Edited by Thomas Wirth

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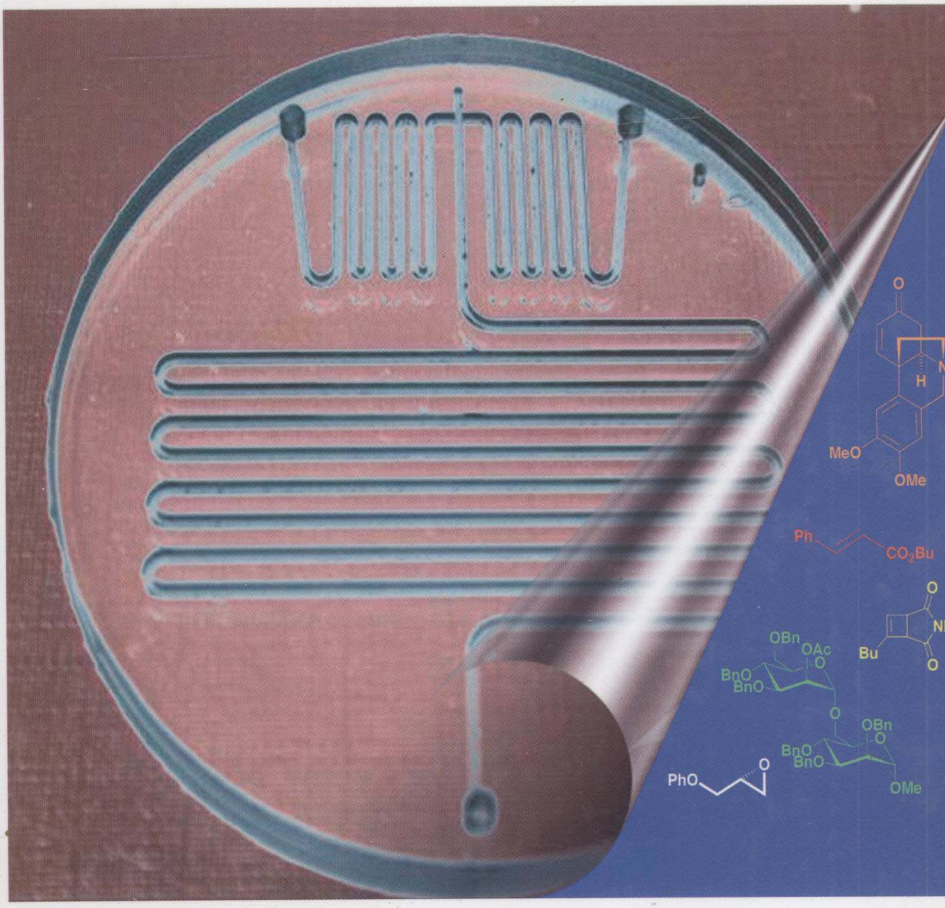
Microreactors in Organic Synthesis and Catalysis



GREEN CHEMISTRY

Microreactors in Organic Synthesis and Catalysis

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Preface

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

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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 van Hest *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.

August 2007

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Contents

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1
Fabrication of Microreactors Made from Metals and Ceramics

Juergen J. Brandner

The material used to manufacture microstructure devices is heavily dependent on the desired application. Factors such as the temperature and pressure range of the application, the corrosivity of the fluids used, the need to have catalyst integration or to avoid catalytic blind activities, thermal conductivity and temperature distribution, specific heat capacity, electrical properties as well as some other parameters have a large influence on the choice of material. Finally, the design of the microstructures itself is an important consideration. Very specific designs are achievable only with special materials because certain manufacturing techniques are needed for them. It might also be necessary to take care of a special surface quality, which is achievable only with certain manufacturing techniques and materials.

Moreover, depending on the number of the devices needed, some manufacturing techniques are considered suitable while others are not.

In this section, fabrication as well as bonding and packaging of microstructure components and devices made from metals and ceramics will be described briefly. The manufacturing processes of both metal microstructure components and ceramic microstructure devices will also be described setting the focus on some well-established technologies. The detailed description of all these techniques can, however, be found in Refs [1–5]. A very short bonding section in which the most common bonding and sealing techniques are briefly described will complete the description of metals and ceramics [4,6].

Two different principal manufacturing techniques, that is erosive and generative have been considered with the discussed materials. Following this, other techniques such as embossing or molding are included into the list of generative manufacturing techniques.

1.1
Manufacturing Techniques for Metals

Metals and metal alloys are the most often used materials for conventional devices in process engineering, and thus applied in microprocess or technology as well. The

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range of materials is spread from noble metals such as silver, rhodium, platinum or palladium via stainless steel to metals such as copper, titanium, aluminum or nickel-based alloys [1,4–6]. Most manufacturing technologies for metallic microstructures have their roots either in semiconductor (in most cases, silicon) device production or in conventional precision machining. Of these, the techniques that are well known have been used for microstructure dimensions. Further, they have been adapted and improved to reach the desired precision and surface quality. In some rare cases, it was possible to use the same manufacturing process for macroscale and microscale devices and to get the desired results. In most of the cases, substantial changes in the design of the device, the methodology of the process and the manufacturing process itself were more or less necessary to provide the accuracy and quality needed for microstructure devices suitable for process engineering. Almost all but one technique used for microstructures in metals are abrasive, and the exception (selective laser melting SLM) will be discussed later.

1.1.1 Etching

Dry and wet etching techniques based on silicon and other semiconductor technologies are well known. For many metals, etching is a relatively cheap and well-established technique to obtain freeform structures with dimensions in the submillimeter range. This technique is well described in the literature [1–5,7]. A photosensitive polymer mask material is applied on the metal to be etched. The mask is exposed to light via a primary mask with structural layers. Here, different technologies are applicable, and their details can be found in the literature on semiconductor processing or in Refs [1–3]. The polymer is then developed. This means that the non-exposed parts are polymerized in such a way that they cannot be diluted by a solvent that is used to remove the rest of the polymer covering the parts to be etched. Thus, a mask is formed, and the metal is etched through the openings of this mask. To generate the etching mask, other techniques such as direct mask writing with a laser are also possible and common.

When etching techniques are used, two main considerations have to be given. First, the aspect ratio (the ratio between the width and depth of a structure), for wet chemical etching, can only be <0.5 at the optimum. As a result of the isotropic etching of the wet solvents, the minimum width of a structure is two times the depth plus the width of the mask openings. Dry etching (e.g. laser) is not limited to this aspect ratio, but it shows other limitations and is rather expensive (see Ref. [1]). Second, wet chemical etching always results in semielliptic or semicircular structures, which is again due to the isotropic etching. Dry etching often leads to other channel geometries. Here, rectangular channels are also possible. In Figure 1.1, a stainless steel microchannel structure manufactured by wet chemical etching is shown. The microchannels are used to build a chemical reactor for heterogeneously catalyzed gas-phase reactions. They are about 360 μm wide and 130 μm deep. Figure 1.2 shows the entrance area of such a microchannel. The semicircular structure is clearly seen. Detailed descriptions of the etching processes and etching agents can be found in Refs [1,4,7,8].