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Second, Completely Revised and Enlarged Edition

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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

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1
Properties and Use of Microreactors

David Barrow, Shan Taylor, Alex Morgan, and Lily Giles

1.1
Introduction

Microreactors are devices that incorporate at least one three-dimensional duct, with one or more lateral dimensions of <1 mm (typically a few hundred micrometers in diameter), in which chemical reactions take place, usually under liquid-flowing conditions [1]. Such ducts are frequently referred to as microchannels, usually transporting liquids, vapors, and/or gases, sometimes with suspensions of particulate matter, such as catalysts (Figure 1.1) [2]. Often, microreactors are constructed as planar devices, often employing fabrication processes similar to those used in manufacturing of microelectronic and micromechanical chips, with ducts or channels machined into a planar surface (Figure 1.2c and d) [3]. The volume output per unit time from a single microreactor element (Figure 1.2b, c, d and e) is small, but industrial rates can be realized by having many microreactors working in parallel (Figure 1.2f).

However, microreactor research can be conducted on simple microbore tubing fabricated from stainless steel (Figure 1.2a), polytetrafluoroethylene (PTFE), or any material compatible with the chemical processing conditions employed [4]. For instance, inexpensive fluoroelastomeric tubing was employed to prepare a packed-bed microreactor for the catalysis of oxidized primary and secondary alcohols [5]. As such, microreactor technology is related to the much wider field of microfluidics, which involves an extended set of microdevices and device integration strategies for fluid and particle manipulation [6].

1.1.1
A Brief History of Microreactors

In 1883, Reynolds' study on fluid flow was published in the *Philosophical Transactions of the Royal Society* [7]. Reynolds used streams of colored water in glass piping to visually observe fluid flow over a range of parameters. The apparatus used is depicted in a drawing by Reynolds himself (Figure 1.3), which shows flared glass

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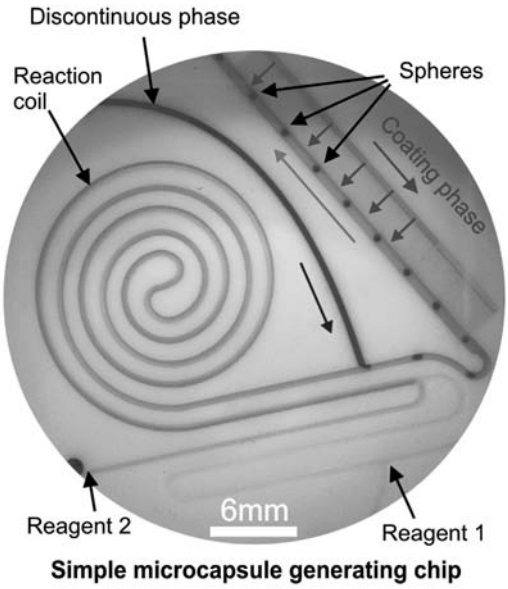

Figure 1.1 Detailed example of a simple duct-based microreactor fabricated from polytetrafluoroethylene (with perfluoralkoxy capping layer). Reagents 1 and 2 interact by diffusive mixing within the reaction coil. The reaction product becomes the continuous phase for an immiscible discontinuous phase, which initially forms elongate slugs. When subject to a capillary dimensional expansion, slugs become spheres, which are then coated with a reagent (that is miscible with the continuous phase) fed through numerous narrow, high aspect ratio ducts made with a femtosecond laser.

tubing within a water-filled tank. Using this setup, he discovered that varying velocities, diameters of the piping, and temperatures led to transitions between "streamline" and "sinuous" flow (respectively known as laminar and turbulent flow today). This paper was a landmark, which demonstrated practical and philosophical aspects of fluid mechanics that are still endorsed and used in many fields of science and engineering today, including microreactor technology [8].

An early example for the use of a microreactor was demonstrated in 1977 by the inventor Bollet, working for Elf Union (now part of Total) [9]. The invention involved mixing of two liquids in a micromachined device. In 1989, a microreactor that aimed at reducing the cost of large heat release reactions was designed by Schmid and Caesar working for Messerschmitt–Bölkow–Blohm GmbH. Subsequently, an application for patent was made by the company in 1991 [10]. In 1993, Benson and Ponson published their important paper on how miniature chemical processing plants could redistribute and decentralize production to customer locations [11]. Later, in 1996, Alan Bard filed a US patent (priority 1994) where it is taught how an integrated chemical synthesizer could be constructed from a number of microliter-capacity microreactor modules, most preferably in a chip-like format, which can be used together, or interchangeably, on a motherboard (like electronic chips), and based upon thermal, electrochemical, photochemical, and pressurized principles [12].

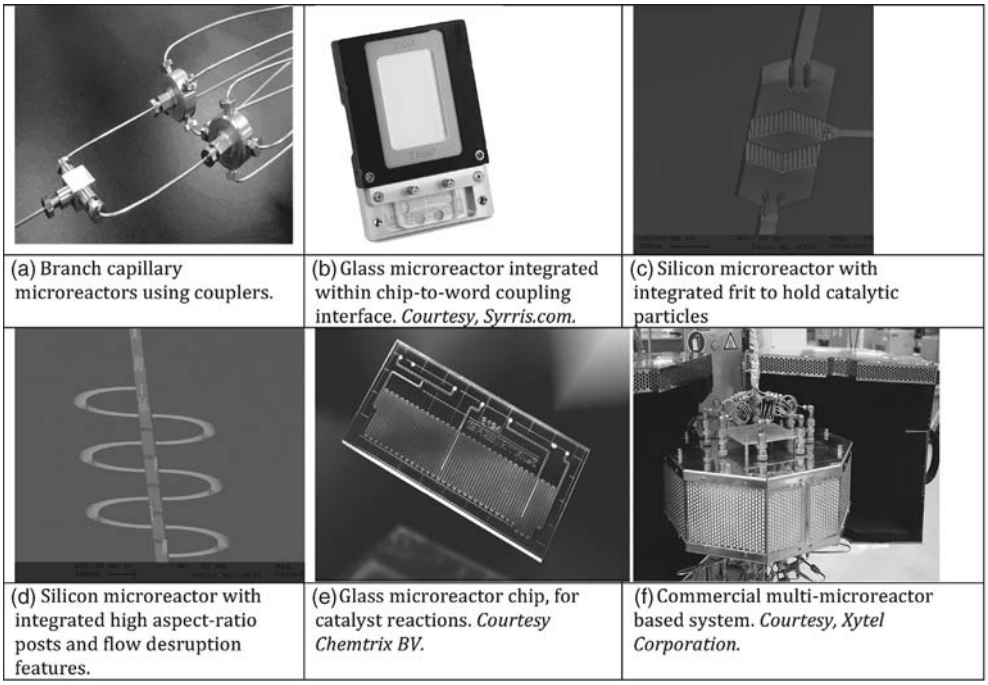

Figure 1.2 Examples of modern-day microreactors and other microfluidic components. (a) *Source*: Reprinted with permission from Takeshi *et al.* (2006) *Org. Process Res. Dev.*, 10, 1126–1131. Copyright (2006) American Chemical Society.

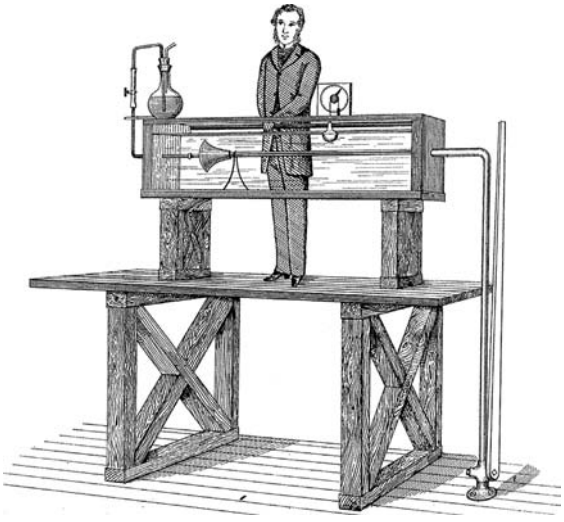

Figure 1.3 The original apparatus used by Osborne Reynolds to study the motion of water [7]. The apparatus consisted of a tank filled with water and glass tubing within. Colored water was injected through the glass tubing, so the characteristics of fluid flow could be observed.

Figure 1.4 Fused silica microfluidic chip compared to the size of a €2 coin. The chip was the first example of synthesis, separation and analysis combined on a single device. *Source*: Photograph courtesy of Professor D. Belder with permission.

Following this, a pioneering experiment conducted by Salimi-Moosavi and colleagues (1997) introduced one of the first examples of electrically driven solvent flow in a microreactor used for organic synthesis. An electro-osmotic-controlled flow was used to regulate mixing of reagents, *p*-nitrobenzenediazonium tetrafluoroborate (AZO) and *N,N*-di-methylaniline, to produce a red dye [13]. One of the first microreactor-based manufacturing systems was designed and commissioned by CPC in 2001 for Clariant [14].

Microreactor systems have since evolved from basic, single-step chemical reactions to more complicated multistep processes. Belder *et al*. (2006) claim to have made the first example of a microreactor that integrated synthesis, separation, and analysis on a single device [15]. The microfluidic chip fabricated from fused silica (as seen in Figure 1.4) was used to apply microchip electrophoresis to test the enantioselective biocatalysts that were created. The authors reported a separation of enantiomers within 90 s, highlighting the high throughput of such devices.

Early patents in microreactor engineering have been extensively reviewed by Hessel *et al*. (2008) [16] and then later by Kumar *et al*. (2011) [17]. From 1999 to 2009, the number of research articles published on microreactor technology rose from 61 to 325 per annum (Figure 1.5a) [17]. The United States of America produced the majority of research articles, followed by the People's Republic of China and Germany (Figure 1.5c) [17]. The number of patent publications produced was also highest in the United States of America; the data are given in Figure 1.5b [17]. The number of patent publications is highest in the field of inorganic chemistry, but of particular interest, organic chemistry comes second out 18 fields of chemical applications investigated [16].

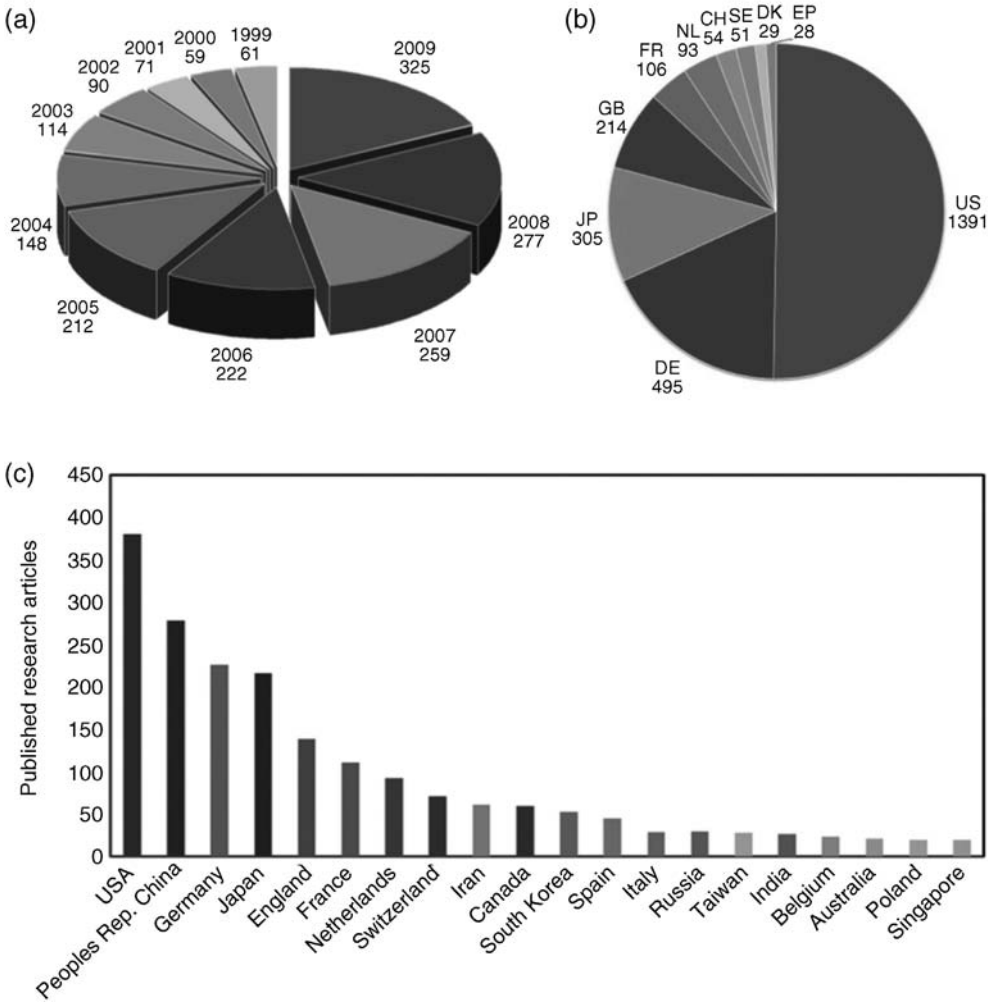

Figure 1.5 (a) The number of research articles published on microreactors from the years 1999 to 2009. (b) Distribution of patent publications produced from 10 different countries. (EP: European; US: United States; DE: Germany; JP: Japan; GB: United Kingdom; FR: France; NL: Netherlands; CH: Switzerland; SE: Sweden). (c) Distribution of published research articles from various countries. *Source*: Images reprinted from Ref. [17], with permission from Elsevier.

Microreactor technology has been widely employed in academia and is also beginning to be used in industry where clear benefits arise and are worthy of new financial investment. Companies contributing considerably to the development of microreactors include Merck Patent GmbH, Battelle Memorial Institute, Velocys Inc., Forschungszentrum Karlsruhe, The Institute for Microtechnology Mainz, Chemical Process Systems, Little Things Factory GmbH, Syrris Ltd, Ehrfeld

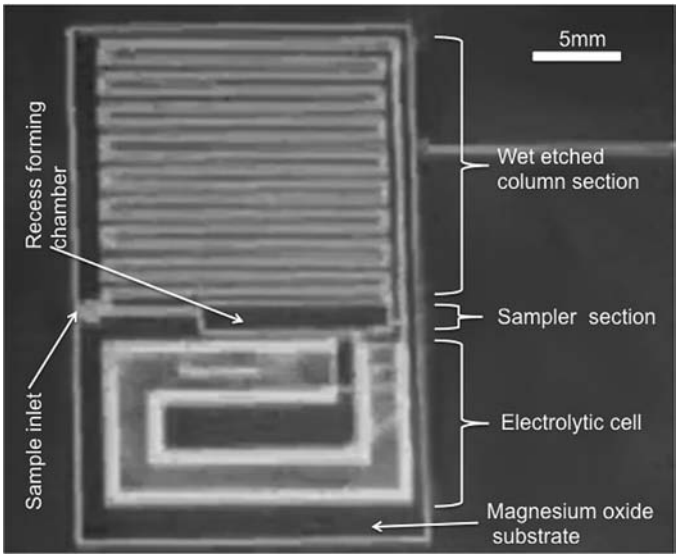

Figure 1.6 Image of a planar chip chromatograph, microfabricated from wet etched magnesium oxide, described in US patent 3,701,632 filed in 1970 by James Lovelock. Image is a screen capture from a movie of Dennis Desty talking about innovations in chromatography. *Source*: Courtesy, Prof. Peter Myers, Liverpool University UK.

Mikrotechnik BTC, Micronit BV, Mikroglas chemtech GmbH, Chemtrix BV, Vapourtec Ltd, Microreactor Technologies Inc., Xytel Corporation, and more [16,18].

To place microreactors clearly within an historical context, we can relate the emergence of such devices to their nearest neighbors, these being from the wider field of microfluidics, which includes the flow of gases. With respect to this, we can see that some of the earliest examples of microfluidic devices go back at least to 1970, when James Lovelock filed patent US3,701,632 describing a planar chip-based chromatograph fabricated from wet-etched magnesium oxide (Figure 1.6).

1.1.2 Advantages of Microreactors

Flow chemistry is long established for manufacturing large quantities of materials [19]. However, this can sometimes be time consuming and expensive due to the amount of materials used. Also, scaling up a small process to a much larger industrial sized application can be challenging and often results in batch processing. This type of processing can lead to variances between each batch, ultimately yielding inconclusive and unreproducible results [19]. In contrast, the use of microreactors enables chemical reactions to be run continuously [20], usually in a flowing stream, and from this the topic of microprocess chemistry was born [21]. Microreactors are therefore seen as the modern-day chemists' round-bottom flask [19] and can

potentially revolutionize the practice of chemical synthesis [4]. For instance, using microscale reactors, reactions can be carried out under isothermal conditions with well-defined residence times, so that undesirable side reactions and product degradation are limited. The distinctive fluid-flow and thermal and chemical kinetic behavior observed in microreactors, as well as their size and energy characteristics, lend their use to diverse applications [22,23] including:

- high-purity chemical products [24],
- highly exothermic reactions [25,26],
- screening for potential catalysts [27,28],
- precision particle manufacture [29],
- high-throughput material synthesis [30],
- emulsification and microencapsulation [31],
- fuel cell construction [32],
- point-of-use, miniature, and portable microplants [33].

These new application horizons are enabled by the following advantages: (i) reduced size through microfabrication, (ii) reduced diffusion distances, (iii) enhanced rates of thermal and mass transfer and subsequent processing yields [34,35], (iv) reduced reaction volumes, (v) controlled sealed systems avoiding contamination, (vi) use of solvents at elevated pressures and temperatures, (vii) reduced chemical consumption, (viii) facility for continuous synthesis [36], and (ix) increased atom efficiency [37]. Microreactor research and development has been particularly promoted for high-throughput synthesis in the pharmaceutical industry, where large numbers of potential pharmaceutically beneficial compounds need to be generated, initially, in small quantities, as a component of the drug discovery process [38]. In this chapter, the key functional properties of microreactors are reviewed in the context of use in diverse fields.

1.2 Physical Characteristics of Microreactors

1.2.1 Geometries

1) *Size*: Microreactor systems incorporate structures for the directed transport or containment of gases or fluids that have a dimensional property in at least one direction usually measured in micrometers, sometimes up to 1 mm. These structures may comprise microscale ducts (e.g., channels and slots) and pores, larger features (e.g., parallel plates) that cause fluid to flow in thin films, and others that cause fluid to flow in microscale discontinuous multiphase flow (e.g., bubbles and emulsions). More specific details of these types of structure are explained in Chapters 9 and 10. In addition, small containment structures such as microwells have been fabricated in an analogous format to traditional microtiter plates, rendering potential compatibility with existing robotic handling

systems as used in many high-throughput screening laboratories. Extending the notion of a microreactor, an increasing number of studies are demonstrating how separated droplets may act as nanoscale-based reactors [39]. For instance, the use of solvent droplets resulting from controlled segmented flow has been proposed as individual nanoliter reactors for organic synthesis [40–42]. Similarly, reverse micellar structures have been shown to provide reactors for the controlled synthesis of nanometer-scale particulates [43,44]. Also, giant phospholipid liposomes (~10 μm diameter) have been utilized as miniature containers of reagents and can be manipulated by various external mechanisms, such as optical, electrical, and mechanical displacement and fusion [45]. Liposome-based microreactors, manipulated in this manner, hold the potential to enable highly controlled and multiplexed microreactions in a very small scale [46].

2) *Architecture*: Geometries employed in microreactor design and fabrication may range from simple tubular structures, where perhaps two reagents are introduced to form a product, to more sophisticated multicomponent circuits, where several functionalities may be performed, including reagent injection(s), mixing, incubation, quench addition, solvent exchange, crystallization, thermal management, extraction, encapsulation, or phase separation.
3) *Multiplicity*: Microreactors may comprise single-element structures from which small quantities of reaction products may be obtained, or, massively parallel structures where output on an industrial scale can be realized. Examples of numbering-up of microreactors are shown in Figure 1.7. In Figure 1.7a, 10 glass microreactors are placed on top of each other to form one single, multileveled device [47]. The microchannels were produced by photolithography and wet

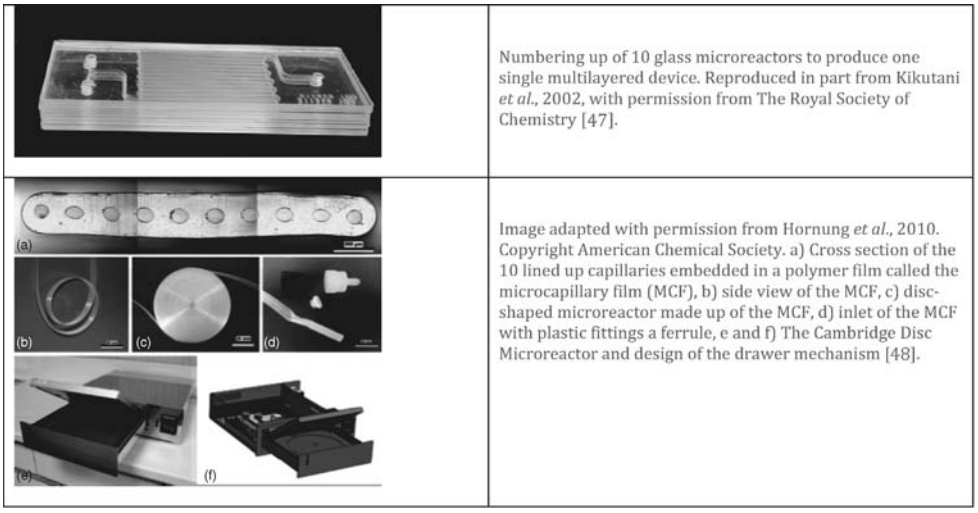

Figure 1.7 Examples of multiple microreactors used in parallel for higher throughput and yield of products [47,48]. *Source*: Figures reprinted with permission, copyright (2010), American Chemical Society.