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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
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.

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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
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 semieliptic 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].
Figure 1.1 Wet chemically etched microchannels in a stainless steel foil.

Figure 1.2 Structure of the microchannels from Figure 1.1. The semielliptic shape of the channels is clearly seen. The dimension of the microchannel is about 360 μm wide and 130 μm deep.
1.1.2 Machining

Not all materials can be etched in an easy and cheap way. Especially, noble metals or tantalum are stable against most of these corrosive structuring methods. Hence, precision machining may be used to generate microstructures from these metals as well as from standard metal alloys such as stainless steel or hastelloy. Depending on the material, precision machining can be performed by spark erosion (wire spark erosion and countersunk spark erosion), laser machining or mechanical precision machining. In this case, mechanical precision machining means milling, drilling, slotting and planning. Although the machining technology used is comparable to the techniques well known from conventional dimensions in the millimeter range or above, the tools used are much smaller. Whereas spark erosion and laser machining are suitable for any metal, the use of mechanical precision machining and the tools suitable for this type depend on the stability of the alloy. For brass and copper, natural diamond microtools are suitable and widely used, while for stainless steel and nickel-based alloys, hard metal tools are needed. Figure 1.3 shows a natural diamond cutter, whereas Figure 1.4 shows a hard metal drill. Figure 1.5 shows photos of a rhodium honeycomb microchannel catalyst system. The channels have been machined by wire spark erosion and therefore show a semicircular face area that is shown in detail in Figure 1.6.

The range of surface quality reached with the different techniques is widespread depending on the material as well as on the machining parameters. Spark erosion techniques lead to a considerably rough surface. The surface quality obtained with laser ablation heavily depends on the material to be structured and on the correct parameter settings. Values between some 10 μm and about 1 μm are common. In
Figure 1.4 Microdrill made from hard metal. The diameter of the drill is about 30 μm.

Figure 1.5 Rhodium honeycomb catalyst microstructure device. The microchannels have been manufactured by wire erosion.
1.1.3 Generative Method: Selective Laser Melting (SLM)

A special method to manufacture metallic microstructures is SLM. It is one of the rare generative methods for metals and is normally taken into the list of rapid prototyping technologies. The technique is completely different than the abrasive techniques described so far. On a base platform made of the desired metal material, a thin layer of a metal powder is distributed. A focused laser beam is ducted along the structure lines given by a 3D CAD model, which is controlled by a computer. With the laser exposure, the metal powder is melted, forming a welding bead. The first layer of welding beads forming a copy of the 3D CAD structure is generated. After this, the platform is lowered by a certain value, new powder is distributed and the process is repeated. Thus, microstructures are generated layer by layer. In principle, any metal
powder can be used for SLM as long as the melting temperature can be reached with the help of the laser. For metal alloys, some problems might occur with dealloying by melting. Details of this relatively new technology can be found in Refs [16–18]. Figure 1.9 gives a schematic sketch of the working principle of this technique, whereas Figure 1.10 shows a picture of a microstructure stainless steel body manufactured by the process of SLM.

1.1.4 Metal-Forming Techniques

Almost all technologies described so far are suitable for prototyping or for small series production only. It simply takes a lot of time and is therefore costly to manufacture a large number of microstructures by laser ablation or wire erosion and by milling or SLM. This is not so in the case of the etching techniques. Here, a large number of microstructure devices can be very easily generated.

Another possibility to obtain a large number of microstructures is by embossing. As it was shown [19], even microstructures ranging down to a few 10 μm structure size can be easily realized with embossing technology. For embossing, a tool providing the negative structure design has to be cut into a hard metal. This negative is then pressed into the desired material using high mechanical forces, generating the positive of the structure design.
Figure 1.8 Surface quality obtained in oxygen-free copper by micromachining, followed by an electropolishing step. The mean roughness is about 30 nm.

Figure 1.9 Schematic sketch of the SLM technology for metals.
1.1.5 Assembling and Bonding of Metal Microstructures

Although assembling of a number of device parts is not really a problem in the macroscale world, it needs to be delicately handled in the microscale world. The main point is the adjustment and alignment accuracy of the parts. Moreover, problems of sealing, fixation and bonding technology may also occur depending on the material and the parameters of the designated process of the device. Depending on the surface quality and the bonding technology applied, aligning errors may reach similar dimensions compared to the microstructure itself. An example of the same is shown in Figure 1.11. Here, a number of wet chemically etched microstructure foils have been aligned in a poor way to form elliptically shaped microchannels. Figure 1.12 shows two correctly aligned foils forming nearly circular microchannels. Misalignment will lead to non-regular channels and therefore may interfere with the bonding technique; in severe cases, it may lead to the destruction of the complete device. A correct alignment will lead to only small deviations from the desired elliptical shape, and the distortion while the bonding process takes place will be minimum. Alignment techniques used to avoid errors can be simple mechanical methods (e.g. use of alignment pins), edge catches in a specially designed assembling device or optical methods such as laser alignment. These methods are easily automated as shown in the semiconductor technology. In fact, most of the methods come from silicon processing technology where precise alignment of multiple mask layers is needed to guarantee the functionality of the manufactured devices [1,3].

Another problem of the microscale is the surface quality of the single parts of a device. Burr formation generated by mechanical micromachining or laser machining
may lead to significant problems while assembling of device parts as well as bonding is performed. Thus, special attention has to be paid to burr microstructures or to avoid burr formation. It might even be necessary to apply special techniques such as electropolishing to burr the single parts.

Bonding of metals can be done by numerous techniques. The common techniques for microstructures are welding (laser, e-beam, etc.), brazing, diffusion bonding and low-temperature as well as high-temperature soldering. Even clamping and sometimes, for very specific applications, gluing, including different sealing techniques, might be the other options. Details of the processes can be found in Refs [1,2,4,5,20–28].

For high-pressure applications and very secure run of chemical reactions, diffusion-bonded metal devices are the optimum choice. As a result of the process

Figure 1.11 Photo of an arrangement of wet chemically etched microchannel foils. Owing to misalignment, in some layers the microchannels are not formed correctly to elliptically shaped channels.

Figure 1.12 Photo of two wet chemically etched foils arranged and aligned correctly to form nearly circular microchannels.
of diffusion bonding (stacking, applying defined mechanical pressure force to the
stack, heating in vacuum or inert atmosphere ranging to about 80% of melting
temperature and cooling down while the mechanical pressure force is applied), a
more or less monolithic block including microstructures is generated, which is
extremely stable at high pressures. Owing to the diffusion of material from one foil to
another, no borderline limitations between single foils in terms of heat transfer exist
any more. Thus, the thermal behavior of diffusion-bonded devices is superior in
comparison to that of the devices manufactured by other bonding techniques. In
Figure 1.13, the diffusion bonding process chain is shown clockwise, starting with
the single foils stack of a cross-flow stainless steel device. Figure 1.14 shows a cut
through a diffusion-bonded stainless steel device. It is clearly visible that there was a
crystal growth across the foil borderlines.

It is obvious that the choice of the bonding technique has to be made depending on
the process parameters. It is not possible to run a device bonded by low-temperature
soldering at some 100 °C. Thus, the most relevant parameters for the choice of

Figure 1.13 Diffusion bonding process chain. Starting top left:
stacking, diffusion bonding furnace with mechanical pressure
force, diffusion bonding and a cut through a microchannel system
after diffusion bonding.
bonding technique are process temperature, process pressure and corrosivity of the process chemicals.

1.2 Ceramic Devices

Microstructure devices made from ceramic and glass can be used for processes with reaction parameters that are reachable neither with metals nor with polymers. High temperatures measuring above 1000 °C, absence of catalytic blind activity and some easy ways to integrate catalytic active materials make ceramics a very interesting material. Glass is chemically resistant against almost all chemicals and also provides good resistivity at elevated temperatures. In addition, optical transparency of glass leads to some very interesting possibilities such as photochemistry or a closer look into several fluid dynamics and process parameters with online analytical methods using optical fibers. Nevertheless, microfabrication of components made from glass and ceramics is limited only to some known technologies and thus is not very cost efficient.

The conventional way to obtain ceramic microstructures is to prepare a feedstock or a slurry, fluid or plastic molding, injection molding or casting (CIM, HPIM and tape casting), demolding, debinding and sintering. Most ceramic materials will
shrink during the sintering process, thus a certain tolerance to the dimensions have
to be added. Solid free-form techniques such as printing, fused deposition or
stereolithography are also possible with ceramic slurry. There are certain ceramic
materials that can be machined mechanically. Details of these manufacturing
processes can be found in Refs [6, 29–40].

During the previous year, efforts were made to apply SLM with ceramics, and it
proved to be successful. This is a new technology available now for ceramic materials.
The principle of this technique has been described earlier. First preliminary experi-
ments show promising results [18].

Independently of the manufacturing process, the grain size of the ceramic
powder used to generate the precursor or the slurry has to be small enough to
reproduce precisely all details of the desired microstructure. Even after sintering,
which is normally accompanied by a coarsening of the grain size, the grains should
be at least one order of magnitude smaller than the smallest dimension of the
device. Additives also play an important role in the manufacturing process. Removing
additives in a wrong way may lead to distortions and cracks, or even
to debinding of microscopic parts of the desired microstructure device. Densifica-
tion of the material is achieved by sintering; for example, for alumina, a tempera-
ture of about 1600 °C is needed, whereas for zirconia temperatures around 1500 °C
only will be needed.

The most crucial point is the correct microstructure design. Owing to the specific
properties of ceramics, it is not suitable simply to transfer the design of metallic or
polymer devices to ceramic devices. Special needs for sealing, assembling and
joining as well as interconnections to metal devices have to be considered. Moreover,
guidelines for the micrometer design are still missing, and experiences obtained with
macroscopic devices cannot be transferred directly down to microscale [6]. The
interconnection between conventional process engineering equipment and ceramic
devices is also critical because the thermal expansion of those materials is different.
This may lead to thermal stress, weakening of the connections or ruptures.

Another possibility of ceramic material application is the use of coatings and foams
inside, for example, metallic microstructure devices. Here, well-known technologies
such as CVD processes, sputtering, electrophoretic deposition, sol–gel methods in
combination with either spin coating or dip coating or wash coating methods or the
use of anodic oxidation for aluminum-based devices will lead to either dense,
protective ceramic coatings or porous layers used as a catalyst support. In Figure 1.15
an example of a sol–gel layer is given. Here, the dark sol–gel layer surrounds the
rectangular microchannels completely. Figure 1.16 shows a porous layer obtained by
anodic oxidation. The overview photo shows how the ceramic layer surrounds the
microchannel, whereas the detailed picture shows the porous system within the
ceramic layer. With anodic oxidation, the size and number of pores can be controlled
to a certain amount by the choice of the electrolyte and the applied voltage and current
density.

Ceramic foams can be inserted into microstructure devices made from metals and
polymers to enhance the surface area, act as catalyst supports or even work as heaters.
Details of these processes can be found in Refs [29–42].
Joining of ceramic materials should only involve materials with similar properties. Especially, the thermal expansion coefficient is a crucial point while either joining ceramic materials to each other or, even worse, joining ceramics to metals. The ideal joining of ceramics to each other is done in the green state before the firing process. When the firing process takes place, the ceramics are bound together tightly to form a single ceramic body from all parts. Another possibility is the soldering with, for example, glass–ceramic sealants. Here, the working temperature of the device is limited by the melting temperature of the sealant. Reversible assembling and sealing with clamping technologies or gluing are also possible. Conventional seals such as