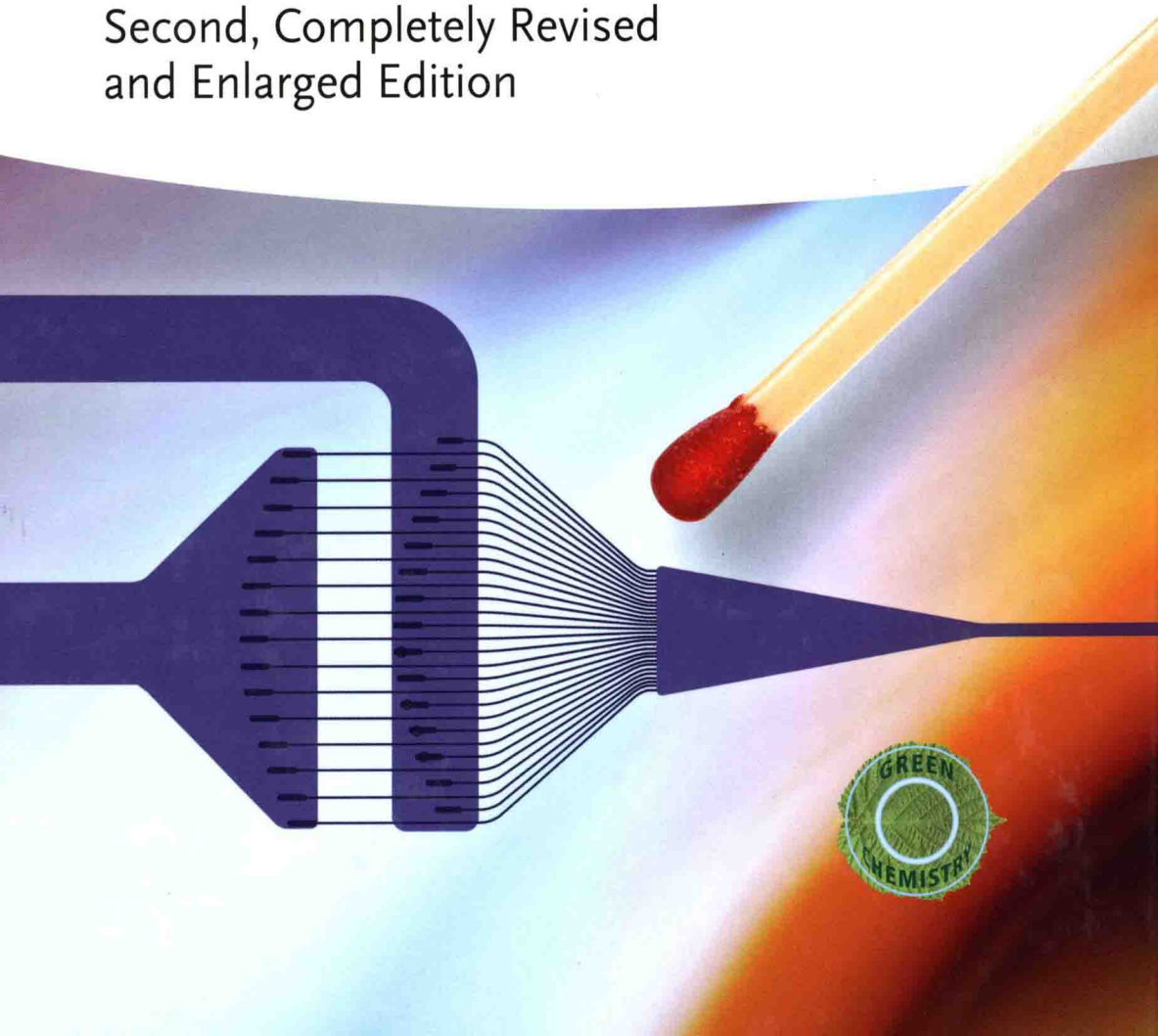
Edited by Thomas Wirth

Microreactors in Organic Chemistry and Catalysis

Second, Completely Revised and Enlarged Edition



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The Editor

Prof. Dr. Thomas Wirth
Cardiff University
School of Chemistry
Park Place Main Building
Cardiff CF10 3AT
United Kingdom

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Contents

Preface to the First Edition

Microreactor technology is no longer in its infancy and its applications in many areas of science are emerging. This technology offers advantages to classical approaches by allowing miniaturization of structural features up to the micrometer regime. This book compiles the state of the art in organic synthesis and catalysis performed with microreactor technology. The term "microreactor" has been used in various contexts to describe different equipment, and some examples in this book might not justify this term at all. But most of the reactions and transformations highlighted in this book strongly benefit from the physical properties of microreactors, such as enhanced mass and heat transfer, because of a very large surface-to-volume ratio as well as regular flow profiles leading to improved yields with increased selectivities. Strict control over thermal or concentration gradients within the microreactor allows new methods to provide efficient chemical transformations with high space–time yields. The mixing of substrates and reagents can be performed under highly controlled conditions leading to improved protocols. The generation of hazardous intermediates *in situ* is safe as only small amounts are generated and directly react in a closed system. First reports that show the integration of appropriate analytical devices on the microreactor have appeared, which allow a rapid feedback for optimization.

Therefore, the current needs of organic chemistry can be addressed much more efficiently by providing new protocols for rapid reactions and, hence, fast access to novel compounds. Microreactor technology seems to provide an additional platform for efficient organic synthesis – but not all reactions benefit from this technology. Established chemistry in traditional flasks and vessels has other advantages, and most reactions involving solids are generally difficult to be handled in microreactors, though even the synthesis of solids has been described using microstructured devices.

In the first two chapters, the fabrication of microreactors useful for chemical synthesis is described and opportunities as well as problems arising from the manufacture process for chemical synthesis are highlighted. Chapter 1 deals with the fabrication of metal- and ceramic-based microdevices, and Brandner describes different techniques for their fabrication. In Chapter 2, Frank highlights the microreactors made from glass and silicon. These materials are more known to the organic chemists and have therefore been employed frequently in different

laboratories. In Chapter 3, Barrow summarizes the use and properties of microreactors and also takes a wider view of what microreactors are and what their current and future uses can be.

The remaining chapters in this book deal with different aspects of organic synthesis and catalysis using the microreactor technology. A large number of homogeneous reactions performed in microreactors have been sorted and structured by Ryu *et al.* in Chapter 4.1, starting with very traditional, acid- and base-promoted reactions. They are followed by metal-catalyzed processes and photochemical transformations, which seem to be particularly well suited for microreactor applications. Heterogeneous reactions and the advantage of consecutive processes using reagents and catalysts on solid support are compiled by Ley *et al.* in Chapter 4.2. Flow chemistry is especially advantageous for such reactions, but certain limitations to supported reagents and catalysts still exist. Recent advances in stereoselective transformations and in multistep syntheses are explained in detail. Other biphasic reactions are dealt with in the following two chapters. In Chapter 4.3, we focus on liquid–liquid biphasic reactions and focus on the advantages that microreactors can offer for intense mixing of immiscible liquids. Organic reactions performed under liquid–liquid biphasic reaction conditions can be accelerated in microreactors, which is demonstrated using selected examples. The larger area of gas–liquid biphasic reactions is dealt with by Hessel *et al.* in Chapter 4.4. After introducing different contacting principles under continuous flow conditions, various examples show clearly the prospects of employing microreactors for such reactions. Aggressive and dangerous gases such as elemental fluorine can be handled and reacted safely in microreactors. The emergence of the bioorganic reactions is described by vanHest *et al.* in Chapter 4.5. Several of the reactions explained in this chapter are targeted toward diagnostic applications. Although on-chip analysis of biologic material is an important area, the results of initial research showing biocatalysis can also now be used efficiently in microreactors are summarized in this chapter. In Chapter 5, Hessel *et al.* explain that microreactor technology is already being used in the industry for the continuous production of chemicals on various scales. Although only few achievements have been published by industry, the insights of the authors into this area allowed a very good overview on current developments. Owing to the relatively easy numbering up of microreactor devices, the process development can be performed at the laboratory scale without major changes for larger production. Impressive examples of current production processes are given, and a rapid development in this area is expected over the next years. I am very grateful to all authors for their contributions and I hope that this compilation of organic chemistry and catalysis in microreactors will lead to new ideas and research efforts in this field.

Cardiff
August 2007

Thomas Wirth

Preface to the Second Edition

The continued and increased research efforts in microreactor and flow chemistry have led to an impressive increase in publications in recent years and even to a translation of the first edition of this book into Chinese. This is reflected not only in an update and expansion of all chapters of the first edition but also in the addition of several new chapters to this second edition.

In the first three chapters, Barrow, Brandner, and Frank, respectively, describe properties and fabrication methods of microreactors. In Chapter 4, Moore and Jensen give detailed insights into current methods of online and offline analyses, the potential of rapid optimization of reactions using flow technology, and the combination of analysis and optimization. For better readability, the material on organic synthesis has been split into five different chapters. Ryu *et al.* have extended their chapter on homogeneous reactions in microreactors, while Watts and Wiles have elaborated the topics of photochemistry, electrochemistry, and radiopharmaceutical synthesis in a new chapter as reactions in these areas are very suitable for being carried out using flow chemistry devices and many publications have recently appeared.

Takasu has written a comprehensive chapter on heterogeneous reactions in microreactors and a many different reactions can be found in this part. We have updated our chapter on liquid–liquid biphasic reactions and Hessel *et al.* have provided an update on the gas–liquid biphasic reactions. The chapter on bioorganic and biocatalytic reactions by Miyazaki *et al.* is a comprehensive overview of the developments in this area and highlights the advantages that flow chemistry can offer for research in bioorganic chemistry.

The final chapter by Hessel *et al.* on industrial microreactor process development up to production has seen a dramatic increase as in many areas industry is now adopting flow chemistry with all its advantages for research and for small- to medium-scale production.

I am again very grateful to all authors for providing updates or completely new contributions and I hope that this compilation of chemistry and catalysis in microreactors will stimulate new ideas and research efforts.

Cardiff
January 2013

Thomas Wirth

List of Contributors

Batool Ahmed-Omer
Cardiff University
School of Chemistry
Main Building
Park Place
Cardiff CF10 3AT
UK

David Barrow
Cardiff University
Cardiff School of Engineering
Laboratory for Applied Microsystems
Cardiff CF24 3TF
UK

Juergen J. Brandner
Karlsruhe Institute of Technology
Institute for Micro Process
Engineering
Campus North
Hermann-von-Helmholtz-Platz 1
76344 Eggenstein-Leopoldshafen
Germany

Maria Portia Briones-Nagata
Measurement Solution Research
Center
National Institute of Advanced
Industrial Science and Technology
807-1 Shuku, Tosu
Saga 841-0052
Japan

Ivana Dencic
Eindhoven University of Technology
Department of Chemical
Engineering and Chemistry
Laboratory for Micro-Flow Chemistry
and Process Technology
STW 1.37
5600 MB, Eindhoven
The Netherlands

Thomas Frank
Porzellanstr. 16
98693 Ilmenau
Germany

Takahide Fukuyama
Osaka Prefecture University
Graduate School of Science
Department of Chemistry
Sakai
Osaka 599-8531
Japan

Lily Giles
Cardiff University
Cardiff School of Engineering
Laboratory for Applied Microsystems
Cardiff CF24 3TF
UK

Volker Hessel
Eindhoven University of Technology
Department of Chemical Engineering and Chemistry
Laboratory for Micro-Flow Chemistry and Process Technology
STW 1.37
5600 MB Eindhoven
The Netherlands

Takeshi Honda
Measurement Solution Research Center
National Institute of Advanced Industrial Science and Technology
807-1 Shuku, Tosu
Saga 841-0052
Japan

Matthew J. Hutchings
Cardiff University
School of Chemistry
Main Building
Park Place
Cardiff CF10 3AT
UK

Klavs F. Jensen
Massachusetts Institute of Technology
Department of Chemical Engineering
Room 66-566
77 Massachusetts Avenue
Cambridge
MA 02139
USA

Masaya Miyazaki
Measurement Solution Research Center
National Institute of Advanced Industrial Science and Technology
807-1 Shuku, Tosu
Saga 841-0052
Japan

Jason S. Moore
Massachusetts Institute of Technology
Department of Chemical Engineering
Room 66-566
77 Massachusetts Avenue
Cambridge
MA 02139
USA

Alex Morgan
Cardiff University
Cardiff School of Engineering
Laboratory for Applied Microsystems
Cardiff CF24 3TF
UK

Md. Taifur Rahman
Osaka Prefecture University
Graduate School of Science
Department of Chemistry
Sakai
Osaka 599-8531
Japan

and

School of Chemistry and Chemical Engineering
David Keir Building
Queen's University
Belfast BT9 5AG
Northern Ireland
UK

Ilhyong Ryu
Osaka Prefecture University
Graduate School of Science
Department of Chemistry
Sakai
Osaka 599-8531
Japan