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The Scale-Up of Microwave-Assisted Organic Synthesis

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Abstract Single-mode microwave reactors have been very successful in the past few years in the field of method development and optimization. Future trends clearly indicate the use of microwave technology for the development of completely new reaction routes for organic synthesis, with increasing demand for large-scale microwave production of chemical substances (> 100 g per run). For microwave-assisted synthesis to become a fully accepted industrial technology in the future, there is a need to develop techniques that can ultimately routinely provide products on a multikilogram scale. Thus, the further development of large reactors, at least in the pilot plant scale to enable multikilogram production of lead compounds, is required. Herein are discussed several already known scale-up processes in microwave-assisted organic chemistry in a ≥ 50 mL batch scale and experiments performed with both continuous flow and stop-flow techniques. Furthermore, the available instrumentation for scale-up at laboratory scale and beyond is presented.

Keywords Batch · Continuous flow · Microwave · Scale-up · Stop-flow

Abbreviations

AcOH	Acetic acid
aq	Aqueous

BTF	Benzotrifluoride (trifluoromethyl benzene)
t-Bu	BuOH, 1-butanol
CF	Continuous flow
CFR	Continuous flow reactor
conv	Conversion
CMDR	Continuous microwave dry-media reactor
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DI(P)EA	Diisopropyl ethylamine
dmphen	2,9-Dimethyl-[1,10]phenanthroline
GHz	Gigahertz
GLP	Good laboratory practice
GMP	Good manufacturing practice
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
K10	Montmorillonite K10 clay
KSF	Montmorillonite KSF clay
LC-MS	Liquid chromatography-mass spectroscopy
MAOS	Microwave-assisted organic synthesis
MBR	Microwave batch reactor
MW	Microwave irradiation
NMM	*N*-Methyl morpholine
NMP	*N*-Methyl pyrrolidinone
ppb	Parts per billion
ppm	Parts per million
PTFE-TFM	Modified branched polytetrafluoroethylene
RCM	Ring closing metathesis
SF	Stop-flow
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TEA	Triethylamine
o-tolyl	*ortho*-Methylphenyl

1 Introduction

1.1 Microwave-Assisted Synthesis – A Brief History

In the past two decades, heating and accelerating chemical reactions by microwave energy have been increasingly popular themes in the scientific community [1, 2]. Microwave energy has found a variety of technical applications in chemical and related industries since the 1950s, in particular in the food-processing, drying, and polymer industries. Other applications range from analytical chemistry (microwave digestion, ashing, extraction) [3], to biochemistry (protein hydrolysis, sterilization) [3], pathology (histoprocess-

ing, tissue fixation) [4] and medical treatments (diathermy) [5]. However, microwave heating was not introduced to organic synthesis until the mid 1980s. The first academic reports on the use of microwave heating to mediate organic chemical reactions were published by the groups of Gedye [6] and Giguere [7] in 1986. These early experiments of microwave-assisted organic synthesis (MAOS) were typically carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements. Although there were several violent explosions due to the rapid uncontrolled heating of organic solvents in those early days, an increasing number of scientists started to investigate this new technology. In the 1990s the first attempts at solvent-free microwave chemistry (so-called dry-media reactions), which eliminated the danger of explosions, were made [8–13]. Particularly at the beginning of MAOS, the solvent-free approach was very popular since it allowed the safe use of domestic microwave ovens and standard open vessel technology. While a large number of interesting transformations using dry-media reactions have been published [8–13], technical difficulties relating to non-uniform heating, mixing, and precise determination of the reaction temperature remained unsolved, especially when scale-up approaches needed to be considered.

Besides the dry-media attempts, microwave-assisted synthesis in solution has been carried out under open vessel conditions. However, if solvents are heated by microwave irradiation at atmospheric pressure in an open vessel, the boiling point of the solvent limits the reaction temperature. In order to nonetheless achieve high reaction rates, good microwave-absorbing solvents with high boiling points have been frequently used in open-vessel microwave synthesis [14, 15]. However, the use of such solvents (e.g. DMF, NMP, ethylene glycol) presented serious challenges during product isolation and recycling of the solvent. Because of the recent availability of modern microwave reactors with on-line monitoring of both temperature and pressure, MAOS in dedicated sealed vessels using standard solvents – a technique pioneered by Christopher R. Strauss in the mid 1990s [16–18] – has renewed its attractiveness to chemists in recent years. This is clearly evident from a survey of the recently published (since 2001) literature in the area of controlled MAOS. Due to the beneficial combination of rapid heating by microwaves with sealed vessel (autoclave) technology, this approach will most likely be the method of choice for performing MAOS on a laboratory scale in the future. Additionally, recent innovations in microwave reactor technology allow controlled parallel and automated sequential processing under sealed vessel conditions, and the use of continuous flow (CF) reactors or stop-flow (SF) reactors for scale-up purposes, as will be discussed in the following sections.

Regardless of the nature of the observed rate-enhancements ("microwave effects" [19, 20]), which will undoubtedly be an ongoing debate for many years in the academic world, microwave synthesis has now truly matured and has moved from a laboratory curiosity in the late 1980s to an established tech-

nique in organic synthesis, popular in both academia and industry. The initial low interest in the technology in the late 1980s and 1990s has been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating. The risks associated with the flammability of organic solvents in a microwave field and the lack of available dedicated microwave reactors allowing for adequate temperature and pressure control were major concerns.

Today's available instrumentation (Sect. 2), "dedicated" microwave reactors, allow for careful control of time, temperature, and pressure profiles, ensuring reproducible protocol development, scale-up, and transfer from laboratory to laboratory and from instrument to instrument. In the so-called multimode instruments (conceptually similar to a domestic oven), the microwaves that enter the cavity are being reflected by the walls and the load over the typically large cavity. In the much smaller single-mode cavities, only one mode is present and the electromagnetic irradiation is directed through an accurately designed rectangular or circular wave guide onto the reaction vessel mounted in a fixed distance from the radiation source, creating a standing wave. The key difference between the two types of reactor systems is that whereas in multimode cavities several reaction vessels can be irradiated simultaneously in multivessel rotors (parallel synthesis), in single-mode systems only one vessel can be irradiated at a time.

Since the year 2000, when the first dedicated single-mode reactors were established among academic laboratories, the number of publications related to MAOS has increased dramatically, reaching an overall number of about 3000 by the end of 2005. Considering this fact, it might be assumed that in a few years most chemists will use microwave energy as the standard procedure to heat chemical reactions on a laboratory scale [1, 2]. Besides the drastic reduction of reaction times, microwave heating is also known to suppress side reactions, increase yields, and improve purity and reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a technology for rapid reaction optimization, efficient synthesis of new chemical entities, and for exploring chemical reactivity.

1.2 The Need for Scale-Up of Microwave-Assisted Transformations

Most examples of microwave-assisted chemistry published until this day have been performed on a scale of less than 1 g, with a typical reaction volume of 1–5 mL. The main applications have been to accelerate and optimize well-known and established synthetic procedures. This is in part a consequence of the availability and popularity of dedicated single-mode microwave reactors (i.e., Biotage Initiator, CEM Discover models) that allow the safe processing of small reaction volumes under sealed vessel conditions by microwave irradiation. Due to limitations in the vessel and microwave cavity size of these

single-mode reactors, microwave-assisted synthesis so far has focused predominantly on reaction optimization and method development on the small scale (< 10 mmol). Although these instruments have been very successful in this field, future trends indicate the use of microwave technology for the development of completely new reaction avenues for organic synthesis. Today, the demand for large-scale microwave production (> 100 g per run) of chemical substances increases not only within research and development departments.

To accomplish the task of industrial scale-up, the development of effective flow-through systems is currently under investigation. It seems to be clear that for microwave-assisted synthesis to become a fully accepted industrial technology in the future, there is a need to develop larger scale MAOS techniques that can ultimately routinely provide products on a multikilogram (or even higher) scale. Thus, the further development of large reactors, at least in the pilot plant scale, to enable multikilogram production of lead compounds, is required. As discussed in this chapter and in particular in Sect. 3, several microwave-assisted scale-up processes are already known today.

1.3 Scale-Up Limitations

Microwave-enhanced chemistry is based on the efficient heating of materials by "microwave dielectric heating" effects. Microwave dielectric heating is dependent on the ability of a specific material (i.e., a solvent or reagent) to absorb microwave energy and convert it into heat. When irradiated at microwave frequencies, the dipoles or ions of the sample align in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the so-called loss tangent $\tan \delta$. A reaction medium with a high $\tan \delta$ is required for efficient absorption and, consequently, for rapid heating. Further details on the rather complex microwave dielectric heating phenomena are described in relevant review articles [21–23].

The big challenge for process scale-up involving microwave technology is to establish a reliable and safe process setup where issues like physical properties (i.e., penetration depth), temperature control, and reactor design have to be carefully considered. Using batch reactors, the user is confronted with problems in heating large volumes due to the limited penetration depth of microwave irradiation. Dependent on the dielectric properties of the solvent (loss tangent, $\tan \delta$, see Table 1), microwave penetration into absorbing media (i.e., reaction mixtures) is usually only in the order of a few centimeters (Table 2), which limits the maximum size of a batch reactor.

Table 1 Loss tangents (tan δ) of different solvents (2.45 GHz, 20 °C)[a]

Solvent	tan δ	Solvent	tan δ
Ethylene glycol	1.350	DMF	0.161
Ethanol	0.941	1,2-dichloroethane	0.127
DMSO	0.825	Water	0.123
2-Propanol	0.799	Chlorobenzene	0.101
Formic acid	0.722	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Ethyl acetate	0.059
1-Butanol	0.571	Acetone	0.054
2-Butanol	0.447	Tetrahydrofuran	0.047
1,2-Dichlorobenzene	0.280	Dichloromethane	0.042
NMP	0.275	Toluene	0.040
Acetic acid	0.174	Hexane	0.020

[a] Data from [24]

Table 2 Microwave penetration depth (245 GHz) in some common materials[a]

Material	Temperature [°C]	Penetration Depth [cm]
Water	25	1.4
Water	95	5.7
Ice	–12	1100
Glass	25	35
Porcelain	25	56
Poly (vinyl chloride)	20	210
Teflon®	25	9200
Quartz glass	25	16 000

[a] Data from [25]

These limitations have been overcome in part by using a parallel scale-up approach, which means that the same experiments are run simultaneously using several (smaller) vessels. However, this methodology again creates two major problems. Firstly, as the reaction volume increases, it becomes more and more difficult to heat up the reaction mixtures. Consequently, more microwave power is needed to reach identical reaction temperatures when performing large scale experiments. Generally, the most common multimode instruments for microwave-assisted synthesis (Biotage Advancer, Milestone MicroSYNTH and UltraCLAVE, CEM MARS-S, Anton Paar Synthos 3000) provide a comparatively high microwave power output (> 1000 W) from stan-

dard air-cooled magnetrons, which prove sufficient to effectively heat mixtures of up to 500 mL in comparable rates comparable to those in single-mode experiments [26]. As the capacity of the microwave reactor increases to 5000 W and beyond, more sophisticated oil-based or water-based cooling is required and this introduces extra size, complexity, and cost to microwave reactors [16–18]. Another aspect is that the energy efficiency of the conversion of electricity into microwave power can be relatively low (70% or less), which can make the microwave approach less attractive for very large scale preparations [16–18].

Obviously, heating rates are somewhat lower when processing larger volumes as compared to small volumes, but no adverse effects on the yield or product purity are usually noted. The crucial point for the reaction outcome is generally the overall hold time at the desired reaction temperature. On the other hand, difficulties may arise in attempting the scale-up of small-scale procedures if low absorbing solvents, such as toluene, are employed [27]. In this case, a certain concentration of high microwave-absorbing reagents should be present in the reaction mixture to introduce some heat. If the concentration is low and the used vessel materials are not microwave self-absorbing (thus heating up the reaction mixture by convection and conduction phenomena), almost no temperature increase can be observed.

An additional key point in processing comparatively large volumes under pressure in a microwave field is the safety aspect, as any malfunction or rupture of a large pressurized reaction vessel will have a significant impact. Thus, minimizing the reaction volumes in the microwave contact zone would reduce the risk of this hazard significantly. Furthermore, time becomes an issue when performing parallel reactions, keeping in mind that the individual reaction vessels need to be filled with reagents and loaded into the cavity manually. Thus, flow systems operate more effectively on a larger scale. Accordingly, published examples of MAOS scale-up experiments (> 500 mL) are rare, particularly those involving complex organic reactions. However, plans to manufacture larger microwave systems in batch and CF mode are currently being considered as the demand of industrial laboratories, in particular from the pharmaceutical and fine chemical industries, is increasing.

These are the main reasons for the development of CF reactors, where the reaction mixture is passed through a relatively small microwave-heated flow cell, thus not only minimizing the hazards but also avoiding the above-mentioned penetration depth issues. Other benefits of CF reactors are financial. CF reactors are usually less expensive than commercially available batch reactors and they can be implemented in industrial processes where their operation can be fully automated. Additional benefits of using CF processing have been demonstrated in small-scale microwave protocols involving heterogeneous catalysis, employing a custom-built microflow reactor [28–30].

Filling the flow cell with an immobilized catalyst provides effective product isolation and improved control of the catalyst–reactant contact time. Moreover, the catalyst is only required in comparatively small quantities and can be easily recovered for reuse.

The major drawback of CF processing, however, is the incompatibility with heterogeneous reaction mixtures and highly viscous liquids. Apart from the fact that obtaining a temperature measurement directly from a reaction mixture under flow can be complicated, the adaptation of conditions from small-scale batch reactions to a CF cell may be time-consuming.

A combination of certain advantages from batch and CF processing can be achieved with a so-called stop-flow reactor [27, 31]. Such a system provides a small reaction cavity and a peristaltic pump that pumps the reaction mixture in and out of the reaction vessel (e.g. CEM Voyager reactor). Apparently, considerable time is required for the entire process, including loading the vessel, irradiation of the reaction mixture including the time for reaching the set temperature, cooling down, and finally pumping out the product. But nevertheless, in contrast to batch processing, this can be a fully automated procedure improving the efficiency of microwave-assisted synthesis [27, 31].

In conclusion, there are three different approaches for microwave synthesis on a large scale (> 100 mL volume). While some groups have employed larger batch-type multimode or single-mode reactors ($\leq$ 1000 mL processing volume), others have used CF or SF techniques (multi- and single-mode cavities) to overcome the inherent problems associated with MAOS scale-up.

1.4 The Range of Scale-Up

The scale-up of microwave-mediated transformations can be defined in different ranges, leading to the use of different concepts and varying instrumentation. Depending on the user, the term "scale-up" will have different meanings. In the case of method development, scale-up starts with processing a 50 mL reaction mixture, corresponding to a ten- to 100-fold scale-up of reactions performed in standard single-mode microwave vials with a 0.5–5.0 mL processing volume. In fact, this is a significant amount from a medicinal chemist's point of view, providing multigram product quantities for, e.g., biological screening or pharmacokinetic studies. Employing different vessel types, today's single-mode instruments enable similar scale-up ranges for batch synthesis from 0.2 to 20 mL (Biotage Initiator EXP Series) or from 0.5 to 50 mL (CEM Discover Platform, see Sect. 2), respectively.

A possibility for further scale-up using the above-mentioned instrumentation would be using the "numbering up" approach, e.g., running the same reaction several times in sequence. This approach is aided by existing robotic equipment, which allows unattended vessel transfer in and out of the microwave cavity. Alternatively, those reactions can also be performed by par-

allel synthesis in corresponding multivessel rotor systems switching to multimode instruments ([32] and references cited therein).

From an industrial viewpoint, scale-up means process development and highest possible throughput that virtually excludes the use of batch reactors. In fact, the productivity and not the size of the vessel is important, which clearly indicates that flow systems, regardless of whether applied in SF or CF manner, have distinct benefits over batch process reactors.

Scale-up as defined for this chapter covers batch reactions in closed vessels at the ≥ 50 mL scale, flow systems employing flow cells ≥ 5 mL, and SF containers of ≥ 50 mL volume. Microwave-mediated scale-up reactions under open vessel conditions are not discussed in detail as up to date only a few examples have been published [33–37] and most of the beneficial rate enhancements have been reported under sealed vessel conditions.

2 Different Techniques and Instrumentation

The scale-up of microwave-assisted reactions is of significant interest to many industrial laboratories. Scale-up can be accomplished in different ways, and these methods are presented in more detail in the following section. After an initial discussion of batch synthesis we will present the currently commercially available instrumentation for flow processing, which can be divided into SF or CF techniques.

When going to larger scale with successfully optimized reactions, a major issue is the direct scalability of the method, i.e., the operation at different scales without the need for further optimization steps. In this context, batch synthesis (defined as processing a mixture in one vessel at a time) has a definitive advantage over flow techniques since reaction times are usually identical to small-scale experiments, whereas flow processes require longer reaction times. Batch synthesis in general allows for the use of heterogeneous and highly viscous mixtures or suspensions, whereas the risk of clogging of lines is evident when performing such transformations under CF. Furthermore, precipitation of the products or starting materials may be troublesome in flow reactors. On the other hand, the safety issues are less of a concern for flow systems, as the heating zones are smaller and lower volumes are processed in the microwave irradiation area. Moreover, the energy transmission is higher in smaller cavities and therefore the process is more economical. Furthermore, physical limitations regarding penetration depth and power constraints limit the maximum size of a single batch reaction container.

Today's laboratory-scale batch microwave reactors generally offer a maximum batch size of 1 L reaction volume, in most cases divided into several smaller reaction vessels (multivessel rotor systems). According to the definition given at the beginning, this would not exactly match the "one vessel"

philosophy, but the parallel setup allows for the processing of several batches of either the same reaction mixture or of closely related mixtures. In fact, this combination of batch synthesis and parallel processing can furnish either compound libraries on the gram scale or a larger amount of one single compound in a short time. Although the Milestone UltraCLAVE system provides a 3.5 L single vessel cavity, it has turned out to be more effective to heat smaller volumes in parallel rather than one big batch, given that identical microwave output power is applied [27, 37]. This is caused by limitations due to the penetration depth (see above), as microwaves lose their intensity when interacting with dielectric media. On the other hand, this indicates clearly that any attempt to process larger volumes has to be applied using flow-through systems, either in CF or SF mode.

2.1 Batch Processing and Parallel Synthesis

Laboratory scale-up in *single-mode reactors* to produce gram amounts of material can be performed either by the above-mentioned sequential batch processing using various vessel sizes (up to 50 mL) or by employing CF or SF reaction cells (5–50 mL). Conversely, *multimode instruments* allow for parallel synthesis or applications in large batches up to 1 L total volume and even CF and SF approaches utilizing $\geq$ 300 mL cells (see below).

Batch synthesis in single-mode reactors is definitely limited in scale as the size of the utilized microwave cavities is restricted to being monomodal. However, the Biotage Initiator EXP series allows a 100-fold linear scale-up when employing the different available vessel sizes, going from 0.2 mL to 20 mL operation volume (Fig. 1). Repetitive reaction cycles using the au-

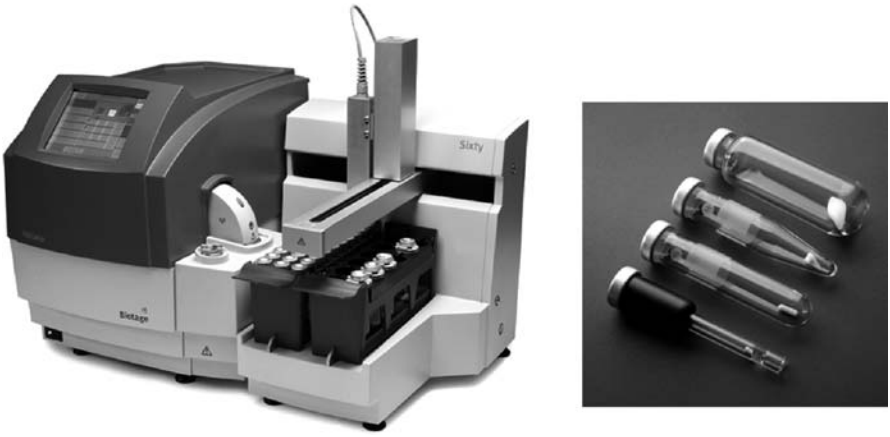


Fig. 1 Biotage Initiator EXP Sixty and its various reaction vessels

tomation upgrade Initiator Sixty (up to 60×5.0 mL or 24×20 mL) allows multigram synthesis by sequential batch reactions [38].

Similarly, the CEM Discover platform (Fig. 2) allows a 100-fold scale-up of small-scale batch synthesis when switching from the standard vial (0.5–5.0 mL operation volume) to the large reaction vessel (50 mL maximum filling volume). Automation is only possible for the small standard vials with the "Explorer" robotic extension (24×5.0 mL) but the large vessel can be utilized for SF processing as well [27, 39].

An interesting contribution to the field of single-mode equipment has been recently presented by Milestone. The MultiSYNTH instrument (Fig. 3) is a kind of "hybrid" reactor as it combines the inherent advantages of single-

Fig. 2 CEM Discover

Fig. 3 Milestone MultiSYNTH Hybrid Instrument

mode technology with beneficial features of multimode cavities. A single magnetron delivers 800 W pulsed or unpulsed microwave output power. In the single-mode setup the corresponding reaction vessel (0.25–35 mL operating volume) is located in a position correlated with the highest energy intensity. A unique vessel vibration system ensures homogeneous temperature distribution even in the large vessel. In the multimode setup the cavity can be equipped with a carousel suitable for up to 12 reaction vessels (1–5 mL operation volume). Furthermore simple laboratory glassware can be employed for reflux reactions at atmospheric pressure up to 500 mL volume. Sufficient agitation in each vessel can be accomplished by adding magnetic stir bars. Temperature measurement is achieved by an IR sensor mounted in the side wall, optionally an immersed fiber-optic probe can be utilized. Each vessel is assembled with a pressure jacket comprising a spring-type safety valve for individual pressure control. The multimode carousel comprises glass or quartz vessels in three sizes featuring operation limits of 200 °C and 20 bar. For single-mode applications additional 70 mL TFM-vessels (35 mL operation volume) are available for reactions up to 200 °C and 30 bar. Reactions under reflux can be carried out at a maximum of 250 °C. However, at the time of writing, no applications with this device have been published.

In contrast to single-mode reactors, dedicated multimode instruments allow scale-up to be performed in multivessel rotor systems utilizing various types of sealed vessels. In these systems, reactions can be carried out in batch to synthesize multiple gram quantities ($\leq$ 250 g) of material in typically up to 1 L processing volume. Most of the multimode instruments available for organic synthesis have been derived from closely related sample preparation equipment [39–41]. The MARS Microwave Synthesis System (Fig. 4) is based

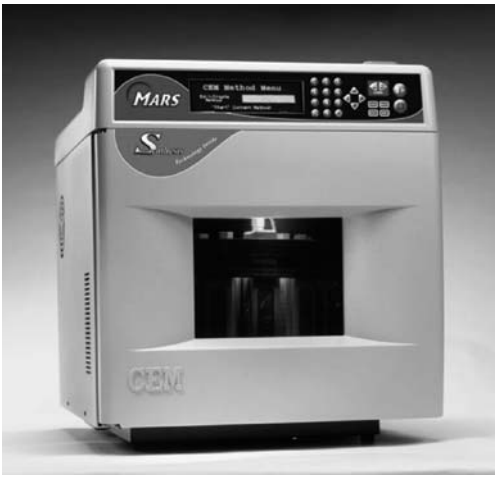


Fig. 4 MARS Synthesis Reactor

on the MARS 5 digestion reactor and offers different sets of rotor systems with several vessel designs and sizes for various synthesis applications [39].

Even reactions at atmospheric pressure can be performed, employing standard laboratory glassware like round bottom flasks of 0.5–3 L [35]. A protective mount in the ceiling of the cavity allows for connection of a reflux condenser or distillation equipment as well as for addition of reagents and sample withdrawal. However, publications presenting large-scale microwave reactions under atmospheric pressure are rare [35] as the vast majority of efficient microwave reactions are carried out under sealed vessel conditions. For this purpose, the HP-500 Plus rotor (14 × 100 mL vessels), the XP-1500 Plus rotor (12 × 100 mL vessels) or the Xpress rotor (40 × 55 or 75 mL vessels) for high-throughput synthesis at elevated pressure can be used with the MARS instrument (Fig. 5).

Temperature measurement, as the most crucial parameter control in MAOS, is conducted in those rotor systems by an immersed fiber optic probe in one reference vessel or by an IR sensor on the surface of the vessels from the bottom of the cavity. Pressure measurement in HP- and XP-rotors is achieved by an electronic sensor in one reference vessel, whereas the MARS Xpress employs "self-regulating" vessels to prevent over-pressure. All the high-pressure vessels have a unique open-architecture design that allows airflow within the cavity to cool the vessels quickly [39]. The general maximum output power of the instrument is 1200 W, but two low-energy levels with unpulsed microwave output power of 300 and 600 W, respectively, are available as well. This feature avoids overheating of the reaction mixture and unit, if just small amounts of reagents are used.

Similar to the CEM equipment, Milestone offers the modular MicroSYNTH platform, which is based on the ETHOS digestion instrument [40]. The diversity of different rotor and vessel systems enables reactions from 3 to 500 mL under open and sealed vessel conditions in batch/parallel manner up to 50 bar of pressure. The START package offers simple laboratory glassware for reactions at atmospheric pressure under reflux conditions (Fig. 6). A protective

Fig. 5 Parallel pressure rotors HP-500, XP-1500m, Xpress (*left* to *right*)

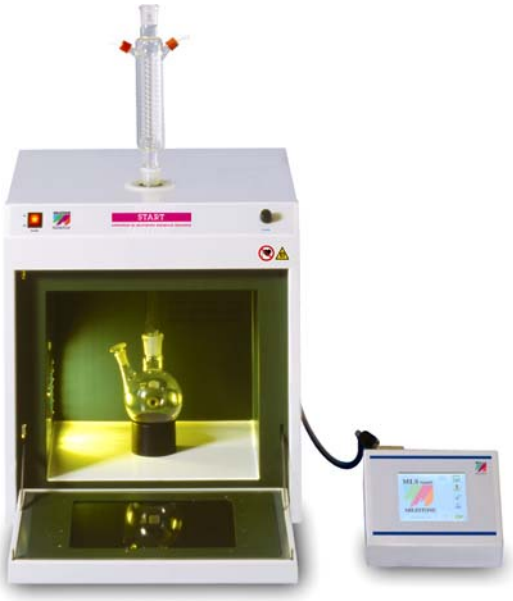


Fig. 6 MicroSYNTH Start package

mount in the ceiling of the cavity enables the connection of reflux condensers or distillation equipment. An additional mount in the sidewall allows for sample withdrawal and flushing of gas to create inert atmospheres. The basic system can be upgraded by several accessories like the research laboratory kit, equipped with the so-called MonoPREP module for single small-scale batch experiments (3–30 mL) in the multimode cavity. In addition, equipment for combinatorial chemistry approaches (CombiCHEM kit, microtiter well-plates up to 96 × 1 mL), and other special applications is available [40].

Accurate temperature measurement is achieved by the use of a fiber optic probe, immersed in one single reference vessel. Optionally available is an IR sensor for monitoring the outside surface temperature of each vessel, mounted in the sidewall of the cavity. The reaction pressure is measured by a pneumatic sensor connected to one reference vessel. Therefore, the parallel rotors should be filled with identical reaction mixtures to ensure homogeneity. The available parallel rotors employing sealed vessels for elevated pressure have been adapted for synthesis purposes from the original digestion systems (Fig. 7). The PRO 16/24 high-throughput rotor utilizes 16 or 24 reaction containers. Each PTFE-TFM vessel offers 35 mL working volume at 200 °C up to 20 bar. Two variations of parallel high-pressure rotors are available. The MPR-12 comes with 12 segmented 100 mL PTFE-TFM vessels for reactions up to 260 °C or 35 bar. For somewhat extended conditions the HPR-10 serves ten segmented 100 mL PTFE-TFM vessels enabling reac-

Fig. 7 Parallel pressure rotors Pro24, HPR-10, MPR-12 (*left* to *right*)

tions up to 250 °C at 55 bar. Several other rotor systems are available for the MicroSYNTH platform but a detailed description would extend the scope of this book. For further information the reader is referred to the Milestone website [40].

The most recently released microwave synthesis equipment is the Anton Paar Synthos 3000 (Fig. 8) [41]. This microwave reactor is dedicated for scale-up synthesis in quantities of up to approximately 250 g per run and designed for chemistry under high-pressure and high-temperature conditions. The instrument enables direct scalability up to 1 L total volume of already elaborated and optimized reaction protocols from single-mode cavities without changing the reaction parameters.

Two magnetrons (1400 W continuously delivered output power) allow mimicking of small-scale runs to produce large amounts of the desired compounds within a similar time frame. The homogeneous microwave field guarantees identical conditions at every position of the different rotors, resulting in good reproducibility of experiments, as has been verified for several syn-

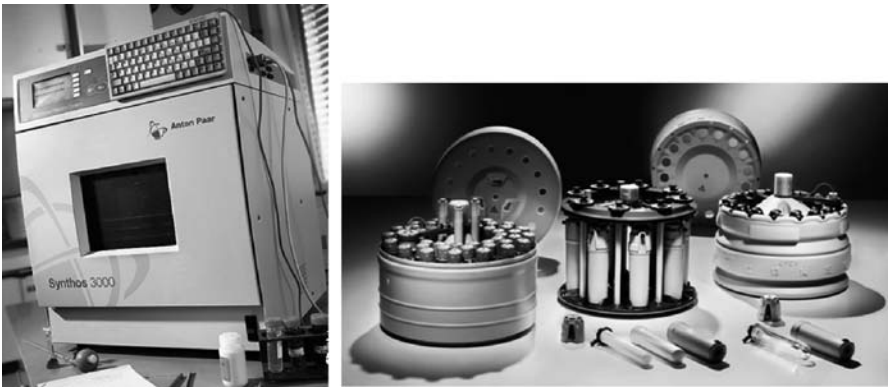


Fig. 8 Synthos 3000 – rotors and vessel types

thetic transformations [26]. Offering advanced operation limits (80 bar at 300 °C) the equipment facilitates the investigation of new reaction avenues, such as near-critical water chemistry [42]. The instrument can be operated with either an 8-, 16- or 48-position rotor, for generation of small compound libraries in multigram scale. The rotors can be equipped with several vessel types for different pressure and temperature conditions. Various accessories allow for special applications like creation of inert/reactive gas atmospheres, reactions in prepressurized vessels [26, 43], as well as solid-phase synthesis or photochemistry.

A dedicated instrument exclusively for one-vessel batch-type reactions is the Biotage Advancer (Fig. 9). This equipment features a multimode cavity for operations with a single 350 or 850 mL Teflon reaction vessel for use at elevated pressure conditions [38]. An operating volume of 50–500 mL at a maximum of 20 bar enables the production of 10–100 g product within one run. Homogeneous heating is ensured by a precise field-tuning mechanism and vigorous magnetic and/or overhead stirring of the reaction mixture. The maximum output power of the Advancer is 1100 W to reach the maximum temperature of 250 °C for 300 mL reaction volume in comparable times to the single-mode experiments. Several connection ports in the chamber head (Fig. 9) enable addition of reagents during irradiation, sample removal for

Fig. 9 Biotage Emrys Advancer Scale-Up and its multifunctional chamber head (*right*)

analysis, creation of inert/reactant gas atmosphere, and even in situ monitoring by real-time spectroscopy. Cooling is achieved by an effective certain gas-expansion mechanism to ensure drastically shortened cooling periods (e.g. 200 mL ethanol within 1 min from 180 to 40 °C). This instrument (160 × 85 × 182 cm) is a custom-built, user-specified product, manufactured on request. Initial examples of Mannich-type reactions [44] or oxidative Heck couplings [45] to verify the performance and direct scalability by translating optimized reaction conditions from the Emrys/Initiator system to the larger scale have already been published.

Another alternative for microwave-assisted batch synthesis is the Milestone UltraCLAVE (Fig. 10). In similarity to many of the other instruments, this reactor was initially designed for sample preparation applications but has recently been adapted for organic synthesis. Its 3.5 L stainless steel vessel allows single-batch reactions in a 400 mL to 2.5 L range at maximum operation limits of 260 °C and 200 bar [40]. The cavity is also capable of accommodating 6 × 120 mL or 40 × 20 parallel rotors employing Teflon reaction containers. The maximum output power of this device is 1000 W; the vessels are kept closed by an external pressure of nitrogen. Thus, extremely high pressures of

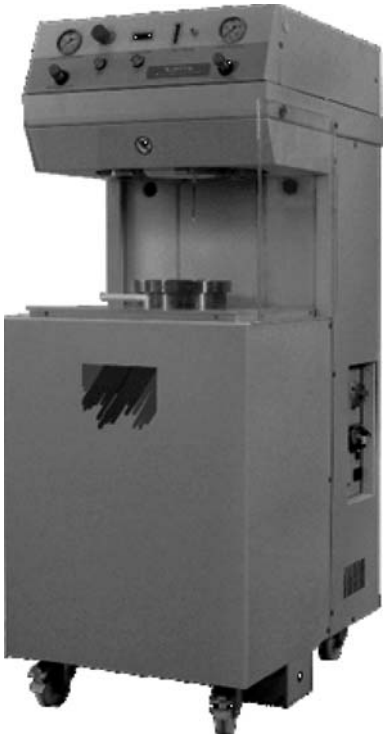


Fig. 10 Milestone UltraCLAVE

up to 200 bar can be reached. However, at the time of writing no scientific synthesis work with this equipment has been published.

2.2 Flow Reactors for Single-Mode Instruments

Laboratory scale-up utilizing flow techniques in single-mode instruments is currently only possible with the CEM Voyager system. Special flow-through cells for both CF and SF modes are available [39]. The CF system (Fig. 11) offers reaction coils made of glass or Teflon with a maximum flow rate of 20 mL min^{-1} and operation limits of 250 °C or 17 bar. In addition, active flow cells, charged with catalysts or scavengers on solid support, can be applied. The Voyager SF system is operated with a special 80 mL vessel (Fig. 12), utilizing reaction limits of 200 °C or 14 bar and a maximum filling volume of 50 mL for heterogeneous mixtures, slurries, and solid phase reactions.

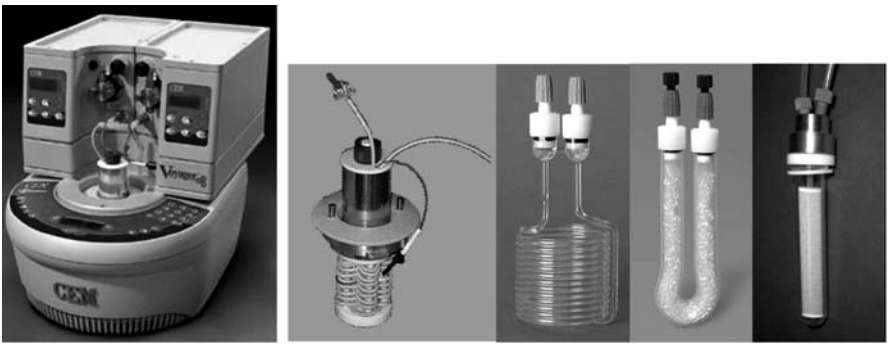


Fig. 11 CEM Voyager CF and its flow cells

Fig. 12 CEM Voyager SF and its 80 mL reaction vessel

2.3 Scale-Up Beyond Laboratory Scale

The instrumentation presented so far enables scalability in academic and industrial labs from milliliters to approximately 1 L reaction volume or flow rates of several milliliters per minute, respectively. A daily output of some 100 g should be possible with those units. However, industrial users of microwave technology expect solutions for even larger applications as well, dealing with kilogram production per day. Investigations and instrument developments are currently being pursued by most of the instrument vendors. Milestone, for example, already offers two large-scale flow systems (Fig. 13) to close the gap between technical limitations and customer demands [40].

The original CF equipment ETHOS CFR applies quartz or ceramic flow-through cells of various sizes (10–60 mm diameter) inside the regular ETHOS cavity. The reagents are pumped through the microwave field from the bottom to the top of the cavity at maximum operating conditions of 250 °C or 40 bar. The flow rate is dependent on the cell used, but their design generally also allows reactions involving suspensions and inhomogeneous mixtures. Temperature and pressure control via the entire course of the process is achieved by an in-line thermal sensor and an in-line pressure-control valve, respectively. Published examples with this equipment involving methylation reactions have been presented by the group of Shieh [46, 47]. Additionally, available 380 mL MRS-batch tubes, made from fused silica or ceramics, are also applicable in the SF technique at operation limits of 200 °C or 14 bar.

Fig. 13 Milestone scale-up reactors: contFLOW (*left*) and FlowSYNTH station (*right*)

A recent update of Milestone's initial flow equipment resulted in the FlowSYNTH station. The setup is similar to the CF reactor, but operation limits have changed to 200 °C and 30 bar. The most important improvement is an incorporated mechanical stirrer in the 300 mL reaction tube (PTFE in ceramics), providing sufficient agitation of the reaction mixture. The products are pumped out at the top into a heat exchanger for rapid cooling. So far, no experiments have been published with this new device.

The prototype ETHOS pilot 4000 labstation (Fig. 14) is designed for scale-up in the kilogram scale and is built from two regular Milestone cavities. The reaction mixtures can be heated either in CF or batch-type manner. The delivered microwave output power is 2500 W, which can be extended to 5000 W if required [40]. The reaction tubes (quartz or ceramics) are custom built with several diameters and lengths available, covering a broad range of flow rates and pressure conditions. For reaction control, the temperature is monitored over the whole length of the reaction cell, similar to the contFLOW system. As a model reaction to demonstrate the high performance capabilities of this reactor, the esterification of linalool at a 25 kg scale, applying a flow rate of 2.2 L h^{-1}, has been performed [48].

The largest microwave reactor for organic synthetic applications so far is a pilot plant scale prototype installed at Sairem in France, developed and designed in collaboration with BioEurope and De Dietrich. This custom-built 1 m^3 reactor (Fig. 15) with a powerful 6 kW microwave generator is used for the production of Laurydone [49]. Running in a batch-type recycling process, the equipment accomplished a 40% power reduction compared to the

Fig. 14 ETHOSpilot 4000

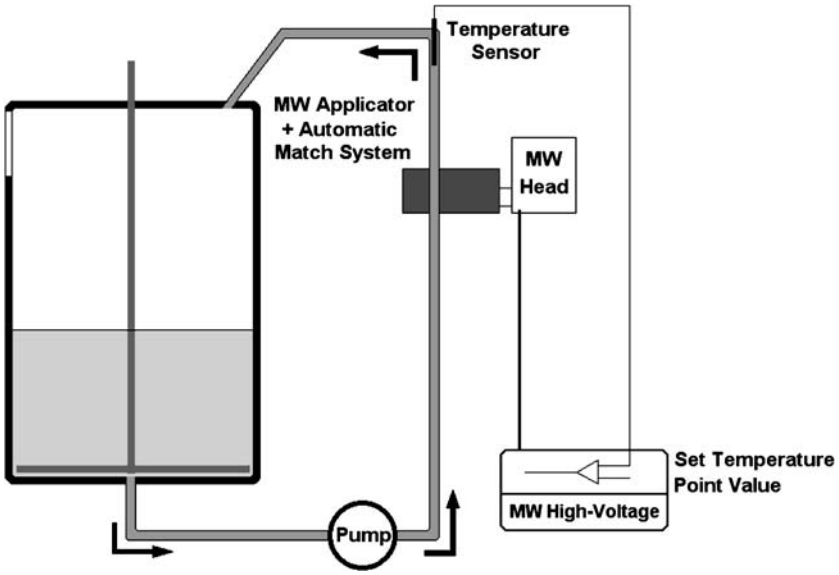


Fig. 15 Recycle batch 1 m^3 prototype microwave reactor

classical thermal approach. Moreover, the overall processing time could be reduced by 80%, which clearly shows the potential of microwave-mediated applications even at production scale.

3
Literature Survey

This survey on microwave-assisted organic chemistry will cover only batch reactions at a $\geq$ 50 mL scale and experiments performed in CF or SF manner.

3.1
Batch and Parallel Processing

Whereas batch synthesis on the small scale is the standard procedure in microwave-assisted synthesis and has been extensively reviewed ([50–52] and references cited therein), protocols in the 50 mL range are rather rare. In this section, scale-up of volumes $>$ 50 mL in sealed vessels will be discussed. An important issue for the process chemist is the potential of direct scalability of microwave reactions, allowing rapid translation of previously optimized small-scale conditions to a larger scale. Several authors have reported independently the feasibility of directly scaling reaction conditions from small-scale single-mode (typically 0.5–5 mL) to larger scale multimode

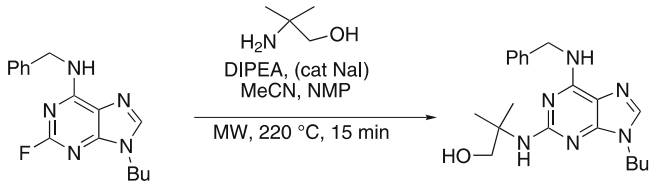
batch microwave reactors (20–500 mL) without re-optimization of the reaction conditions [26, 44, 45, 53–55].

Modern single-mode microwave technology allows the performance of MAOS in batches of very small reaction volumes (< 0.2 mL). A detailed study by Takvorian and Combs highlights the advantage of performing microwave chemistry in very small reaction vessels applicable in, e.g., the Biotage Initiator EXP equipment [56]. The ultralow volume vials utilized in this study (0.2 mL) enabled the authors to run reactions in a very concentrated fashion, minimizing reaction times and utilizing only limited amounts of sometimes expensive scaffolds and reagents (Scheme 1).

With those single-mode reactors that do not require a minimum filling volume (CEM Discover platform; temperature measurement is performed from the bottom and not from the side by an external IR sensor) even volumes as low as 50 μL can be processed [57]. With the commercially available single-mode cavities of today, the largest volumes that can be processed under sealed vessel conditions are ca 50 mL, with different vessel types being available to upscale in a linear fashion from 0.05 to 50 mL. Under open vessel conditions higher volumes (> 1000 mL) have been processed under microwave irradiation conditions, without presenting any technical difficulties as, e.g., described for the synthesis of various ionic liquids on a 2 mol scale [35].

A comprehensive study on the scalability of optimized small-scale microwave protocols in single-mode reactors to large-scale experiments in a multimode instrument has been presented by Kappe and coworkers [26]. As a model reaction, the classical Biginelli reaction in acetic acid/ethanol (3 : 1) as solvent was run in parallel in an eight-vessel rotor system of the Anton Paar Synthos 3000 synthesis platform (Fig. 8) on a 8 × 80 mmol scale [26]. Here, the temperature in one reference vessel was monitored with the aid of a suitable probe, while the surface temperature of all eight quartz reaction vessels was also monitored (deviation less than 10 °C, see Fig. 16). The yield in all eight vessels after 20 min hold-time at 120 °C was nearly identical, resulting in an overall amount of approximately 130 g of the desired dihydropyrimidine.

To extend this study, numerous other transformations have been carried out on different scales. The results of these scale-up experiments are summarized in Scheme 2 [26]. In all cases, the yields obtained in the optimized small



Scheme 1 Amination of purine scaffolds on a 0.2 mL scale

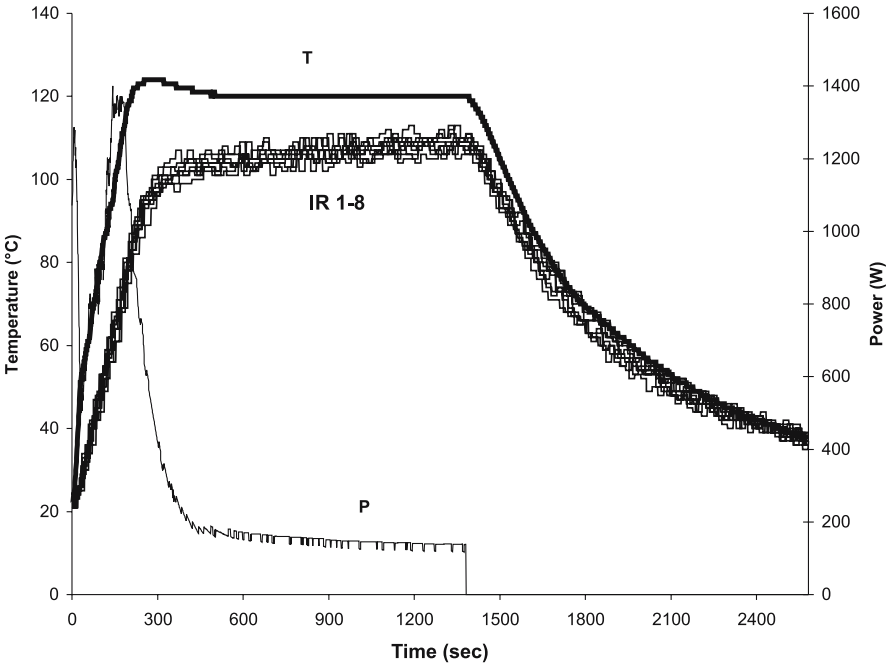
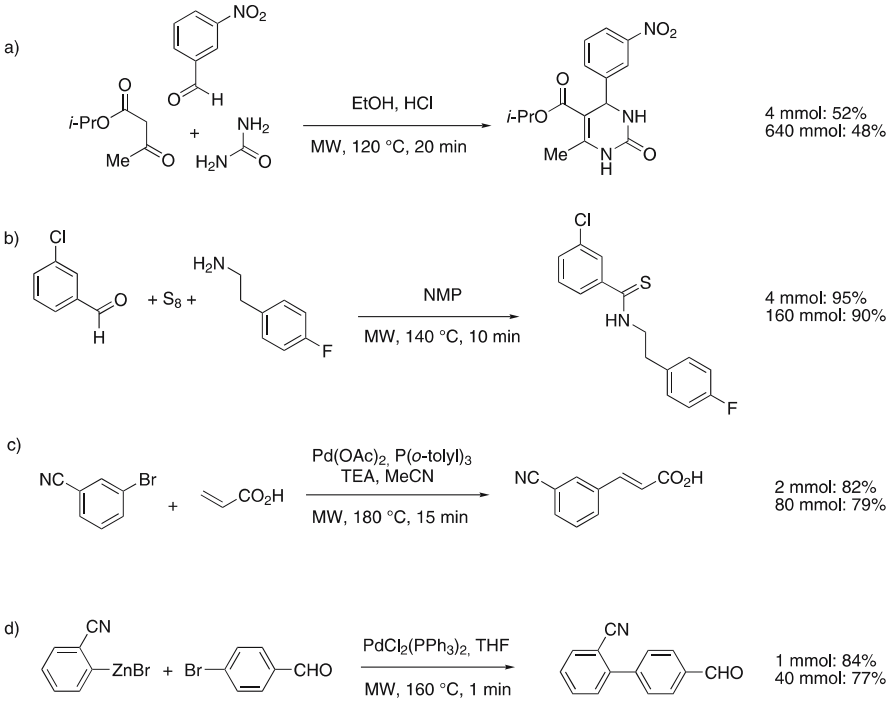


Fig. 16 Temperature and power profiles for a Biginelli condensation (Scheme 2a) under sealed vessel/microwave irradiation conditions. Shown is the temperature measurement in one reference vessel via an internal gas balloon thermometer (T), the surface temperature monitoring of the eight individual vessels by IR thermography (*IR 1–8*), and the magnetron power (*P*, 0–1400 W). Reproduced with permission from [26]

scale single-mode experiments (1–4 mmol) performed on an Emrys Liberator (Biotage) could be reproduced on a larger scale (40–640 mmol) without modifications of the reaction conditions. Dependent on the chemistry and the applied scale, 10–100 g of product could be isolated from a single run. It has to be noted, however, that in many cases the rapid heating and cooling profiles seen in a small-scale single-mode reactor with high power density ("microwave flash heating") cannot be replicated on a larger scale. The heating profile for the Biginelli cyclocondensation shown in Scheme 2a is reproduced in Fig. 16. Despite the somewhat longer heating and cooling period, no appreciable difference in the outcome of the reactions studied was found.

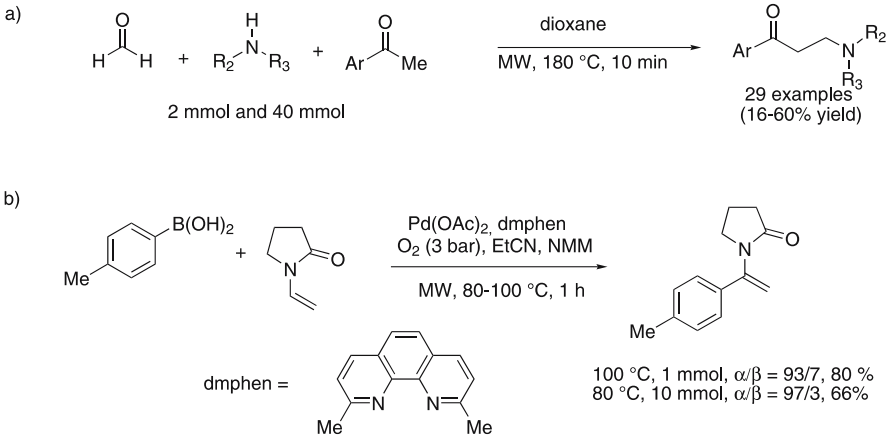
Similar scale-up results were obtained by Luthman and coworkers for Mannich reactions [44] and by the group of Larhed for oxidative Heck couplings [45] (Scheme 3) utilizing a different multimode batch reactor with a single reaction vessel (Emrys Advancer). As expected, yields were comparable on going from a small-scale single-mode reactor to a larger multimode reactor. Here, rapid cooling after the microwave heating step is possible by a patented expansion cooling process.



Scheme 2 Direct scalability of microwave synthesis from small scale single mode reactors to large scale multimode batch reactors

Similar work on comparatively large scale microwave synthesis was earlier published by Strauss [58] utilizing a prototype laboratory-scale microwave batch reactor (MBR), and by other authors using a larger single-mode device (Synthewave 1000 reactor by Prolabo) [36, 37]. The MBR consists of a large reaction vessel for 100 mL operating volume equipped with a fiber optic thermometer and a cold finger. To demonstrate the performance of this prototype, several transformations such as oxidations, esterifications, Claisen rearrangement in water, and Willgerodt reactions have been performed on various scales [58]. This MBR prototype was the early predecessor of the above-mentioned Emrys Advancer, therefore reaction details are not presented in this section.

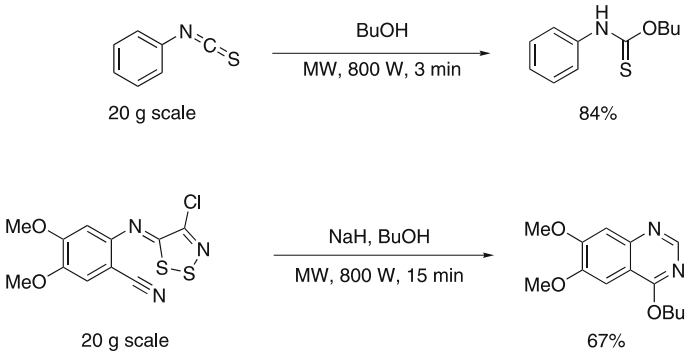
An early investigation on small- and large-scale applications was discussed by the group of Besson [34]. Therein the authors compared two microwave reactors of the French company Prolabo, namely the Synthewave S402 for small-scale and the Synthewave S1000 reactor for larger scale applications, which were commercially available in the 1990s [59]. Two reactions, the conversion of phenyl isocyanate to phenyl-*n*-butyl-thiocarbamate and the transformation of *N*-arylimino-4-chloro-5*H*-1,2,3-dithiazole to 4-*n*-butoxyquinazoline-



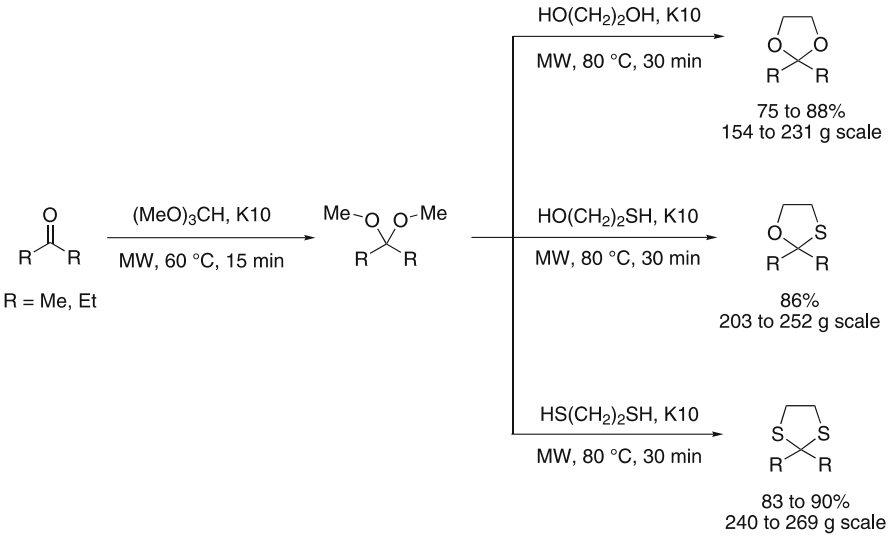
Scheme 3 Direct scalability of microwave synthesis from small scale single mode reactors to large scale multimode batch reactors

2-carbonitrile, were carried out in order to evaluate the differences in reaction time and yield when going from small scale (1 g) up to a 20 g scale (Scheme 4). In the latter example the same yields were obtained but with dramatically reduced reaction times as compared to the small-scale experiments, probably due to the higher power capacity of the large-scale reactor (800 W for the S1000 instead of 300 W for the S402).

In a related study, the scale-up and synthesis of dioxolanes, dithiolanes, and oxathiolanes was performed by Hamelin and coworkers [36]. Employing the Synthewave S1000 apparatus from Prolabo, the authors investigated the synthesis of the protected carbonyls on a 2 mol scale under open vessel conditions employing high-boiling glycols and K10, an acidic clay, as catalyst (Scheme 5). Proving that the reaction conditions (regarding time and temperature) were exactly the same going from 10 mmol to a 2 mol scale,



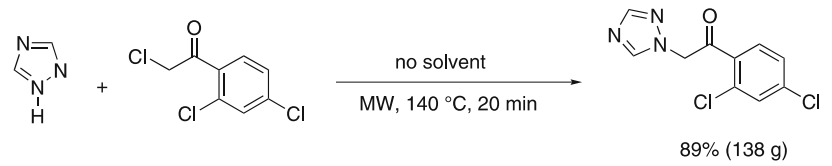
Scheme 4 Scale-up synthesis of thiocarbamates and quinazolines in single-mode reactors



Scheme 5 Scale-up synthesis of dioxolanes, oxathiolanes, and dithiolanes

they observed an easier work-up for the large scale experiments owing to the possibility of removing the formed alcohol by continuous distillation under microwave irradiation in the Synthewave S1000.

In a more recent study, the group of Loupy presented a series of solvent-free reactions scaled up to several hundred grams utilizing the Synthewave 1000 batch reactor [37]. After optimization at a 50 mmol scale employing the Synthewave 402, the alkylation of potassium acetate with *n*-bromooctane was performed on a 2 mol scale (622 g product) within 5 min, although the heating ramp was somewhat slower than in the small-scale run. An interesting result was obtained for the phenacylation of 1,2,4-triazole (Scheme 6). Whereas thermal heating furnished a mixture of the 1- and 4-alkylated triazoles as well as the quarternary salts, the microwave-assisted phenacylation resulted in the exclusive formation of the 1-alkylated product, regardless of the scale used [37]. As an additional example, the selective dealkylation of 2-ethoxyanisole using KO*t*-Bu has been carried out solventless, with 20 min irradiation yielding 108 g of the corresponding phenol.



Scheme 6 Phenacylation of 1,2,4-triazole

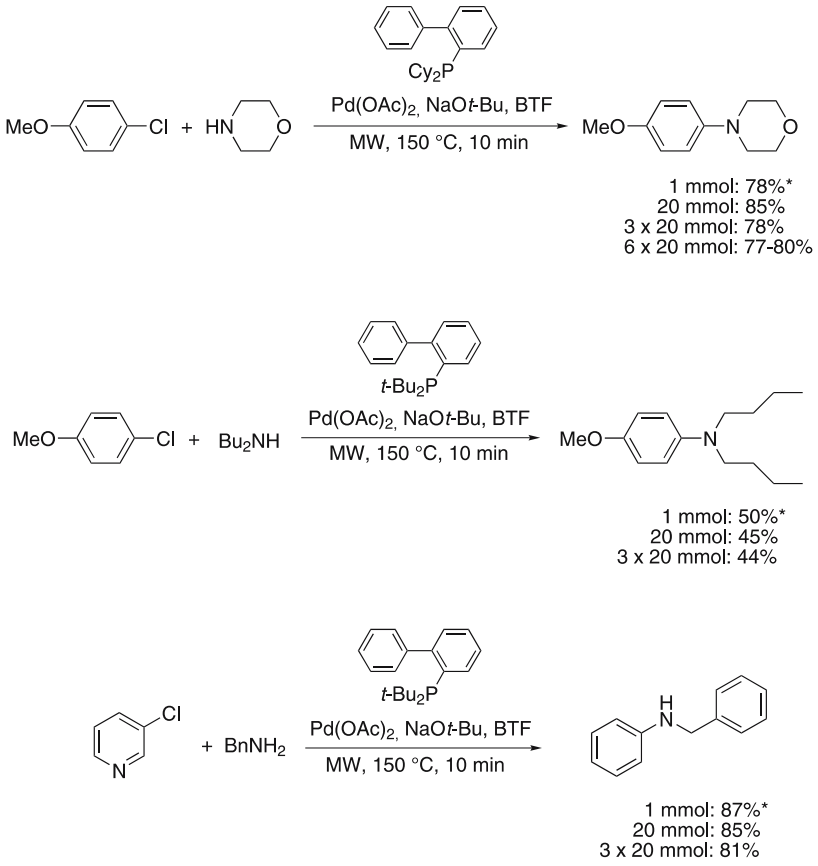
With these results in hand, several examples in carbohydrate chemistry have been performed including glycosylations, peracetylations, saponifications, and epoxidations of glucose derivatives. Within 2–10 min (depending on the chemistry and the scale) 60–220 g of the desired compounds have been generated, showing the easy access of products in the multigram level by solventless microwave-assisted chemistry [37].

Maes and coworkers recently presented one of the rare direct comparisons of single-mode and multimode instruments in batch and flow processing, respectively [27]. The authors compared the performance of the multimodal Milestone MicroSYNTH and the CEM MARS reactors with the single-mode instruments CEM Discover and its SF extension Voyager SF (Sect. 2). Buchwald–Hartwig aminations in toluene were used as test reactions to investigate initially the direct scalability going from a 10 mL (1 mmol) vessel to an 80 mL (20 mmol) vessel in a Discover apparatus. In contrast to the small-scale experiment, the final temperature could not be reached in the 80 mL vessel due to the poor coupling properties of toluene with microwave irradiation ($\tan \delta = 0.04$). Although polar reagents are present in the reaction mixture in a higher concentration compared to the small-scale experiment, the poor coupling characteristics of toluene are obviously responsible for the failure of the scale-up experiment [27].

A 20-fold scale-up has been performed using a more polar solvent (BTF), going from a 10 mL to an 80 mL vessel in the Discover, 3×20-fold (60 mmol) by employing the Voyager SF, and 6×20-fold (120 mmol) by employing parallel rotors in the MARS and microSYNTH reactors. Similar results regarding yield and product purity were obtained with each platform, demonstrating that the success of the reactions is neither dependent on the equipment used nor on the scale applied (Scheme 7).

To investigate these findings further the authors determined heating rates of the employed multimode instruments and the Discover unit, once again using toluene as solvent. After 10 min irradiation at a constant maximum power output for each microwave reactor, different final temperatures were measured (Fig. 17). Furthermore, it could be shown that the observed differences in temperature are not only related to the different heating efficiencies of the instruments but also to the specific vessel material [27]. Usually the vessel material itself is not completely microwave-transparent and therefore it is at least partially responsible for heating of the irradiated solvent via conventional thermal conduction [42].

Not surprisingly, the final temperature of the solvent relies on the volume used, especially if experiments are performed at constant power. In such experiments, a decrease of the final temperature was observed with increased volume. Obviously, it is not possible to directly compare single-mode experiments with multimode experiments at an identical output power. Due to the significantly higher power density, the heat transfer of single-mode reactors is substantially higher.



Scheme 7 Scale-up of Pd-catalyzed Buchwald–Hartwig aminations utilizing different microwave instruments

In case of the Buchwald–Hartwig reactions, all those previously mentioned problems could be minimized using alternative solvents like trifluoromethylbenzene (BTF), which is a far better microwave absorber than toluene. Utilizing such modified reaction mixtures the authors found comparable yields in single-mode and in multimode reactors for small- as well as for large-scale experiments (Scheme 7). Thus, the above-mentioned aminations have been performed efficiently on a multigram scale producing a daily output of 261 g of a morpholine-containing compound [27].

Baxendale and Ley [60] employed the Smith Synthesizer as well as the Emrys Optimizer from Biotage [59] for conducting neat KO*t*-Bu mediated trimerizations of various liquid nitriles to give aryl- and alkyl-substituted 4-

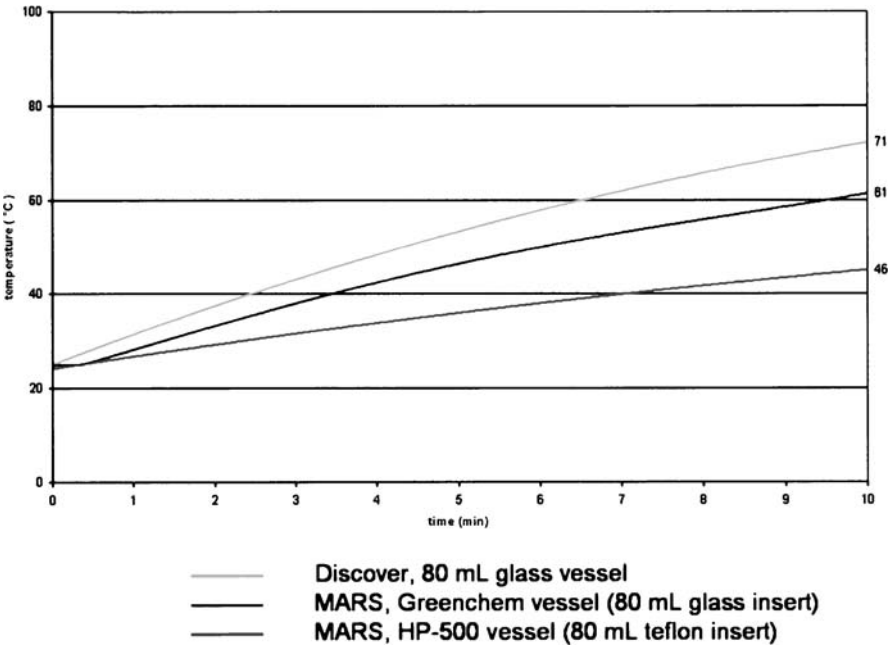
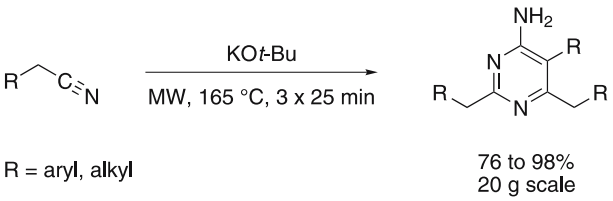


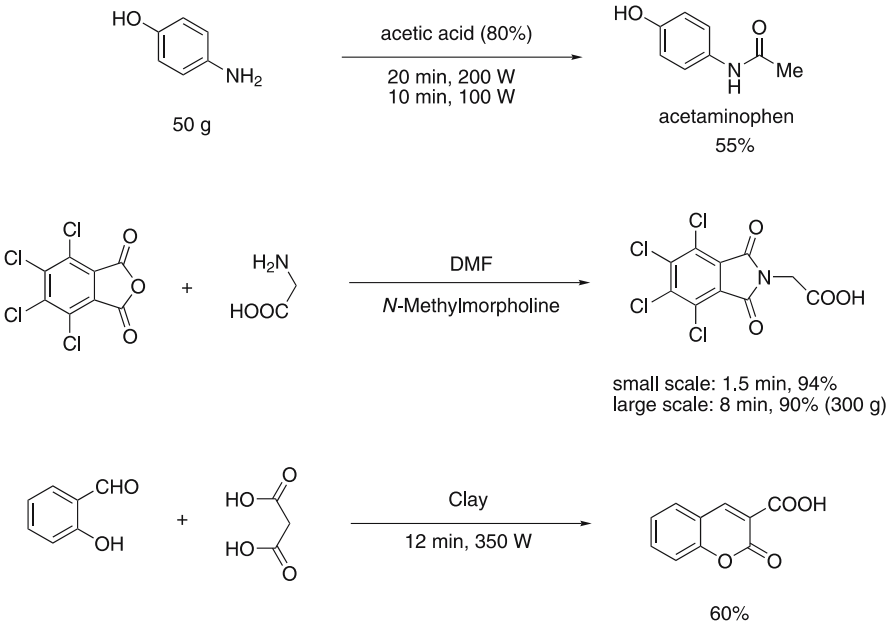
Fig. 17 Heating profile of 20 mL of toluene in several commercially available microwave systems, irradiated in a power/time experiment at a constant power of 300 W for 10 min. Reproduced with permission from [27]

aminopyrimidines (Scheme 8). A set of 23 different nitriles was reacted on 1, 5, and 20 g scales. For the large-scale attempts, a 3×25 min heating circle was required whereas three successive 15 min runs were found to be enough for high overall yields and excellent purities in the 1 g and 5 g scale reactions.

Bose and coworkers have performed known chemical processes in various kitchen microwave devices to explore microwave chemistry at a larger scale [33]. Representative examples for multigram-scale synthesis without optimization of reaction conditions have been presented, such as the rapid preparation of 500–800 g of acetylsalicylic acid (Aspirin). Another valuable pharmaceutical compound, Tylenol (acetaminophen, paracetamol), could be



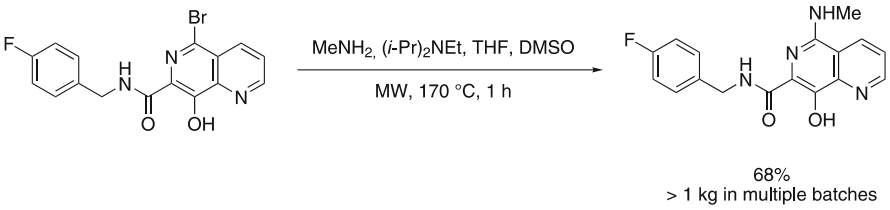
Scheme 8 Gram-scale generation of a 23-membered aminopyrimidine library



Scheme 9 Model reactions for microwave-scale-up in open vessels (no temperature control)

produced in good yield within 4 min irradiation in a simple domestic microwave oven (Scheme 9). Up-scaling of this process (25-fold) required sequential irradiation at different power outputs to achieve an almost similar yield. The other examples presented in Scheme 9 also required somewhat prolonged reaction times in the scale-up attempt compared to the initial optimized protocols [33].

In the context of a medical chemistry project, Hazuda and coworkers proved the necessity for large-scale production of an HIV integrase inhibitor in order to be able to carry out several clinical tests [61]. The required precursor presented in Scheme 10 was prepared by a team from Merck in



Scheme 10 Microwave-mediated process for the synthesis of an HIV integrase inhibitor precursor

multiple batches employing a 300 mL single-mode batch reactor (Emrys Advancer) [62–64]. The total required amount of the corresponding bromide was generated within 35 h total processing time under microwave conditions in several batches, whereas the process performed at the same scale under thermal heating would have required 30 days [64].

3.2 Scale-Up Using Continuous Flow Methods

Mainly because of safety concerns and issues related to the penetration depth of microwaves into absorbing materials such as organic solvents, the preferable option for processing volumes of > 1 L under sealed vessel microwave conditions is a CF technique, although here the number of published examples using dedicated microwave reactors is still limited [46, 47, 65–68]. In such systems the reaction mixture is passed through a microwave-transparent reaction container that is placed in the cavity of a single- or multimode microwave reactor. The previously optimized reaction time under batch microwave conditions now needs to be related to a "residence time" (i.e., the time the sample stays in the microwave-heated coil) at a specific flow rate. While the early pioneering work in this area stems from the group of Strauss [65], others have made notable contributions to this field in the past, often utilizing custom-built microwave reactors or modified domestic microwave units [69–73].

Already in 1990, the group of Wang pointed out the inherent hazard of violent explosions due to the high pressure/high temperature conditions in closed vessels under microwave irradiation [74]. Organic transformations like esterifications, racemizations, hydrolysis, cyclization, and substitution reactions have been reported on a scale > 20 g using a CF reaction process in a modified kitchen-type microwave oven [74].

An efficient application of microwave-mediated synthesis by a CF technique has been presented by Esveld and coworkers [72]. In their work, the formation of waxy esters using montmorillonite clay as a catalyst under solventless microwave conditions has been intensively studied. To avoid side reactions and to aim for the highest reaction rate, microwave heating was used in order to keep the temperature constant for a certain period of time. Equimolar composition, microwave heating, and montmorillonite clay catalysts have been combined to achieve the scale-up of these esterification reactions by a continuous process without the use of any organic solvent. The employed equipment, a prototype continuous microwave dry-media reactor (CMDR), consists of a previously described multimode tunnel microwave cavity (150 × 40 × 35 cm), delivering an output power of 4.4 kW from a diagonal slotted waveguide (Fig. 18) [71]. The solid mixtures are transported on a Teflon-coated glass fiber web conveyor (1.5 m) up to 17 cm min^{-1}. With this apparatus – on a scale of 12 kg h^{-1} – it has been shown that dry-media and

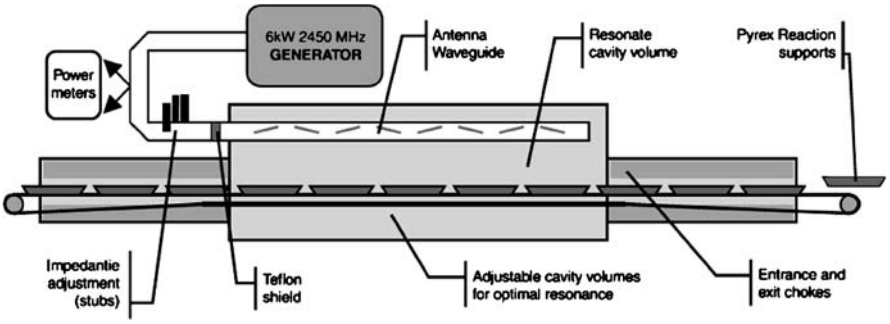
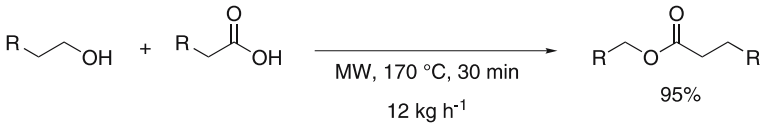


Fig. 18 Continuous microwave dry-media reactor (CMDR) for kg-scale dry-media reactions. Reproduced with permission from [71]

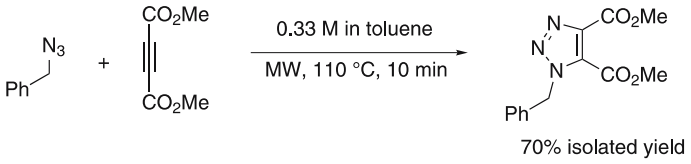
solvent-free reactions can be scaled to pilot processes, without altering the main reaction conditions. The continuous production capacity of the CMDR has been fully exploited, resulting in a day production of about 100 kg of corresponding waxy esters in high purity (Scheme 11).

A more recently published example of organic microwave synthesis under CF conditions is the 1,3-dipolar cycloaddition chemistry in the CEM CF Voyager system (Fig. 11). Savin and coworkers presented the cycloaddition of dimethyl acetylene dicarboxylate with benzyl azide in toluene, which was first carefully optimized with respect to solvent, temperature, and time under batch conditions. The best protocol was then translated to a CF procedure where a 0.33 M solution of both building blocks was pumped through a Kevlar-enforced Teflon coil (10 mL total capacity) heated in the single-mode reactor at 110 °C (10 min residence time) [66]. This method provided a 91% conversion to the desired triazole product (Scheme 12).

In the context of elaborating a degradation method for hazardous and toxic halogenated aromatic hydrocarbons, Varma and coworkers reported on



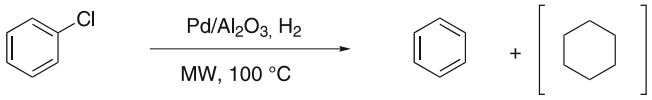
Scheme 11 Waxy ester production in pilot scale



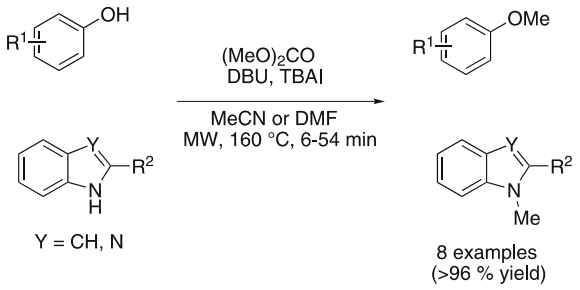
Scheme 12 1,3-Dipolar cycloaddition reactions under CF conditions

the hydrodechlorination of chlorinated benzenes using a microwave-assisted CF process that involves "active flow cells" (Scheme 13) [75]. Here a 15 mL quartz U-tube filled with spherical particles of 0.5% Pd/Al_2O_3 catalyst was fitted into the CEM Voyager CF reactor. Chlorobenzene was fed into the reactor at an adjustable flow rate along with a controlled flow of hydrogen from a cylinder. Comparison studies between the microwave and the thermally heated process indicated that the microwave method was both more efficient and selective than the thermal process, which gave formation of undesired cyclohexane byproduct under standard, thermal conditions.

Current single-mode CF microwave reactors allow only processing of comparatively small volumes. Much larger volumes can be processed in CF reactors that are housed inside a multimode microwave system. In a publication from 2001, Shieh and coworkers described the methylation of phenols, indoles, and benzimidazoles with dimethyl carbonate under CF microwave conditions, using a Milestone ETHOS-CFR reactor [46]. In a typical procedure, a solution containing the substrate dimethyl carbonate, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), tetrabutylammonium iodide (TBAI), and a solvent was circulated by a pump through the microwave reactor, which was preheated to 160 °C and 20 bar by microwave irradiation (Scheme 14). Under these conditions, the methylation rate for phenols was accelerated from hours to minutes, representing a nearly 2000-fold rate increase. Similar results were also achieved for benzylations employing dibenzyl carbonate [47], and the same authors also reported the usefulness of this general method for the esterification of carboxylic acid [68]. Benzoic acid, for ex-



Scheme 13 Hydrodechlorination of chlorobenzene using active flow cells in a CF microwave process



Scheme 14 Methylation of phenols, indoles, and benzimidazoles in a multimode CF microwave reactor

ample was converted within 20 min (microwave residence time) to its methyl ester on a 100 g scale, utilizing the dimethyl carbonate, DBU-mediated CF protocol [68].

The CF technique has attracted several research groups to construct unique and unusual prototypes of small-size flow-through reactors for single-mode instruments as well as for domestic ovens. Although these kinds of applicators do not really meet our definition of scale-up we will nevertheless mention the most interesting CF approaches in this context.

In order to investigate the possibility of efficiently performing organic transformations employing immobilized catalysts under microwave irradiation, the group of Bagley [76] developed a special CF microwave reactor for use in the CEM Discover unit. The reactor consists of a standard 10 mL glass tube, fitted with a custom-built steel head, and filled with sand (~ 12 g) between two drilled frits in order to create a lattice of microchannels charged with solvent (~ 5 mL). The tube is sealed using PTFE washers and connected to a regular HPLC flow system with back-pressure regulation (Fig. 19). In order to investigate the aptitude of this reactor for chemical transformations, a simple hydrolysis of thiazole and a Fischer indole synthesis have been performed on the gram scale under CF conditions (Scheme 15). Furthermore, in order to compare the efficiency of this setup with batch processing, a Bohlmann–Rahtz reaction was carried out furnishing pyridines by cyclodehydration of the corresponding aminodienones (Scheme 16) employing a Teflon heating coil. Applying conditions that gave almost quantitative conversion to the pyridine, the processing rates using the glass tube reactor

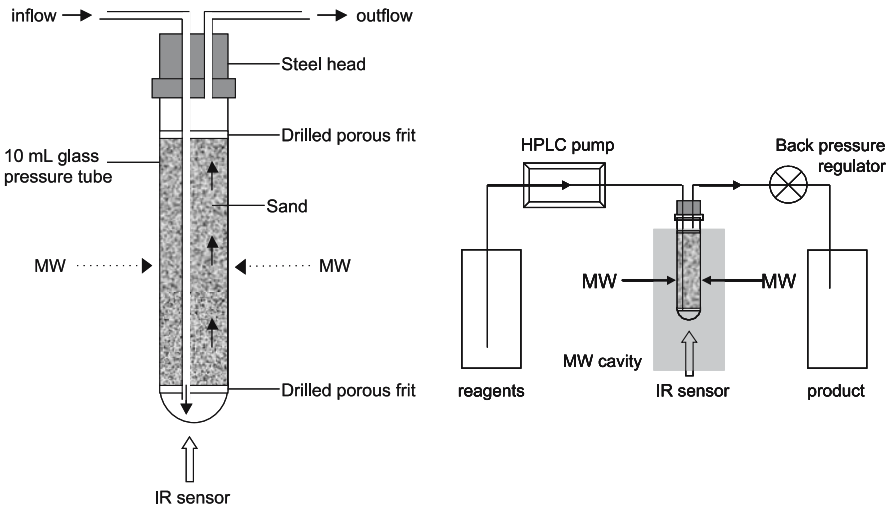
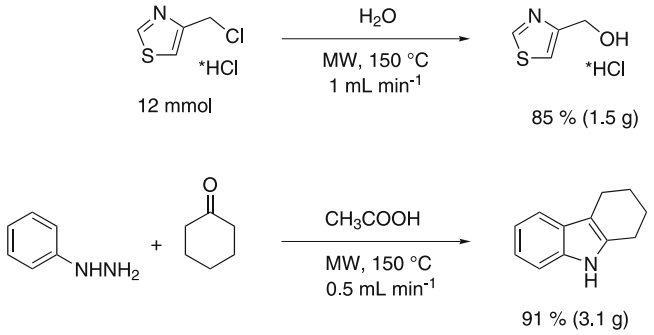
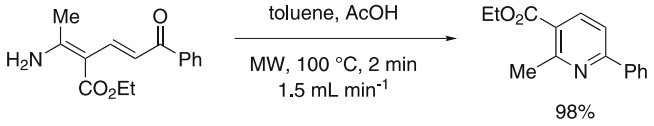


Fig. 19 Schematic diagram of the flow cell/CF reactor. Reproduced with permission from [76]



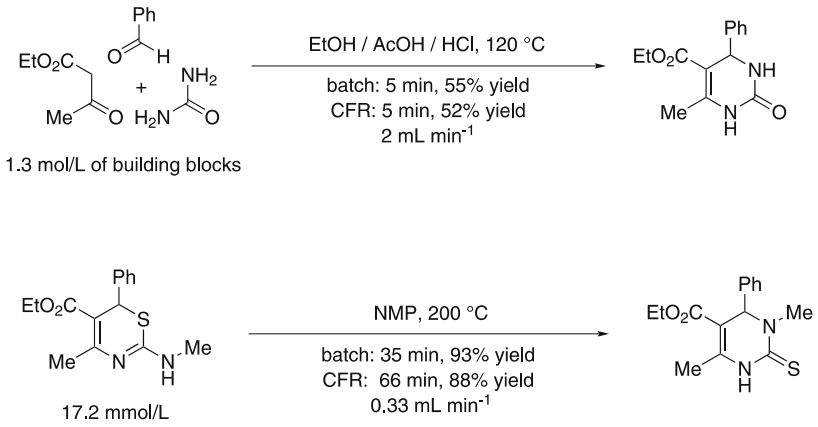
Scheme 15 Model reactions for optimization of the sand-filled CF reactor



Scheme 16 Bohlmann–Rahtz synthesis under CF conditions

were considerably higher, and CF reactions run at the same flow rate also used less magnetron energy in a glass tube than in the heating coil. This demonstrates clearly that a glass tube CF reactor offers (i) improved heating efficiency, (ii) the potential for operation on a large scale, (iii) successful transfer from batch to CF processing, and (iv) improved performance over commercial Teflon heating coils. In principle, replacing the sand by an immobilized catalyst would allow for transformations involving heterogeneous catalysts under CF conditions.

In a related study, the group of Kappe reported on Biginelli reactions and Dimroth rearrangements comparing batch and CF techniques (Scheme 17) [77]. Similar to the above-mentioned setup, a corresponding CF coil for the CEM Voyager unit was charged with 2 mm-sized glass beads in order to create microchannels, which result in increased residence time of the reaction mixture in the microwave heating zone (Fig. 20). The reaction mixture was introduced into the flow cell at the bottom of the vial via a Teflon tube using standard HPLC pumps, and the reaction pressure was controlled by a back-pressure regulator connected to the end of the outlet tubing. Monitoring of the reaction temperature was achieved at the bottom of the flow cell by the IR sensor incorporated into the instrument. The described setup was initially evaluated with the well-known Biginelli reaction going from a milligram to a 25 g h^{-1} scale, and furthermore extended to the microwave-assisted rearrangement of thiazines (Scheme 17). The Biginelli reaction was carried out with equimolar ratios of the building blocks in a concentration of 1.3 M at an adjusted flow-rate of 2 mL min^{-1}, resulting in an



Scheme 17 Biginelli reaction and Dimroth rearrangement via microwave-assisted batch and CF processing

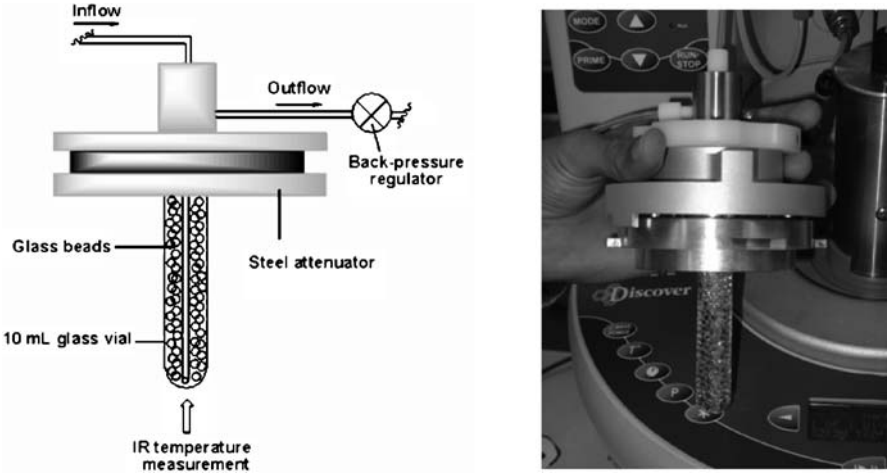


Fig. 20 Flow cell for performing CF microwave synthesis. Reproduced with permission from [77]

identical residence time compared with the batch attempt. In contrast, the Dimroth rearrangement was performed with a flow-rate leading to an almost doubled residence time of the substrate within the microwave heating zone compared to the batch experiments. The results were nicely comparable with the corresponding batch yields.

Wilson and coworkers described a custom-made flow-reactor for the Biotage Emrys Synthesizer single-mode batch reactor (Fig. 21) that was fitted with a glass-coiled flow cell [67]. The flow cell was inserted into the cavity from the bottom of the instrument and the system was operated either under

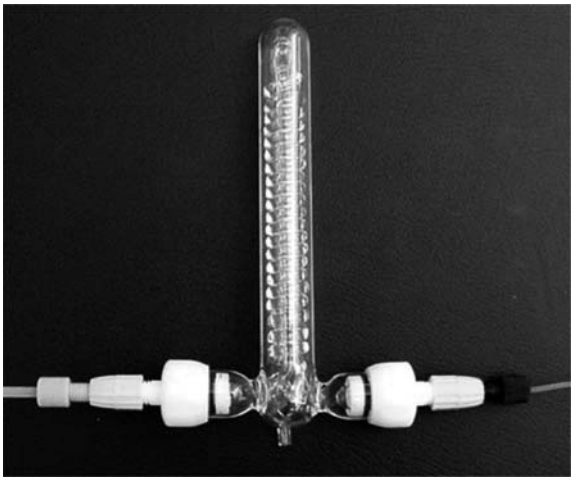
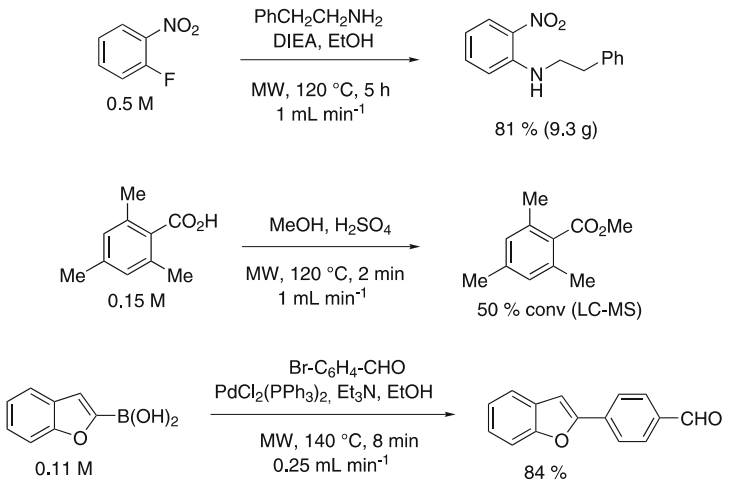


Fig. 21 Flow reactor applied with the Emrys Synthesizer. Reproduced with permission from [67]

open- or closed-loop mode. The temperature was monitored and controlled through the internal IR sensor (located in the cavity) and the instrument software.

The different synthetic transformations investigated with this system included nucleophilic aromatic substitutions, esterifications and Suzuki reactions and are shown in Scheme 18. In all cases, product yields were similar to those using conventional heating and were easily scalable to multigram quantities [67]. Within 5 h more than 9 g of the resulting phenethylamine could



Scheme 18 Various chemistries under CF conditions

be prepared by nucleophilic substitution of the corresponding fluorinated nitrobenzene. However, clogging of the lines and over-pressurization have been observed, and those phenomena are significant limitations of this processing technique.

In a related work, Organ and coworkers portrayed a microcapillary flow-through reactor attached to an Emrys Synthesizer [78, 79]. The microreactor (Fig. 22) can be used in CF as well as in SF mechanisms and has been extended to a simultaneous parallel flow device [78]. Standard glass capillaries with different diameters (200–1200 μm) coated with Pd on the inner surface have been employed. Several classic organic transformations, such as Wittig olefinations, Suzuki–Miyaura couplings, ring closing metathesis (RCM) and nucleophilic aromatic substitutions have been performed in microscale to optimize this tool. Flow rates of 2–40 μL, equal to an average residence time of 4 min, were applied in order to investigate the optimum microwave power and reaction concentration. Furthermore, internal coating of the capillaries with thin films of Pd metal showed tremendous rate accelerations as the metal films themselves are capable of inducing Pd-catalyzed reactions with no ex-

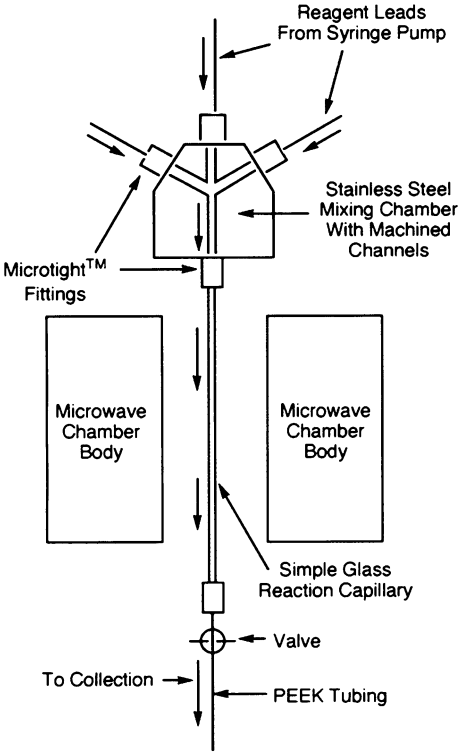


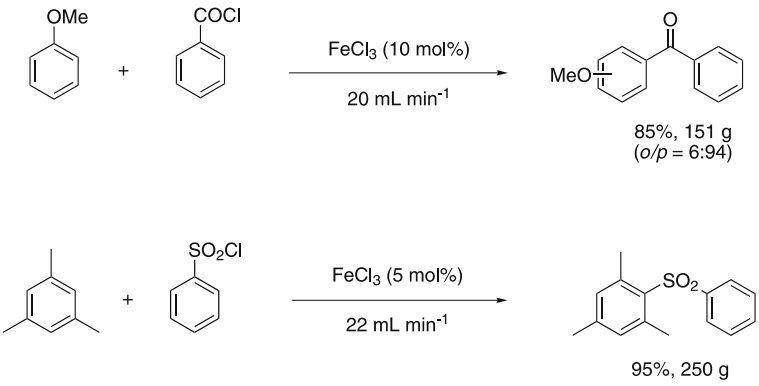
Fig. 22 Basic CF reactor design (consists of a stainless steel holding/mixing chamber with three inlet ports that merge into one outlet). Reproduced with permission from [79]

ogenous catalyst added. Although very thin capillaries have been used, clogging was not an issue as this newly developed flow-reactor consists of short and straight reaction cells. Other systems like the above-mentioned flow cells are coiled or contain spirals and are therefore more prone to clogging [66, 67]. With this data in hand, a sophisticated modification of the microreactor was developed, allowing for sequential synthesis in parallel mode to generate a 2×4 library of biaryls, as demonstrated for Suzuki couplings [78]. With this setup, parallel preparation of drug candidates on the milligram scale can be performed with all reactions heated simultaneously in a microwave reactor with the reaction mixture flowing through the individual capillaries.

Earlier, the group of Laporterie reported on another prototype CF microwave reactor [80]. Solvent-free Friedel–Crafts reactions have been successfully carried out employing only catalytic amounts of the $FeCl_3$ catalyst (Scheme 19). At a flow rate of 20–22 mL min^{-1} the corresponding substrates have been circulated in a molar scale (2 : 1 ratio) in the apparatus. Thus, 150–250 g products could be isolated. Excess substrates have been recovered by evaporation and recycled in the process.

A very interesting approach to process intensification was recently presented by Jachuck and coworkers. The authors described the development and performance of an isothermal CF reactor to be used in a domestic microwave oven [81]. The small (270 μL) CF reactor consists of two sections, a microwave transparent PTFE part for the reaction side and an alumina part for heat transfer (Fig. 23). The heat generated due to the activation by microwave irradiation was rapidly absorbed by the heat transfer liquid (H_2O) pumped through the alumina part. Inlet and outlet temperatures of both the reaction mixture and the heat transfer liquid were monitored using a PICO temperature recorder.

The beneficial effect of isothermal conditions on chemical reactions under microwave irradiation was investigated by performing the simple oxidation



Scheme 19 Friedel–Crafts reactions in a prototype CF reactor

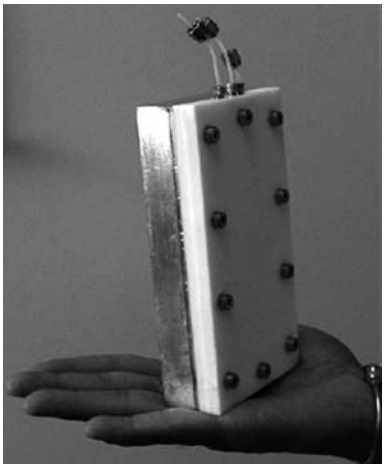
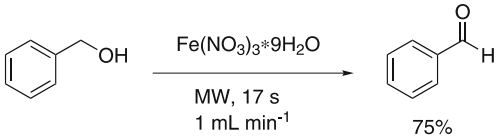


Fig. 23 Isothermal CF reactor. Reproduced with permission from [81]



Scheme 20 Oxidation of benzyl alcohol employing the novel isothermal CF reactor

of benzyl alcohol (Scheme 20). A range of residence times corresponding to different flow rates at varying microwave densities was applied to find the optimum conditions. Best results were obtained employing a residence time of 17 s, equal to a flow rate of 1 mL min^{-1}. Further development of this reactor might have some potential commercial value as dozens of inexpensive domestic microwave ovens can be used in parallel to produce chemical feedstock by isothermal microwave conditions.

Another rather unusual application of CF microwave processing within a CEM Discover unit was described by the group of Haswell [28, 29]. Microwave energy was used to deliver heat locally to a heterogeneous Pd-supported catalyst (Pd/Al_2O_3, catalyst channel: $1.5 \times 0.08 \times 15$ mm) situated within a microreactor device (Fig. 24). A 10–15 nm gold film patch, located on the outside surface of the base of a glass microreactor, was found to efficiently assist in the heating of the catalyst, allowing Suzuki cross-coupling reactions to proceed very effectively (Scheme 21). However, under these conditions the catalyst surface temperature is hard to estimate as it is simultaneously cooled by the reagent flow and heated by microwave absorption into, mainly, the catalyst.

In order to investigate those temperature sensing difficulties the same group have recently presented an electrical conductivity method for in situ temperature monitoring within the capillary flow reactor under microwave ir-

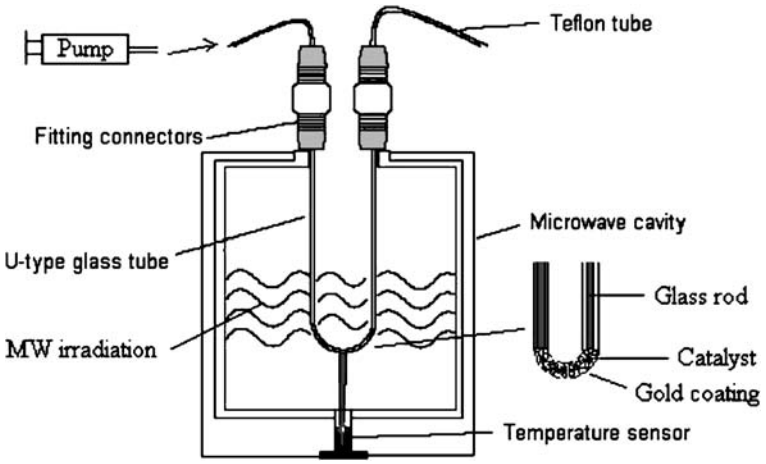
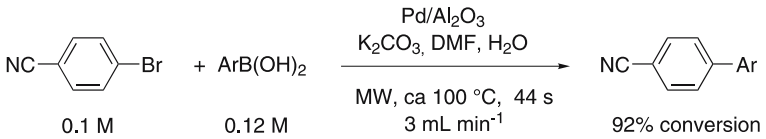


Fig. 24 Schematic diagram of the setup for MW-assisted coupling reactions. Reproduced with permission of [28, 29]



Scheme 21 Suzuki reactions in a microreactor environment

radiation [30]. With two electrodes positioned at both the inlet and the outlet of the capillary tube, the exact temperature of each section can be measured as well as the average temperature of the main U-shaped capillary. To demonstrate the suitability of the proposed methodology, the alkylation reaction of 2-pyridone with benzyl bromide was employed observing similar temperature values for the average conductivity measurements and for the IR sensor. However, the presence of a localized hot zone within the capillary was confirmed by showing that the outlet temperatures were significantly higher than the IR values.

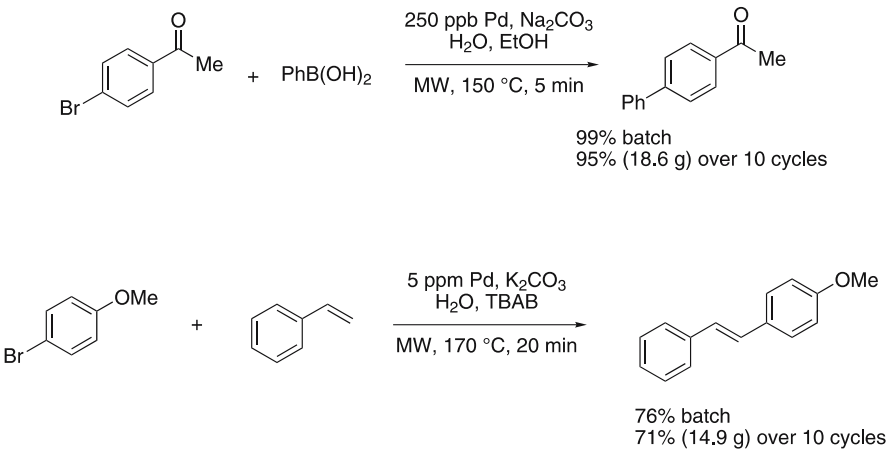
3.3 Scale-Up Using Stop-Flow Methods

Two serious problems with CF reactors is the clogging of lines and the difficulties in processing heterogeneous mixtures. Since many organic transformations involve some form of insoluble reagent or catalyst, both single- and multimode so-called SF microwave reactors have been developed where peristaltic pumps – capable of pumping slurries and even solid reagents – are used to fill a batch reaction vessel (80–380 mL) with the reaction mixture.

After microwave processing in batch, the product mixture is pumped out of the system, which is then ready to receive the next batch of the reaction mixture. As this technique has been just recently developed only few published reports are available [27, 31].

In a recent publication, the group of Leadbeater examined the scale-up of Suzuki and Heck reactions in water using ultralow Pd catalyst concentrations (Scheme 22) [31]. This proof-of-concept study points out the advantages of the CEM Voyager SF system by combining the advantages of a batch reactor with those of a CF reactor. Since only one reaction vessel is used, the time taken to cool the reaction mixture down to room temperature at the end of the run is significantly shorter than those reported for parallel batch reactors employed in a multimode apparatus (20–30 min). Furthermore, applying conditions directly from small-scale batch experiments and transferring them to the Voyager SF system was possible with only minor modifications of the reaction conditions. Thus, reactions were scaled up from 1 mmol to ten cycles of 10 mmol giving comparable yields. Similar results were also found by Maes and coworkers when comparing single-mode SF with multimode parallel technique, as recently reported (Scheme 7 above) [27].

Critically evaluating the currently available instrumentation for microwave scale-up in batch and CF, one may argue that for processing volumes of < 1000 mL a batch process may be preferable. By carrying out sequential runs in batch mode, kilogram quantities of product can easily be obtained. When larger quantities of a specific product need to be prepared on a regular basis, it may be worthwhile evaluating a CF protocol. Large-scale CF microwave reactors (flow rate 20 L h^{-1}) are currently under development [82, 83]. However, at the present time there are no documented published examples of



Scheme 22 Microwave-promoted Suzuki and Heck couplings for comparison of batch and stop flow techniques

the use of microwave technology for organic synthesis on a production scale level (> 1000 kg), which is a clear limitation of this otherwise successful technology [84].

4 Conclusion

After two decades of applying microwave irradiation to small-scale organic synthesis, the transformation to intermediate multigram scale has been conducted successfully. Various systems ranging from single-mode to larger multimode instruments enable the efficient multigram synthesis of materials without time-consuming re-optimization steps. Continuing efforts in scaling-up microwave-assisted reactions leading to multikilograms of products, and further to the semi-plant scale are necessary to extend the success story of MAOS. Industrial companies need plant reactors that can perform developed reactions with none or minimal re-optimization of their synthetic methods [64]. Therefore, ongoing investigations and comparisons of steady batch platforms with CF reactors are valuable investments for future instrument development. Due to the physical limitations of batch reactors it is likely that future approaches to the process and production scale will be performed in flow systems. As mentioned above, the penetration depth of microwaves at the established frequency of 2.45 GHz limits the maximum size of reactors. Unless there is a switch to different wavelengths, allowing increased penetration of reaction mixtures, reactors similar to the presented 1 m^3 prototype of Sairem [49] will be at the very end of the scale-up range. In daily routine, this reactor can produce kilogram amounts of compounds but the demand for much larger units is obvious. At the time of writing no time frame can be suggested when appropriate instrumentation for process scale-up will be available. Technicians are undoubtedly working hard together with chemical engineers and process scientist to investigate reasonable equipment, and viable solutions will probably be presented within the next couple of years.

Besides technical and physical limitations another important issue, especially for pharmaceutical laboratories, is the guarantee of "good manufacturing practice" (GMP) quality. Whenever new or unusual instrumentation is used in the process of preparing or producing drugs and lead compounds, it has to meet these stringent regulations in order to ensure the clean and reproducible synthesis of pure and contamination-free products. Particularly when using large parallel rotors for batch synthesis, there are still concerns whether the reaction outcome will be identical for all rotor positions. For the laboratory equipment, so far only experimental data can provide corresponding information [26, 27, 31, 82] and it has been shown that the multimode instruments available nowadays provide very homogeneous microwave

fields [26, 82]. Thus, rotors with up to 48 parallel positions furnish identical results at all positions, with variations only within the standard deviation, nicely meeting the requirements of "good laboratory practice" (GLP). It is very likely that this homogeneity and reproducibility will also be achieved in future process-scale reactors, but the agreement with GMP rules has to be verified by physical and technical testing and only certified equipment will be allowed to be used in drug manufacturing processes.

However, within 20 years microwave technology has conquered significant areas of preparative organic and medicinal chemistry. Thus, with all the knowledge and experience accessed in these two decades there is no doubt that the principle of MAOS will shortly reach the next level.

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