Combination of Flow Reactors with Microwave-Assisted Synthesis: Smart Engineering Concept for Steering Synthetic Chemistry on the "Fast Lane"

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Review
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Microreactor technology applied in continuous flow processing is an essential feature in making organic synthesis more economical and environmentally friendly. On the other hand, microwave-assisted chemistry is a key technique that has made a significant contribution to the thermal control of synthetic reactions in the early 90's by speeding up reaction times from days to merely minutes. The combination of both techniques into the same synthetic platform sets the stage for changing forever the way synthetic chemistry is being conducted by providing fast, reliable and labor-free means of synthesizing chemical compounds.

Flow reactors and microwave irradiation theory are analyzed separately in the first part, focusing mainly on the microwave heating and special microwave effects. The second part of this review summarizes several successful applications of microwave-assisted, continuous flow microreactor technology from recent synthetic organic chemistry literature; a snapshot of the state of the art of this technique is also shown at the end.

Key words:

flow synthesis, microwave-assisted synthesis, microwave effects, microreactors, thin metal films

Introduction

Advancements in synthetic methodology, from a technological perspective, have occurred primarily in a traditional vessel format, regardless of the specific chemistry selected. Today, the issue of developing new technological approaches in organic synthesis has become important because of the impact that new technologies have on the chemical and pharmaceutical industries. These new approaches have been lumped together and called "enabling technology", an area that has received increasing attention, as such technology does influence the way in which organic synthesis is being conducted. The broader definition of "enabling technology" includes traditional techniques such as "solid phase synthesis" as well as relatively new ones such as "microwave-assisted synthesis", "continuous flow reactors" etc. (Fig. 1) which were developed to speed up synthetic transformations and ease process workup.[1] It is likely that complex modern syntheses will require the integration of several enabling technologies into a versatile synthetic platform.

The combination of the techniques shown in Fig. 1 is one of several possible; different synthetic platforms will require not only different combination sequences, but also the inclusion of new techniques, as the best combination will have to be determined and optimized.

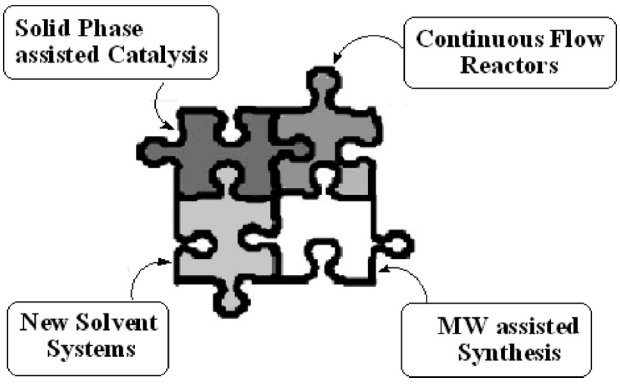

Fig. 1 – *Schematic representation of enabling techniques and possible combinations of such techniques for developing new synthetic platforms*[1]

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The development of continuous flow systems based on microfluidic technology has seen huge steps forward over the last decade, mainly driven by the need to address the following important concerns. Both small-scale chemical research and large-scale industrial applications are conducted mainly in a batch-wise manner, using conventional glassware, whereas flow-through processes are used primarily to satisfy specific industrial production needs.[1,2] This arrangement makes it difficult to adapt the batch protocols to flow-through industrial applications, because the accumulated research data from batch protocols cannot be transferred readily to industrial systems. Continuous flow processes are considered a universal tool to fill this technological gap; such processes allow the quick transition from research platforms to industrial process development, thus eliminating the time and material-consuming optimization process from bench-top reactions to a full production scale.[2] In this respect, this review will not only show that the combination of flow processes and microwave heating is very well suited to achieve this objective; extremely fast results achieved by irradiating thin metallic layers attest to the fact that the full potential of this technology has yet to be realized.

Flow systems and flow microreactors

In particular, continuous flow systems based on microfluidic technology, known as microreactors, are becoming commonly employed in organic synthesis, both on the research scale and in process development.[3]

Continuous flow systems do offer several advantages when compared to batch based protocols, such as:

Process reproducibility and reliability.[3,4] Flow processes are characterized by constant mixture composition; also, the accumulation of unreacted reagents is avoided due to their fast removal from the reaction zone. Because of the small cross-sectional dimensions of the reactor, the heat and mass transfer efficiency is increased and the effects of erratic mixing and thermal gradients are largely avoided.[5]

Facile automation. Not only are considerable amounts of time, materials and human labour involved in identifying the optimal reaction conditions for batch reactions on a small scale, oftentimes these conditions cannot be readily transferred to a scaled-up process. The small dimensions of microstructured continuous flow systems, on the other hand, allow for the use of minimal amounts of reagents and make possible the rapid screening of reaction conditions. The automation of such systems ensures tighter quality control, by allowing immediate information feedback from the in-line analytical modules and the rapid application of this feedback in order to optimize reaction conditions.[6]

Increased process safety. In general, process automation in these devices requires very little human intervention, and this manner of conducting potentially explosive reactions greatly improves safety for individuals.

Process diversification. Linear, divergent, as well as convergent multistep syntheses are also feasible by assembling a series of flow reactors, provided that solvent switching is not required and that full conversion of starting materials in each step is ensured.[7]

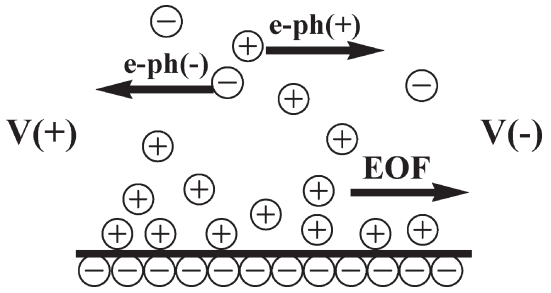
These positive features of flowed synthesis can be utilized successfully by synthetic chemists in order to overcome the hurdles associated with the optimization of chemical transformations conducted in round-bottomed flasks. Furthermore, in order to obtain significant amounts of product, the reactors are simply run longer (the scale-out principle)[8e] or alternatively, several reactors can be placed in parallel (numbering-up)[3] all using identical reaction conditions.[6,8]

In addition to the advantages stated above, the use of microfluidic continuous flow technology brings with it several unique features from an engineering standpoint that significantly enhance the application of such systems.

Diffusion-controlled mass transfer. It is known that the flow regime in microchannels is laminar, the typical Reynolds number representing the ratio of inertia forces to viscous forces is below 10, as compared to a Reynolds number greater than 3000 typically associated with turbulent flow in channels. Under laminar flow conditions, the mass transfer across a channel section will be dominated by diffusion, which allows for relatively accurate predictions of the flow behaviour, leading in turn to a highly controlled manipulation of the flow regime within a microfluidic channel network.[6] A close estimate of the time needed for diffusion across the entire width of the channel is calculated based on Fick's law.[9] This feature of the flow systems enables the operator to accurately control the reaction progress by initiating or quenching reactions in a controlled manner.[2,6]

High surface area-to-volume ratio. Scaling-down of reactor size increases the surface area-to-volume ratio considerably (for example, the surface area-to-volume ratio of a tubular channel follows a $2r{:}r^2$ relationship, where r is the radius) to the extent that it plays an active role by influencing several parameters of the process.

Electro-osmotic flow (EOF). EOF is one of the main surface-dependent applications in these reactors (due to the high surface-to-volume ratio). The operating principle of EOF is shown in Fig. 2. The negative charge of the glass channel wall (created through ionization of immobile surface groups) attracts a nanometers-thick layer of counter-ions, which, under the influence of an electrical field applied along the channel, moves at a constant speed towards the negative electrode, thus dragging the solution along in the channel.[6]



F i g . 2 – *Voltage-driven mobility of different charged species and EOF generated by the diffuse layer of cations adsorbed on the negatively charged glass wall*

In addition to EOF, the charged species within the electric field also have an additional electrophoretic velocity (e-ph vector), with a magnitude comparable to EOF velocity.[10] This application, although limited to glass and high polarity solvents, has several advantages over alternative pumping methods: it can be miniaturized easily as there are no mechanical parts involved, and the voltage sequence can be applied under automated computer control.[11] This feature of using voltage sequences to direct reagents to selected points at specified times, provides the ability to control the spatial and temporal evolution of chemical processes.[6,11]

Surface functionalization. The relatively large surface area of microstructured channels can be utilized in several ways: a) The surface can be modified with specific chemical groups (such as amines) that can bind biologically active molecules, such as antibodies. This bio-functionalized surface can be a rapid, flexible tool for bioanalysis.[12] b) The electrical charge of the surface can be altered by either plasma treatment[13] or surface coating with silanising agents.[14] The charge alteration can in turn alter the EOF direction within the channel. Loading the channel surface with different charges can result in counter-flows within the same channel, which can improve mixing significantly.[15] c) The surface can be coated with either hydrophilic or hydrophobic groups (usually by treating the surface with silanising reagents), in order to change the contact behaviour of reagents with the surface.[14]

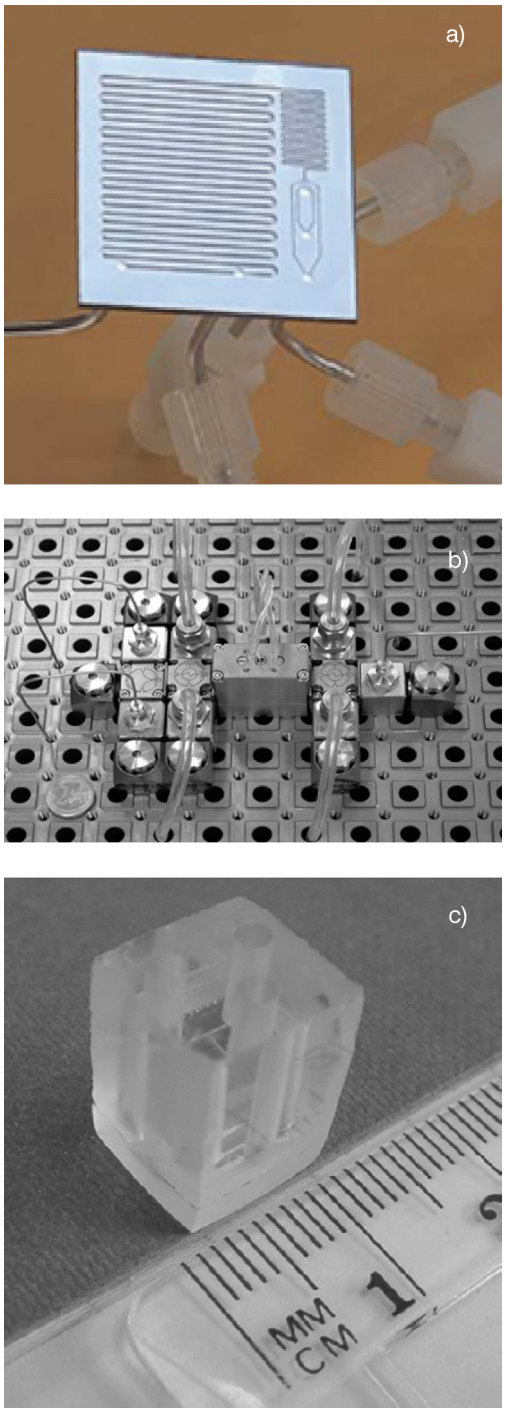
Heat and mass transfer. The heat and mass transfer in channels with a high surface-to-volume ratio is significantly improved due to a significantly higher heat and mass transfer area per unit volume.[2] Furthermore, the heat and mass transfer within a small volume occurs in a shorter time, enabling the quick formation of a homogeneous reaction medium, a factor that will have a positive impact on reaction kinetics and conversion rates. As a specific example, highly exothermic reactions are safely handled in these systems due to relatively small thermal mass and rapid heat dissipation.

In-line integration of chemical analysis and automated processing equipment. The capability to integrate in-line analytical and processing equipment with microreactors for rapid monitoring of reaction conditions is considered a very important feature of such reactors. Using these capabilities, assessing chemical kinetics and identifying optimal conditions of multistep processes is possible in a controlled fashion.[16]

As an added benefit, feedback-controlled optimization of reaction conditions with automated methodology can greatly reduce the time and labour costs associated with development of synthetic protocols.[11] The availability of UV and FTIR detectors has made possible the integration of spectroscopic measurements in microreactors,[17] although the FTIR spectrometers can only be used with silicon reactors which are IR transparent.[18a] Raman spectroscopy has been incorporated also into the microreactor design as an effective monitoring device.[18b] A recent report describes the successful use of NMR spectroscopy to assess the reaction progress during catalytic hydrogenation in microreactors.[19a]

In a typical example, reagents are injected into a lead discovery and optimization system by the pumping array. When the reagents reach the microreactor they mix and react. The reaction time depends on the combination of flow rate and channel size and length. After exiting the reactor, the product slug is detected by an UV-Visible detector. The detection of the slug triggers an injection of part of the slug into the HPLC system, where reaction components are time-resolved. Then, the appearance of a product with appropriate properties, as identified by a mass spectrometer, triggers an entry into the automated flow assay system.[19b] Such multiple modules within one microreactor design can clearly make these systems attractive tools for the pharmaceutical industry, where high throughput and information-rich techniques are constantly being sought for the rapid evaluation of reaction arrays.[2]

From an engineering viewpoint, flow microreactors are continuous flow devices with built-in fluid channels, whose internal diameters (ID) range from fractions of a millimeter up to several millimeters (Fig. 3). The basic reactor design includes an inlet, mixing and reaction, and an outlet. A more advanced design can include built-in chemical or physical sensors and additional sections for concentrating and capturing reagents.[17,20a]



F i g . 3 – *Continuous flow microreactors a) silicon-based Jensen microreactor[21b] b) stainless steel microreactor system[23] c) glass chip microreactor[8d]*

Stainless steel is a popular material for these reactors, due to its robustness and availability. The configuration can be modified easily, due to the wide availability of micromixers and heat exchangers that can fit easily into such systems. These reactors are compatible with organic solvents and can be operated under elevated temperature and pressure conditions; however, they are not compatible with reactions involving corrosive agents such as strong acids or bases.[20b]

Although polymer-based microreactors are easy to manufacture and relatively inexpensive, they show low thermal conductivity and can be affected adversely by reactions involving organic solvents that can dissolve the polymeric material or cause swelling,[20c] thus the application of these reactors is restricted to ambient temperature aqueous chemistry and biochemical processes.[20d,f] Ceramic-based microreactors are stable at high temperatures and chemically inert, but their manufacturing process is complicated by the thermal expansion/shrinkage of ceramic materials during baking.[20g] Glass, is also a popular choice as a material for microreactors, since fabrication methods are well-established; glass is chemically inert and enables the use of visible light detection, however, creating three-dimensional channels in glass is a difficult and costly process.[6,20h] Silicon is receiving wide attention as a material with high mechanical strength and good chemical compatibility. Well-established wet and dry etching techniques enable the controlled creation of microchannels. Also, the oxidation of silicon surface forms a glass layer, making silicon chips functionally equivalent to glass reactors.[20i,j] A protective coating process, such as Ni electroplating, can be applied to silicon surfaces in order to increase the chemical resistance of such reactors.[20k]

Main applications and limitations of flow microreactors

The majority of reactions conducted in continuous flow microstructured reactors involve homogeneous liquid solutions, as the design of such devices is best suited for handling liquids.

A wide range of liquid-phase reactions has been performed in microreactor devices, including epoxidations,[21] aldol reactions,[22] cross coupling reactions,[21,23] multicomponent reactions,[24] nitrations,[25] glycosylations,[21] olefinations,[21,26] peptide couplings,[27] Grignard reactions,[28] and Swern oxidations[29] to name a few. Liquid-phase reactions carried out in flow format benefit from the efficient mass and heat transfer inside microreactors, as well as from the fact that only small amounts of reactants are in the system at any given time.

Chemical processes requiring solid reactants that do not dissolve are difficult to carry out in microreactors, since solids may clog the channel network. Several different approaches have been used to carry out reactions that use solid catalysts. Catalytically-active metals may be immobilized on the inner walls of a reactor or may be placed on miniaturized poles in the reactor channels.[30] Another approach is to load the catalyst on polymer beads in pre-packed reaction cartridges that are placed in the reactor channel.[21,31] In these processes, effective interaction between the phases take place due to a high surface-to-volume ratio which can lead to considerable reaction rate enhancement.

Continuous flow microreactors are particularly suited for liquid-gas reactions, which are generally difficult to perform because of the hazardous nature of reactive gases. The high mass transfer rates promote gas-liquid reactions that are limited by the transport of gas species into the liquid reaction medium in larger vessels.[32] However, reactor design has to incorporate engineering features that allow for the careful control of gas flow in the reactor, as well as the regulation of contact time between gas and liquid, and the separation of the gaseous phase at the end of the reaction.[33] The utility of microreactors for this chemistry has been illustrated for reactions such as fluorination,[34] chlorination,[35] nitration[4] etc.

Important multiphase catalytic processes, such as catalytic hydrogenation and oxidation reactions often suffer from long reaction times due to poor interactions between the different phases. However, recent examples have shown that multiphase reactions can be conducted successfully in flow as well; continuous flow microreactor technology ensures high reaction rates due to an increased surface-to-volume ratio and allows for accurate control of crucial parameters such as temperature and residence time.[36]

The technological scope of the flow microreactor approach has also been tested in the synthesis of natural products. In a recent example, this technology been able to handle multicomponent and multistep operations in order to construct architecturally diverse natural product molecules such as grossamide[37] and oxomaritidine.[38]

Limitations. Continuous flow technology is often superior to batch processing in efficiency and practicability,[3] however, a critical viewing of continuous flow systems is often necessitated by the need to define limitations of such systems. Such limitations include:

Continuous flow reactors often face cost-related issues. The fabrication of chip microreactors requires specialized facilities with fabrication costs running into the thousands of dollars.

These reactors often possess a complex engineering design that requires inclusion of complex heating and mixing modules. Although the laminar flow regime has often been considered a favorable feature due to diffusion-controlled mass transfer[2] it does slow the kinetics of chemical transformations. Also, connecting microreactors to external fluid reservoirs under pressurized conditions is considered a challenging task technically due to potential leakage problems or mechanical stress on the system.[39]

In order to be fully automated, the system design has to incorporate in-line facilities for purification of intermediates or final products: a solution which is both expensive and technically challenging.

Chemical transformations that require solid starting materials or yield solid intermediates and/or products are difficult to carry out, since solids can clog the channels and potentially incapacitate the entire system.

These reactors often face problems associated with different kinetics of reactions and the necessity for different solvents when performing multistep syntheses in the flow-through mode.[1]

Microwave irradiation theory

Microwave irradiation is normally considered the part of the electromagnetic spectrum occurring between infrared and radiofrequency radiation; the wavelengths lie between 0.1 cm and 100 cm and the frequencies between 300 GHz and 300 MHz. Two major applications of microwave emitting devices are telecommunications and heating. Wavelengths between 1–25 cm are used extensively for radar and telecommunication purposes, whereas the heating applications use Industrial, Scientific and Medical (ISM) frequencies which are 27.12 MHz (11.05 m), 915 MHz (37.24 cm) and 2.45 GHz (12.24 cm) respectively. All domestic microwave ovens and dedicated microwave reactors for chemical synthesis use a frequency of 2.45 GHz in order to avoid interference with telecommunications and radar frequencies.

It is known that Gamma Ray and X-Ray photons have sufficient energy to cause excitation of core electrons. Ultraviolet and visible irradiation are also used in photochemical reactions to excite valence electrons. However, by comparing the data in Table 1, it is clear that microwave irradiation cannot induce chemical reactions.[40]

Table 1 – *Radiation photon energies compared to chemical bond energies*[41]

Radiation	Frequency (MHz)	Ouantum Energy (eV)	Bond Type	Bond Energy (eV)
Gamma Rays	$3.0 \cdot 10^{14}$	$1.24 \cdot 10^{6}$	C – C	3.61
X- Rays	$3.0 \cdot 10^{13}$	$1.24 \cdot 10^{5}$	C = C	6.35
Ultraviolet	$1.0 \cdot 10^{9}$	4.1	C – O	3.74
Visible light	$6.0 \cdot 10^{8}$	2.5	C = O	7.71
Infrared light	$3.0 \cdot 10^{6}$	0.012	C – H	4.28
Microwaves	2450	0.0016	O – H	4.80
Radiofrequencies	1	$4.0 \cdot 10^{-9}$	Hydrogen bond Brownian motion	0.04–0.44 0.0017

The microwave photon (calculated by using Planck's law $E = hc/\lambda$) at a frequency of 2.45 GHz carries insufficient energy to cleave chemical bonds.

Microwave-related chemistry relies on the ability of materials to convert microwave irradiation into heat; the "heat generation" mechanism is related to the interaction of the molecules of a given material with microwaves.[42] Microwaves are electromagnetic waves, which consist of an electric wave and a magnetic wave, with the magnetic wave oscillating at a 90° angle to the electric wave. The electric wave has been shown to be the more important in these interactions,[42b,43] although in some instances the magnetic field component has been shown to play a significant role (magnetic field interactions with transition metal oxides).[44]

The main effect derived from the interaction of the electric field component with material molecules is heating. Two main mechanisms[40] are recognized today for this type of interaction: dipolar polarization and ionic conduction.

The *dipolar polarization* mechanism[42] applies only to polar materials and is based on the tendency of the dipoles to follow the inversion of the oscillating electric field (Fig. 4). Molecules, possessing dipole moment, align themselves in the applied electric field in a certain pattern, and as the field oscillates the dipole matrix attempts to retain the induced pattern by realigning itself with the alternating electric field. This generates heat in the process through molecular friction and dielectric loss.[40] The amount of heat generated is proportional to the ability of the applied electric field to generate an optimal phase difference between the orientation of the electric field and that of the dipole matrix. If the phase difference is too large (the dipole matrix has no time to realign under high frequency irradiation) or too small (the dipole matrix re-aligns too quickly under low frequency irradiation), minimal heat is generated. The frequency of 2.45 GHz, used in dedicated microwave equipment, allows the dipole matrix to realign without following the alternating field precisely. The phase difference thus generated causes thermal energy to be gained through molecular friction and collisions, in the form of dielectric heating.

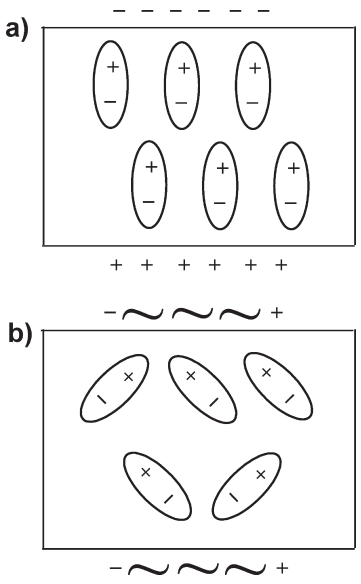


Fig. 4 – *Effects of surrounding electric field on dipole orientation: a) static electric field; b) alternating electric field*

The frequency of microwave irradiation is close to that of the rotational relaxation process, however, it is important to emphasize that the microwave-solvent interaction is not considered a quantum resonance phenomenon. There is no evidence to indicate the involvement of quantized rotational bands; microwave-induced dielectric heating is a collective property involving aggregates of molecules.[40,42,45]

The *ionic conduction* mechanism[42] applies to materials containing charged particles (such as ionic liquids etc). The dissolved charged particles, involved in an oscillatory motion under the influence of an alternating electric field, collide with adjacent molecules, generating heat in the process. The ionic conduction mechanism is considered to be just as efficient as the dipolar polarization mechanism in the heat-generating process.[40]

Microwave-induced dielectric heating

Microwave-induced heating efficiency for different materials is dependent on the dielectric properties of each material. A dielectric material contains either permanent or induced dipoles, such that the material acts as a capacitor when placed in an electric field i.e., the material allows an electrical charge to be stored with no conductivity observed. The polarization of dielectric materials arises from the charge displacement or rotation of dipoles in an electric field. At the molecular level, polarization involves either the distortion of the distribution of the electron cloud within a molecule, or the physical rotation of molecular dipoles,[46] which are particularly important in the mechanism of microwave dielectric heating. The permittivity of a material ε is a physical property which describes the polarizability of that material, whereas the dielectric constant or relative permittivity ε' is the permittivity of the material relative to that of free space.

Dielectric polarization depends primarily on the ability of dipoles to reorient in an applied electric field. In a liquid phase, molecules rotate so rapidly that they are able to respond to field oscillations occurring at a frequency of 10^6 times per second. However, when the material is exposed to electromagnetic radiation, the electric field component is reversed much more rapidly and the dipoles are no longer able to keep up with the oscillating field, at frequencies of 10^9 times per second or higher, thus creating a phase difference. The reorientation of the dipoles and displacement of charge is equivalent to an electric current, known as the Maxwell displacement current,[42b] which is at 90° phase difference with regard to the oscillating electric field (Fig. 5a).

In an ideal scenario, where there is no phase difference between the orientation of the molecules and the variations of the alternating electric field, the Maxwell displacement current is zero (Fig. 5b), and therefore no heating occurs. If the frequency of the electromagnetic radiation reaches that of the microwave, the rotations of the polar molecules in the liquid begin to lag behind the electric field oscillations, and as a result, a phase difference δ is generated (Fig. 5c). This phase displacement contains a

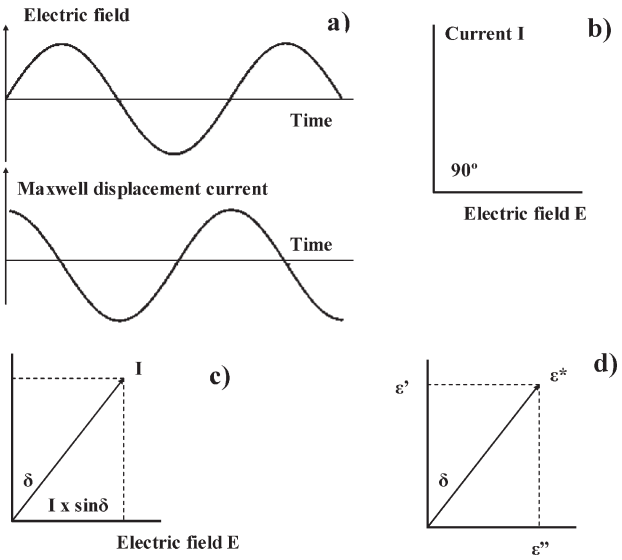


Fig. 5 – *a) Applied sinusoidal electric field (top) and out-of-phase induced Maxwell displacement current (bottom)[42b] b) phase diagram for an ideal dielectric where the energy is transmitted without loss c) phase diagram showing a phase displacement δ and generation of Maxwell displacement current (I · sin δ) d) diagram illustrating the relationship between ε*, ε' and ε"; tan δ = ε"/ ε'*

component ($I \cdot \sin \delta$) aligned with the electric field, and so resistive heating occurs in the irradiated material (formally described as dielectric loss). The total relative permittivity is characterized by the following expression

$$\varepsilon^* = \varepsilon' - j\,\varepsilon'' \tag{1}$$

(ε' is the dielectric constant and ε'' is the loss factor that reflects the conductance of the material).[42b]

As shown in Fig. 5d

$$\tan \delta = \varepsilon''/\varepsilon' \tag{2}$$

is defined as the loss tangent or energy dissipation factor, whose values provide a convenient parameter for comparing the efficiency of conversion of microwave energy into thermal energy. A material with a high $\tan \delta$ is required for an efficient absorption of microwaves. A general classification based on tan δ values can identify materials as high ($\tan \delta > 0.5$), medium ($\tan \delta$ 0.1–0.5) and low ($\tan \delta < 0.1$) microwave absorbers.[40] The loss tangents for several organic solvents are shown in Table 2.[47]

Materials without a permanent dipole moment have no relaxation process in the microwave region, and are therefore considered microwave-transparent. However, the overall dielectric properties of the reaction medium can change due to the polar nature of reagents and/or catalysts, allowing sufficient heating by microwave irradiation. Alternatively, polar additives[48a] (ionic liquids or alcohols) or passive

Table 2 – *Loss tangent values for some common solvents used in organic synthesis*[47]

Solvent	Tan δ	Solvent	Tan δ	Solvent	Tan δ
Ethylene glycol	1.350	2-butanol	0.447	Chloroform	0.091
Ethanol	0.941	1,2-dichlorobenzene	0.280	Acetonitrile	0.062
DMSO	0.825	1-Me -2-pyrrolidone	0.275	Ethyl acetate	0.059
2-propanol	0.799	Acetic acid	0.174	Acetone	0.054
Formic acid	0.722	N,N – DMF	0.161	THF	0.047
Methanol	0.659	1,2-dichloroethane	0.127	Dichloromethane	0.042
Nitrobenzene	0.589	Water	0.123	Toluene	0.040
1-butanol	0.571	Chlorobenzene	0.101	Hexane	0.020

heating elements[48b] (chemically inert, strong microwave-absorbing materials such as SiC) can be included in the reaction medium in order to increase the microwave-absorbing capacity of the medium. The energy transfer between the polar molecules, capable of coupling with microwaves, and the non-polar molecules is rapid,[43a] and therefore provides an effective mechanism for heating non-polar solvents.

The penetration depth is another important consideration in microwave theory, and is calculated based on the standardized value of **1/*e***, that represents the point where the microwave power has been reduced to 36.8 % of the initial value.[41] Penetration depth is inversely proportional to *tan* δ; for this reason materials with high *tan* δ values have low penetration depths for microwave irradiation as it is absorbed in the outer layers of materials. The inner part of the material will then be heated by a conventional convection mechanism (Fig. 6a).

The average relaxation time is also an important parameter in determining the suitability of materials for efficient heating under microwave irradiation. The operating frequency of 2.45 GHz corresponds to a relaxation time of 65 ps (10^{-12} s); therefore all organic molecules with relaxation profiles that incorporate a relaxation time of 65 ps are able to couple efficiently with microwave irradiation at that frequency. This conclusion has been supported by experimental observations for a range of polar organic solvents that satisfy this condition.[42] The average relaxation time is temperature-dependent, as it decreases with an increase of temperature; this directly affects the loss tangent which increases with temperature. On this basis, some organic solvents that appear to be unsuitable candidates for dielectric heating due to long relaxation times at room temperature can begin heating very rapidly as the temperature increases;[45a] therefore, temperature increase will bring a loss tangent increase, thus enabling the solvent to convert more of the microwave energy into thermal energy. The resulting phenomenon is described as thermal runaway.[49] This situation can potentially compromise process safety; however, if the necessary precautions are taken, the temperature of the reaction medium can rise well above conventional boiling temperature (superheating), leading to substantially enhanced reaction rates.[45a]

A somewhat different heating mechanism, defined as *charge space polarization*, has been described for materials possessing free conducting electrons, such as semiconductors or metals.[42b,43a, 50] The microwave irradiation can induce a flow of electrons on the surface that can heat the material via a resistance heating mechanism.[51] The electrons move under a microwave-induced magnetic field, which then induces eddy currents, causing heat in a material due to its resistivity. These eddy currents create a secondary magnetic field opposite to the excitation field, generating a repelling force that opposes the original microwave. This means most of the microwave energy is reflected off the surface of the metallic layer.

Microwave heating or conventional heating?

The traditional conductive heating of organic processes by external heat sources still plays a dominant role in organic chemistry. This process relies on the thermal conductivity of the reaction vessel materials, as well as convection currents within the vessel (Fig. 6a).[40] The conductive heating is generally considered an inefficient method for transferring energy into the reaction; the temperature of the heat source and that of the vessel walls must necessarily be higher than the reaction medium, increasing the possibility of a temperature gradient being developed within the reaction medium from the vessel wall into the reaction bulk and this can lead to local overheating. In contrast, microwave heating is an irradiation process that raises

the temperature of the vessel volume simultaneously, provided that the reaction vessels are not large (Fig. 6b).[40] The reaction vessel itself is not affected thermally by microwave irradiation since it is made of microwave transparent materials, thus an inverted thermal gradient exists from the reaction bulk into the vessel wall, resulting in greatly reduced hot wall effects.[40]

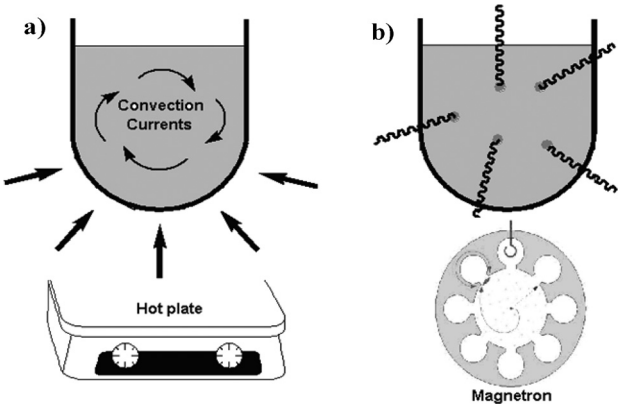


Fig. 6 – *Schematic presentation of conventional (a) and microwave heating (b)*

Several other advantages displayed by microwave dielectric heating over conventional thermal heating are known:

The introduction of microwave energy into a reaction medium can lead to much higher heating rates than those achieved conventionally. Heating rates of 2–4 °C s^{-1} can be achieved readily for common organic solvents; such heating rates would require furnaces heated over 1000 °C using conventional heating methods.[45,52]

The microwave-based technology allows for the remote introduction of microwave energy into the reactor; there is no direct contact between the energy source and the reaction vessel. Not only does it lead to faster heating rates, it also generates a significantly different temperature profile for the reaction (Fig. 7). At higher temperatures, the rate of chemical reactions using microwave irradiation is much higher and the reaction times shorter, so consequently the products need remain a relatively shorter time in the process vessel. The "hot wall" effects are also eliminated as the temperature of the reactor walls is lower than that of the inner liquid volume. There are assumptions in the literature that temperature-sensitive reagents or catalysts may rapidly deteriorate at the hot vessel surface under conventional heating conditions. The elimination of such "hot wall" effects when heating using a microwave can increase the lifetime of catalysts and lead to better conversions. However, the lack of dedicated studies in this area to date makes it hard to quantify such effects.[40]

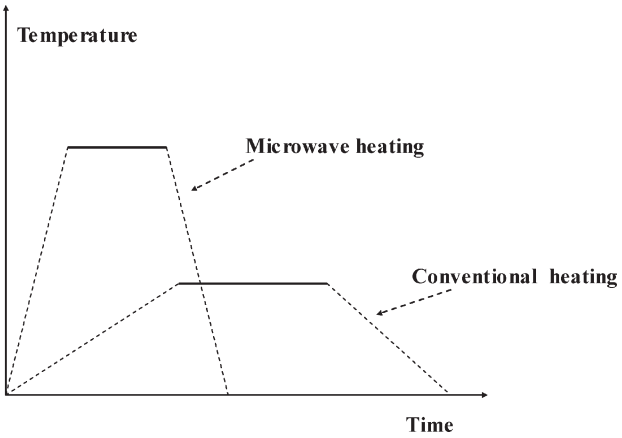


Fig. 7 – *The temperature-time profiles for conventional and microwave dielectric heating (using similar power setting)*

Microwave dielectric heating is a suitable method for accelerating chemical reactions under pressurized vessel conditions. It is possible to increase the temperature of a reaction in common organic solvents over 100 °C above the conventional boiling point of the solvent using microwave irradiation[43a,53] Studies have shown that although the enthalpy of vaporization is the same under microwave and conventional heating conditions,[54] microwave-heated liquids boil at temperatures above their conventional boiling points at atmospheric pressure, mainly due to the remotely introduced mass-heating mechanism that eliminates the role of nucleation points on reactor's surface.[40,49] For example, the microwave dielectric heating of ethanol (bp = 79 °C) in a closed vessel at 164 °C leads to a pressure of 12 atm. Heating at this temperature will lead to an enhancement of about 10^3 in the reaction rate, as calculated by the Arrhenius kinetic equation below.

$$\boldsymbol{K} = \boldsymbol{A}\ e^{(-\boldsymbol{E}/\boldsymbol{RT})} \qquad (3)$$

(***K*** is the reaction rate coefficient, ***R*** is the gas constant, ***A*** is the Arrhenius pre-exponential factor and ***E*** is the activation energy of the reaction).

Components of a reaction medium can have different interactions with microwave irradiation; therefore, selective heating of such a medium can be achieved. This phenomenon can be exploited in several applications, described briefly below.

Heterogeneous reactions involving metal powders and gases. The metal particles interact very strongly with microwaves, whereas gases are transparent to microwave irradiation. Under microwave irradiation conditions, the metal particles begin to heat up rapidly, causing a rapid reaction between

the metal and gas components. Formation of macroscopic hot spots (with temperatures of 100–150 °C above bulk temperature) have been shown to have a pronounced effect on reaction rates.[55a,56a] This strategy has proven effective in the preparation of oxides, halides, sulphides, etc. of transition metals.[55b,c]

Heterogeneous reactions in liquid solvents. Although precautions have to be taken in order to prevent electrical arcing, such as the use of low-microwave settings, high-boiling solvents and small well-dispersed metal particles,[45a] the formation of "hot spots" due to the powerful coupling of microwave irradiation with metal nanoparticles or heterogeneous materials can accelerate greatly reaction rates.[55] It is presumed that the temperature of the catalyst's surface is significantly higher than the bulk reaction medium,[41] and these localized "hot spots" can have an important impact on the outcome of the process. It has been shown that a very small number of superheated areas is sufficient to induce a substantial rate enhancement (2 % of hot spots can increase reaction yield by up to 60 %), even if their effects on the averaged process temperatures cannot be detected.[45b,57a] Several successful strategies have also been reported detailing synthetic protocols that involve reagents on solid supports such as silica and alumina.[58] As an example, the selective heating of Pd/C catalyst was utilized in the hydrogenation of diphenylbutadiene **1** (Scheme 1). Microwave irradiation of this heterogeneous transformation gave complete conversion after 5 minutes, whereas the same reaction performed under conventional heating proceeded with only 55 % conversion. The use of a fiber optic sensor ensured accurate temperature monitoring in both cases.[57b]

Homogeneous reactions containing polar additives. The scope of microwave dielectric heating can be extended to solvents, normally transparent to microwaves, that contain polar additives.[59a,60] The energy of such polar molecules, known as "molecular radiators", is assumed to dissipate extremely fast into cooler surroundings[42,45] because it has been shown that it is not possible to store the microwave energy in a specific part of the polar molecule by selectively activating the polar functional groups.[42b,61] The inclusion of only 2 % methanol in benzene (a microwave-transparent solvent) ensures rapid heating of the solvent mixture under microwave irradiation, which couples effectively only with the methanol molecules. However, the rate of energy transfer through molecular collisions is so fast that the benzene molecules are also heated rapidly.[45a]

Microwave effects

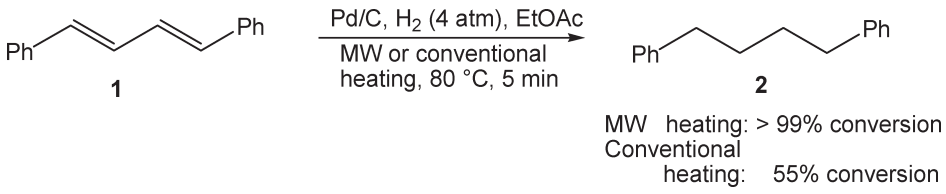
It is now generally accepted that the major contribution of microwave irradiation technology to chemical synthesis is the generation of thermal effects, that are responsible for the dramatic rate enhancements.[59] Such rate enhancement can be rationalized by purely thermal/kinetic considerations[42a] on the basis of the Arrhenius kinetic law (eq. 3). The pre-exponential factor $\boldsymbol{A}$ and activation energy $\boldsymbol{E}$ remain unchanged for the purpose of the thermal effects.[40]

In addition, microwave effects caused by the uniqueness of the microwave dielectric heating mechanisms are also recognized. These effects, known as "specific microwave effects", are capable of accelerating the process kinetics in a manner that cannot be duplicated by conventional heating. However, these effects essentially remain thermal effects.[59a]

Non-thermal effects. In addition to the thermal effects mentioned above, there are believed to be unique effects associated with microwave irradiation that cannot be explained by purely thermal considerations. These non-thermal, or athermal effects result from the direct interaction of the electric field with specific molecules in the reaction medium. This affects the orientation of polar molecules, which affects either the pre-exponential factor ($\boldsymbol{A}$) or the activation energy ($\boldsymbol{E}$) in eq. 3.

It has been argued that the application of a microwave field to dielectric materials induces rapid rotation of molecular dipoles, which increases the probability of contact between molecules and then collision efficiency. The pre-exponential factor $\boldsymbol{A}$, which represents the probability of efficient molecular collisions, is described by the following expression:

$$\boldsymbol{A} = \gamma\lambda^2\Gamma \qquad (4)$$

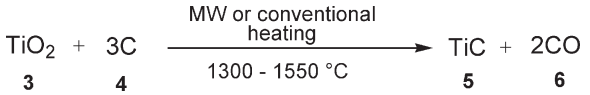


Scheme 1

(γ is a geometric factor which includes the number of nearest-neighbour jump sites, λ the distance between adjacent lattice planes – the jump distance, and Γ the jump frequency, which is directly proportional to the vibration frequency of atoms at the reaction interface).

An increase in molecular mobility under microwave irradiation increases the pre-exponential factor ***A***, therefore increasing the rate of reaction.[58]

A typical example is provided in the microwave synthesis of titanium carbide **5** as shown in Scheme 2.



Scheme 2

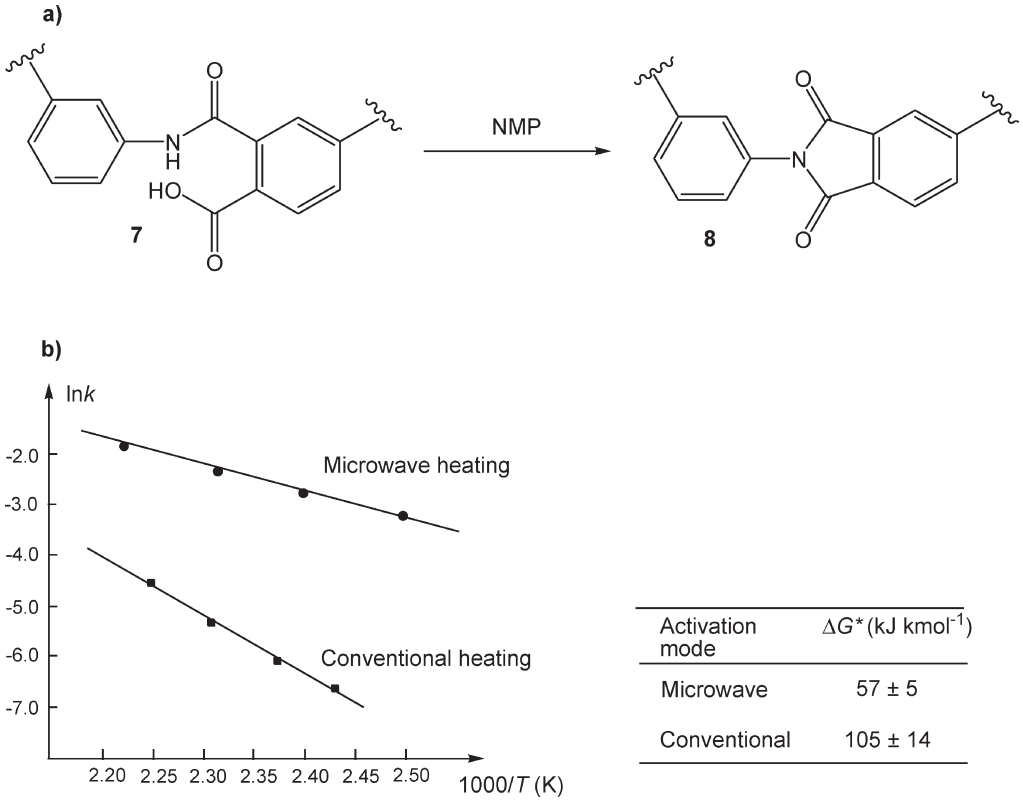
The reaction rate using microwave irradiation was 3.4 times higher than the rate found with conventional heating, [62a] which could be explained by the pre-exponential factor being 3.4 times higher during microwave heating with no change in activation energy.

The decrease in the free activation energy ΔG^* is considered another major non-thermal effect of microwave irradiation. Considering that ΔG^* consists of an enthalpy and an entropy term

$$\Delta G^* = \Delta H^* - T\Delta S^* \quad (5)$$

it has been predicted that microwave irradiation generates a more "ordered" environment as a consequence of dipolar polarization; as a result, the entropy term $T\Delta S^*$ would increase in a microwave-irradiated medium, in turn decreasing ΔG^*.[58,62c,63] Experimental evidence for this assumption has been provided in the microwave-assisted intramolecular imide formation of polyamic acid **7**[63c] (Fig. 8). The ΔG^* factor is clearly reduced in the case of microwave heating and that has been attributed to a non-thermal microwave effect. It has been argued that when the polarity of reaction intermediates or transition state species is increased on going from starting materials to the transition state, the stabilization of the transition state species is more effective than that of the starting materials, resulting in an enhancement of reactivity by a decrease in the activation energy[40,58,62c,64] (Fig. 9).

Similarly, it has been argued that a non-thermal microwave effect should be more pronounced for reactions that occur via a late transition state with high activation energy. The transition state in this case is more prone to developing increased polarity, when compared to a reaction that occurs via an



Activation mode	ΔG^* (kJ kmol^{-1})
Microwave	57 ± 5
Conventional	105 ± 14

Fig. 8 – *a) Intramolecular imide formation of polyamic acid b) Arrhenius plots for the imide formation via microwave irradiation and conventional heating*

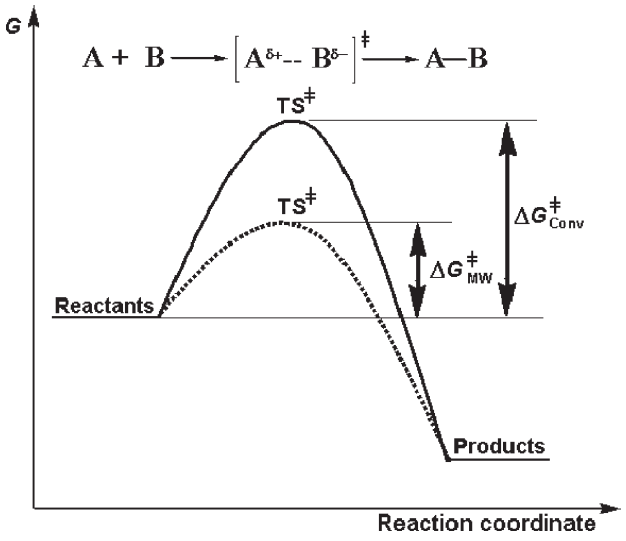


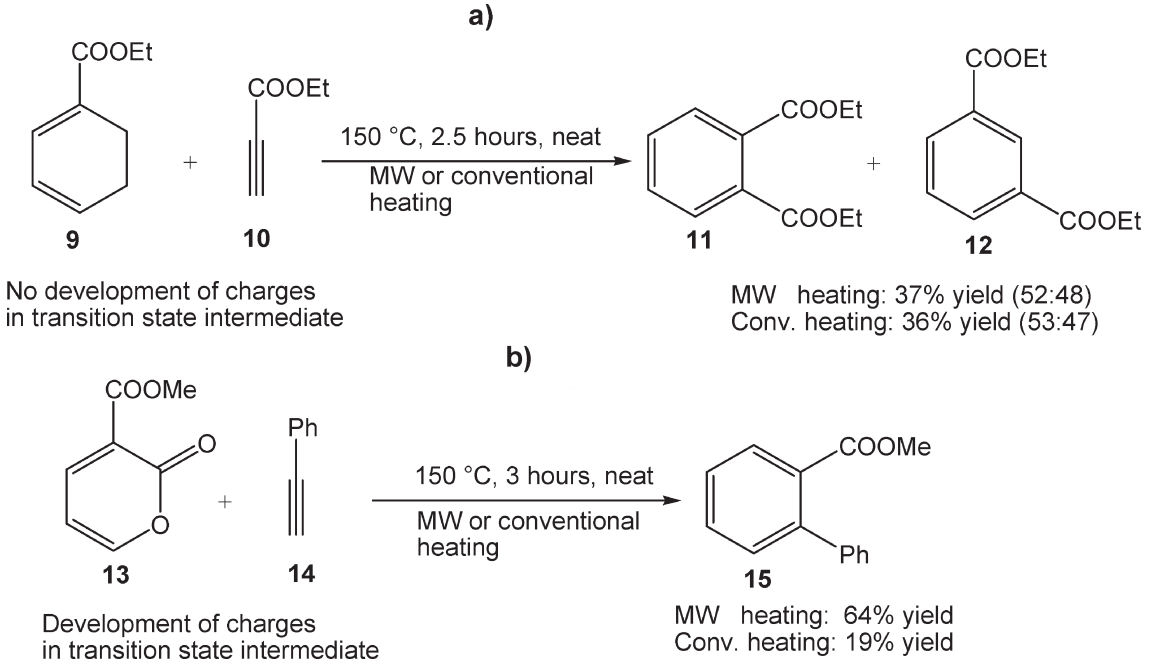
Fig. 9 – *Proposed stabilization of reaction intermediate species under microwave irradiation via lowering of transition state energy*

early transition state with only a small difference in polarity from the starting materials.[40,58,62c,64]

A typical example to support this effect has been provided in the form of two irreversible Diels-Alder cycloadditions, performed over an extended time interval under both conventional heating and microwave irradiation conditions in order to balance any uneven thermal effects (Scheme 3).[65]

Detailed *ab initio* calculations of the two reactions revealed a concerted isopolar mechanism for the first reaction in Scheme 3a with no charges and therefore no polarity developed in the transition state. Performed under microwave irradiation conditions, the yield of this reaction was the same when heated by microwave or conventional heating. On the contrary, the second reaction in Scheme 3b, for which the *ab initio* calculations revealed a significant charge development in the transition state, performed significantly better under microwave irradiation conditions. According to the authors, the difference in the reaction yield for the second reaction is a clear indication of the existence of non-thermal effects that stabilize the polar transition state, thus lowering the activation energy of the microwave-assisted reaction pathway. This consequence does not exist in the first reaction due to the lack of electrostatic interactions of electric field with the transition state.[65] However, a re-investigation of the second Diels-Alder reaction in Scheme 3b, using a fiber-optic sensor technology in order to obtain accurate temperature readings, revealed no differences in yield between oil-bath and microwave irradiation conditions. This result was attributed to thermal effects playing the same role in both heating methods (conducted at an accurately-recorded temperature), rather than invoking a special non-thermal microwave effect.[66]

The above example, as well as other arguments that support the existence of non-thermal microwave effects are still the subject of considerable debate and controversy.[67] It is the opinion of some of the leading experts in this field that the concept of non-thermal microwave effects has to be critically re-examined, and further evidence presented in order to reach a definite conclusion about the existence of such effects.[59]



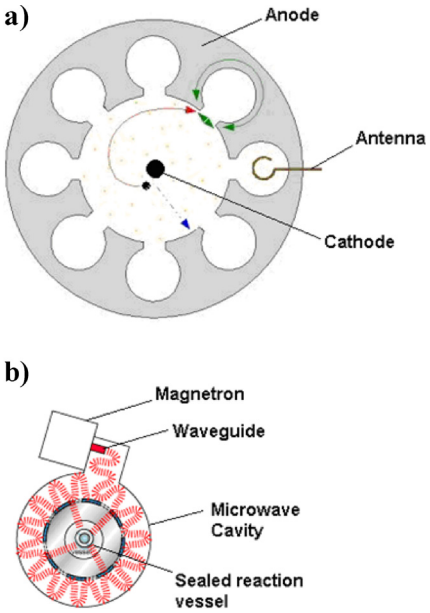
Scheme 3

Microwave technology

The practice in the late1980s and early 1990s of conducting microwave-assisted synthesis in domestic microwave ovens has been abandoned today due to safety concerns.[40] Heating organic solvents in open vessels can lead to explosions induced by electric arcing and the lack of real-time pressure monitoring can lead to vessel rupture. Furthermore, synthetic protocols often suffer from reproducibility problems due to the inhomogeneous nature of pulsed microwave irradiation.

Today, domestic microwave ovens have been replaced by dedicated microwave applicators in most research laboratories, which feature built-in temperature and pressure sensors and software that enables on-line temperature or pressure control. The main components of a dedicated microwave reactor are the magnetron (microwave generator), the waveguide (a transmission line that guides the microwave irradiation into the microwave cavity), and the cavity itself, which accommodates the reaction vessel. The magnetron (Fig. 10a), consists of a cylindrical cathode in the centre of a circular chamber, surrounded by an anode block possessing small cavities and the system is operated under vacuum. The electrons emitted from the cathode due to a high-voltage electric field are deflected by a magnetic field applied parallel to the cathode axis, which causes electrons to spiral outwardly instead of gravitating straight into the anode. Sweeping inside the cavity, these electrons induce a high-frequency electromagnetic field, a portion of which is extracted by a short antenna connected to the waveguide. This in turn directs the induced microwave field into the instrument cavity and the microwave-generating efficiency of these devices is in the 65–70 % range (Fig. 10b).

Early microwave applicators were multi-mode instruments, where the microwaves were reflected by the walls over a large cavity (similar to a domestic microwave oven) and interacted with the sample in a random manner. Although the samples were rotated inside the cavity, the density of the field around individual samples was low, despite the high microwave power being used (1000–1600 W),

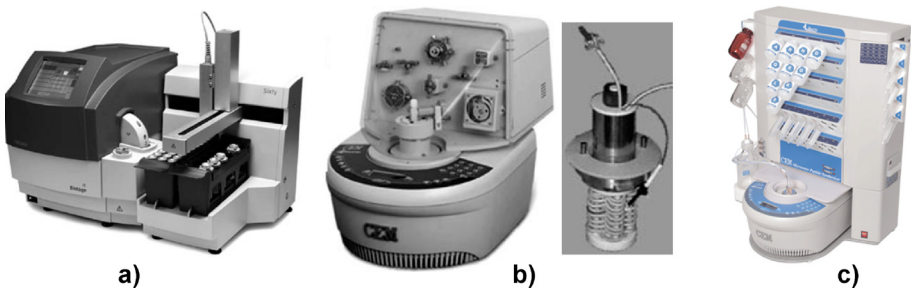


F i g . 1 0 – *a) Cross-sectional view of a magnetron depicting the pathway of electrons under the applied magnetic field b) cross-sectional view of a single-mode microwave cavity*

resulting in poor performance for small-scale reactions. This was addressed largely in modern multi-mode instruments that can accommodate multiple reaction vessels in the presence of a homogeneous field.

The more recent single-mode microwave applicators also generate a homogeneous energy field ofhigh density around a smaller cavity (Fig. 10b) despite relatively low power levels (typically 300–400 W). The homogeneity of the microwave field ensures sustained equipment performance and process reproducibility. The temperature on the surface of reaction vessels can be measured by a remote, built-in IR sensor that does not always represent the actual temperature of the reaction bulk. The more expensive fiber-optic temperature probes that can be immersed directly into the reaction vessel are mainly available in larger, multi-mode microwave instruments.

The steady performance of single-mode microwave instruments has been the driving force behind



F i g . 1 1 – *Single-mode microwave instruments a) Biotage Initiator 60, equipped with a rack and robotic arm b) CEM Voyager (flow instrument) and its flow cell c) CEM liberty peptide synthesizer*

their design development. A number of instruments are now commercially available and in use in research laboratories, offering, among other features, flow-through systems and solid phase peptide synthesis (Fig. 11).[40]

Microwave-assisted continuous flow technique as technological solution to batch microwave scale-up problems

Reported initially in 1986[68] the advantages of microwave-assisted organic synthesis (MAOS) as an enabling technology[1] has led to its use in a wide variety of applications.[40,59,69] The publication of more than 3500 manuscripts in this field[59b] is a strong indicator of the impact that this technique has had on synthetic organic methodology. MAOS protocols have been exploited successfully in drug discovery,[70] total synthesis,[71] biochemical processes,[72] polymer synthesis,[73] nanotechnology[74] and materials science.[75]

The main technical limitation for single-mode microwave devices is the small cavity size, which generally allows the use of vessels no larger than 1–5.0 mL; for that reason, the majority of microwave-assisted reactions published to date have been conducted on a scale of less than 1.0 g.[59,76] However, in order to fulfill the demands of pharmaceutical and industrial applications, there is a need to develop larger-scale microwave-assisted protocols that can ultimately provide products on a multi-gram or even kilogram scale.

The limited penetration depth of microwave irradiation is perhaps the biggest challenge in scaling-up microwave-promoted protocols since it limits the size of the reaction vessel that can be used. Depending on the dielectric properties of particular solvents, the maximum penetration depth of 2.45 GHz microwaves is on the order of a few centimeters.[64f] Therefore, microwave power density inside a large reaction volume may be negligible when compared to the surface density, thus invoking a convection heating mechanism (Fig. 6a) as opposed to microwave dielectric heating.[76] Consequently, as the size of the reaction vessel increases, it becomes more difficult to heat the larger reaction volume, requiring additional microwave power. However, as the capacity of the microwave reactor increases to 5000 W power levels, the standard air-cooling in magnetrons is replaced by more sophisticated oil-based cooling, a factor that introduces more complexity and cost into the system.[76,77] This consideration, the low energy efficiency of converting electricity into microwave power (65–70 %), and safety concerns such as potential rupturing of large pressurized reactors, make the microwave approach less attractive for large-scale processing.[59b,76] It is the opinion of several experts[1,3,59b,76,77,78] in this field that the solution to this problem is the combination of two "enabling" technologies: microwave heating and flow processing, in the form of microwave-assisted continuous flow technology.

In addition to advantages associated with continuous flow methodology, the microwave-assisted, continuous flow approach is an appealing alternative to scaling-up MAOS protocols for several reasons:

It solves the scalability issues without the need for further optimization, by using the scale-out and/or numbering-up approach. Once the reaction conditions are optimized for the continuous flow protocol, substantial amounts of product can be obtained by operating the system for a long time interval or running several reactors in parallel under identical conditions.[78b]

It eliminates the safety concerns associated with powerful microwave heating of large pressurized reactors. These concerns are negligible due to lower reaction volumes, smaller instrument cavities and small-scale reactors.

It bypasses the physical limitations of batch MW instruments such as penetration depth and power constraints. Moreover, energy transmission is higher in smaller cavities; low power magnetrons are suitable and therefore the process is more economical.

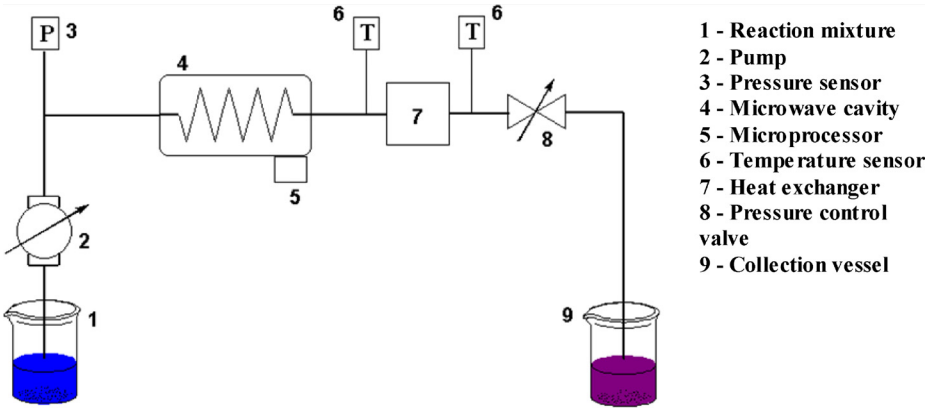
It offers the possibility of full system automation, resulting in a considerable reduction of processing time and labour.[76]

One problem associated with the continuous flow approach is the limited "residence time" that any one plug of a reaction mixture experiences under microwave irradiation. Further, processing heterogeneous mixtures in flow poses its own hurdles. The former problem can be dealt with largely by using coil-based designs for flow reactors that can increase the residence time. As for handling slurries and solid reagents, peristaltic pumps have been demonstrated to be effective in this regard.[40,76]

Microwave-assisted fluidic systems and their applications

Microscale fluidic systems. The numerous microwave-assisted, continuous flow systems in operation today exemplify the successful application of the two "enabling" technologies in conjunction, microwave heating and flow processing.

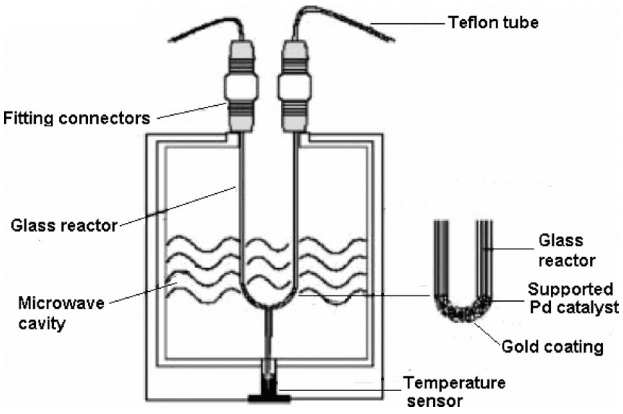
Strauss *et al.*[79] were the first to develop and utilize a microwave-assisted continuous flow quartz reactor (Fig. 12) that provided accurate pressure and temperature control. The reactor was operational at 200 °C, incorporating a backpressure of



F i g . 1 2 – *Schematic design of the continuous flow system developed by Strauss*

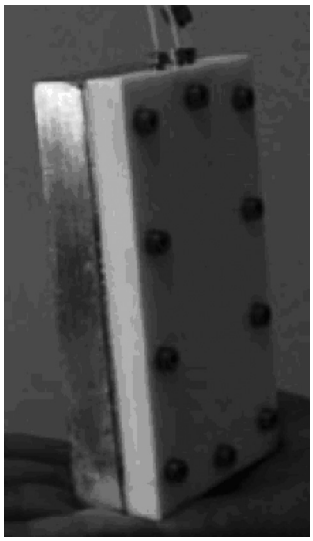
1418.55 kPa. In order to prove the reliability of the microwave-assisted continuous flow concept, over 20 reactions, including nucleophilic substitutions, Diels-Alder cycloadditions, esterifications, base- and acid-catalyzed hydrolyses, isomerizations, decarboxylations, eliminations etc., were performed at temperatures up to 100 °C higher than the boiling point of the solvents at standard conditions, which accelerated the reactions by as much as three orders of magnitude.

A custom-built glass-chip reactor was designed by Haswell *et al.* (Fig. 13) that incorporated an immobilized Pd catalyst (Pd/Al_2O_3), which was re-used several times in a heterogeneous Suzuki-Miyaura cross-coupling protocol (Scheme 4).[80] Coating the outside of the catalyst channel with a strongly microwave-absorbent gold layer proved effective in generating the necessary heat for the reaction.

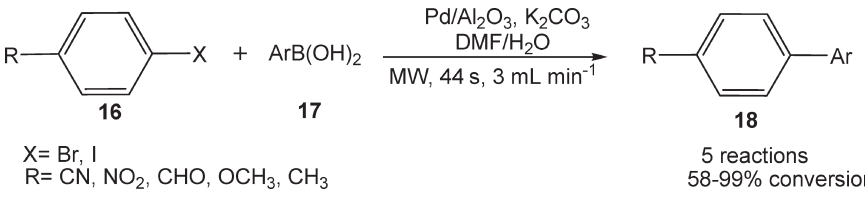


F i g . 1 3 – *Continuous flow reactor built by Haswell*

Jachuck *et al.* have reported the use of an isothermal continuous flow microreactor (Fig. 14) in the oxidation reaction of benzyl alcohol **19** by $Fe(NO_3)_3 \cdot 9H_2O$ (Scheme 5). The sealed polytetrafluoroethylene (PTFE) microreactor consists of reaction zone microchannels (270 μL) that interface with heat exchange microchannels (600 μL). The reactor is placed in a microwave cavity, and the heat generated in the reaction zone is absorbed by water flowing inside the heat exchanger. This approach allowed the system to operate under isothermal conditions where the reaction temperature fluctuated by less than 0.3 °C during the process.[81]



F i g . 1 4 – *Isothermal continuous flow reactor built by Jachuck*



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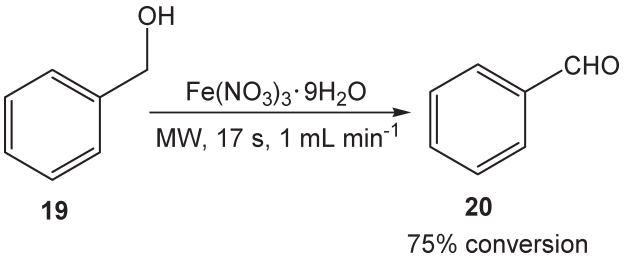


Scheme 5

Ley *et al*. employed successfully a U-shaped continuous flow reactor (Fig. 15) in Suzuki-Miyaura cross-couplings (Scheme 6), using a polyurea microencapsulated Pd catalyst (Pd EnCat).[82] Applying pulsed microwave irradiation followed by short gas-jet cooling extended the life of the catalyst to the point that cross-coupling products were synthesized without the need for catalyst regeneration.

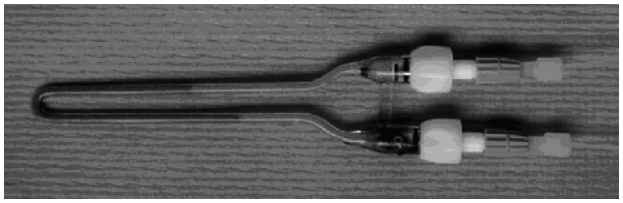
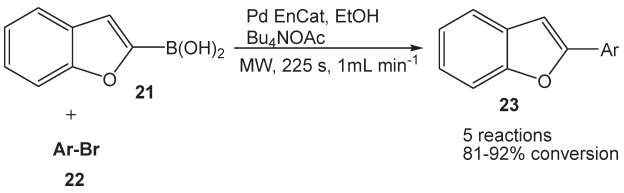


Fig. 15 – *U-shaped tubular microreactor built by Ley filled with Pd EnCat catalyst*



Scheme 6

Kappe *et al*. used a rather unique reactor design (Fig. 16)[83] to conduct a Dimroth rearrangement of 1,3-thiazines **24** into substituted dihydropyrimidines **25** (Scheme 7). The reactor was designed by fitting a standard 10 mL Pyrex tube with a custom-built steel head. The inner space of the reactor was filled with 2 mm-sized glass beads in order to create microchannels that would increase the residence time of the reaction mixture in the microwave heating zone. The system was placed in the cavity of a CEM Voyager (Fig. 11b), and the reaction mixture was pumped from the bottom of the reaction vessel and forced to move upwards through the glass beads.

Using a reactor design similar to the one shown in Fig. 16, although their reactor was filled with sand instead of glass beads, Bagley *et al*. successfully conducted the Bohlmann-Rahtz synthesis of

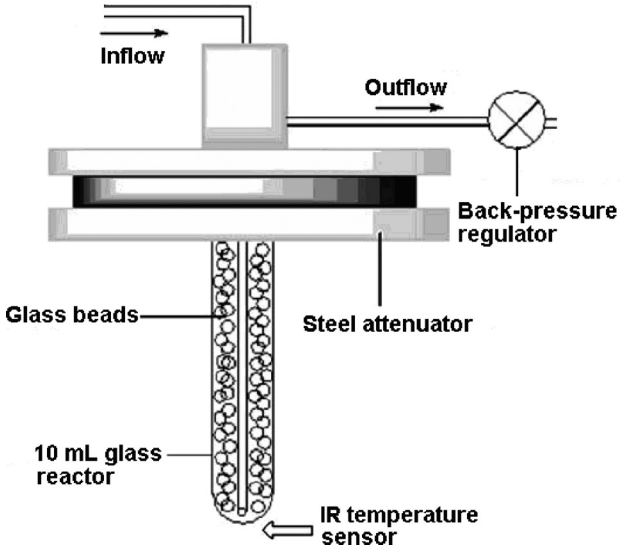
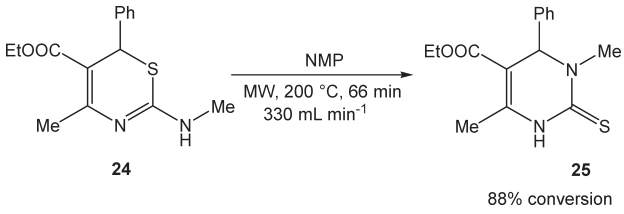


Fig. 16 – *Continuous flow reactor designed by Kappe*



Scheme 7

pyridines by cyclodehydration of the corresponding aminodienones.[84]

Kirschning *et al.* also developed a unique continuous flow reactor[85] composed of composite polymer materials in the form of rings, supported by a steel frame (Fig. 17a). Immobilization of the Pd^0 catalyst on the inner reactor surface was carried out by pumping a Pd solution through the ring wall then reducing Pd with a sodium borohydride solution that led to the formation of Pd nanoclusters on the reactor surface (Fig. 17b). The palladated reactor was placed in the cavity of a CEM Voyager (Fig. 11b), and utilized in several synthetic applications, including a Heck cross-coupling reaction (Scheme 8).

Another custom-made flow reactor was reported by Wilson *et al.*[86] The flow cell, consisting of a glass coil encased in a protective glass sheath (Fig. 18), was designed to process reaction mixtures on a multi-gram scale (4.0 mL total flow cell volume). Inserted into the cavity of a single-mode microwave reactor (Emrys Synthesizer, similar to the one shown in Fig. 11a), the system was operated either in open- or closed-loop mode. Temperature measurements were performed by the internal IR sensor of the instrument, and pressure fluctuations were prevented by the use of a backpressure regulator mounted at the outlet tubing. A variety of

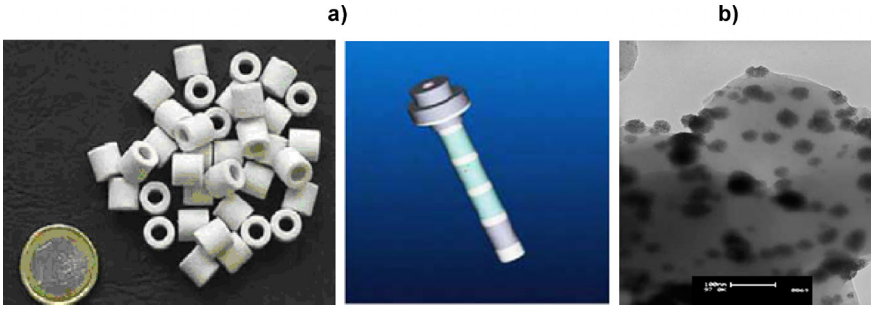
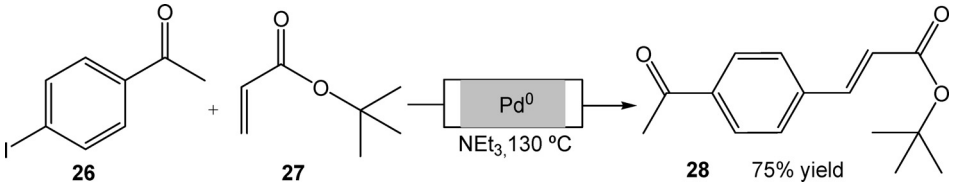


Fig. 17 – *a) The composite ring reactor designed by Kirschning b) SEM image of Pd nanoclusters on the reactor surface (scale shown is 100 nm)*



Scheme 8

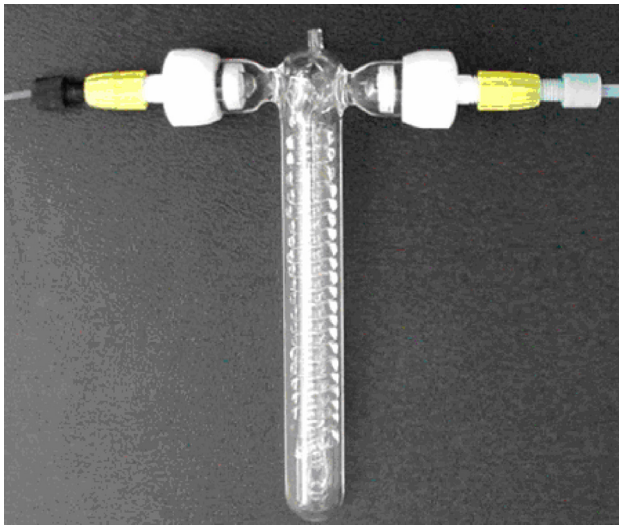
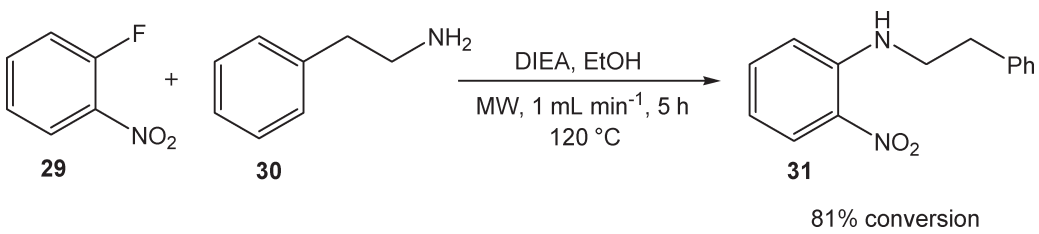


Fig. 18 – *The coiled glass reactor designed by Wilson*

Suzuki-Miyaura cross-coupling reactions, esterifications and nucleophilic aromatic substitutions (the latter are shown in Scheme 9), were efficiently performed under microwave irradiation conditions.

The stop-flow protocol. The Stop-Flow protocol is a microwave-assisted technique developed recently[59b] in order to facilitate microwave processing on a gram scale; the technique is mainly suited to process heterogeneous mixtures that can be incompatible with other fluidic systems. The standard equipment for this technique is the CEM Voyager used in conjunction with the flow cell, as shown in Fig. 13b. The reagent mixtures are pumped into the vessel using peristaltic pumps capable of processing slurries of reagents. The system is sealed and all processing occurs under pressurized conditions; afterwards the processed mixture is discharged from the vessel automatically and the system is ready to receive the next batch.

Using the stop-flow approach, Leadbeater *et al.* successfully scaled-up the Suzuki-Miyaura coupling of phenyl boronic acid and 4-bromoacetophenone as well as the Heck cross-coupling of styrene with 4-bromoanisole.[87] The optimized reaction conditions on a 1.0 mmol scale for both protocols were introduced readily to a stop-flow strategy on a 10 mmol scale using the CEM Voyager instrument. A process cycle of 10 consecutive runs provided, respectively, 18.5 g the Suzuki-Miyaura product (95 % yield, 50 min total time) and 14.9 g of the Heck product (71 % yield, 200 min total time).



Scheme 9

In a similar manner, Maes *et al.* performed several Pd-catalyzed amination reactions of 4-chloroanisole with morpholine using the CEM Voyager reactor.[88] The stop-flow approach allowed for the smooth transition of optimized reaction conditions, from a 1.0 mmol to a 20 mmol scale. A process cycle of 12 consecutive runs provided an overall yield of 76 % for the amination product (190 minutes).

These examples, as well as several others[42,59b] detailing the utility of microwave assisted continuous flow technology for larger scale processes in semi-pilot and pilot plant industrial applications, indicate the great potential of the microwave-assisted continuous flow approach in combinatorial chemistry and other synthetic applications.

State of the Art: Using Metals-in-Microwave approach for extremely fast synthesis in the MACOS system

Introduced in 2005 by Organ *et al.*, Microwave-Assisted Continuous Flow Organic Synthesis (MACOS) system is a custom-made continuous flow reactor that can operate in conjunction with a single-mode microwave instrument. This system was initially used in several flowed reactions[78] including Suzuki-Miyaura cross-couplings, Wittig reactions, nucleophilic aromatic substitutions etc., and at a later time in more complex transformations such as synthesis of tetrasubstituted furans and quinolinones.[89] MACOS is however, better known for the implementation of Metals-in-Microwave approach.[90]

This approach was developed to deal with a sharp problem arising from irradiating reactions in flow format: typically, small fractions of microwave power are converted into heat during the irradiation process resulting in low efficiency of microwave energy transfer to the reaction medium. When considering the usually brief "residence time" (the time that a reaction plug spends inside the flow reactor, ranging from several seconds to several minutes) and the limited number of microwave-absorbing organic solvents, the temperatures achieved inside the flow reactor are often low and the heat thus generated is insufficient to drive reactions to completion. Attempts to use powerful microwave instruments do not truly address this problem because such undertaking does not improve the efficiency of microwave-solvent interactions.

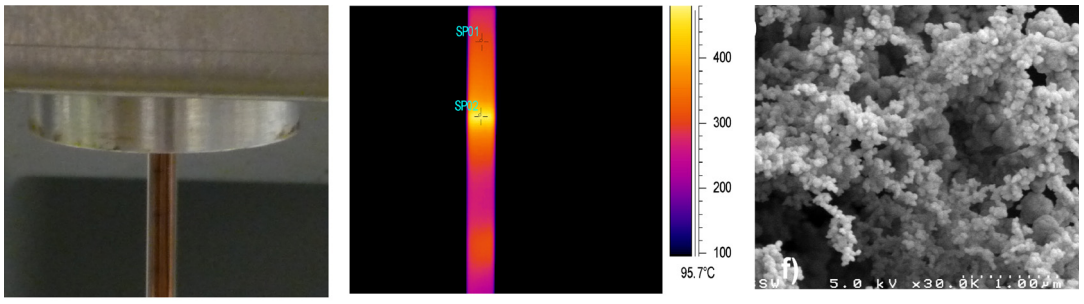
Metals-in-Microwave as a state-of-the-art solution to this problem, focused on changing the conceptual basis on which the previous microwave-assisted, continuous flow technology was founded. Instead of focusing on microwave-reaction medium interactions, this new approach focused on the microwave-reaction vessel interactions in order to instantaneously generate and maintain sufficient process temperatures during the brief residence time.

Based on carefully designed protocols, metal-coated microreactors were prepared (Fig. 19a) in order to serve as reaction vessels under microwave irradiation; the thickness of metal films, as an integral part of these microreactors was maintained between 2–3 μm. There were two advantages that this technological approach brought compared to other microwave-assisted flow systems in use today:

1. Due to an enormous amount of heat generated on the metal film (Fig. 19b) using a *minimal power setting* of 25–35 W the reaction kinetics were tremendously accelerated.

2. The thin metal films, besides serving as heating elements, were also catalytically active under microwave irradiation, due to their porous morphology containing metal nanoclusters, which extended into the reaction medium (Fig. 19c).

This approach was used in a number of diverse syntheses in flow, in which the reaction time was significantly shortened to 2–4 min, down from 48–72 hours typically needed for conventional synthesis.

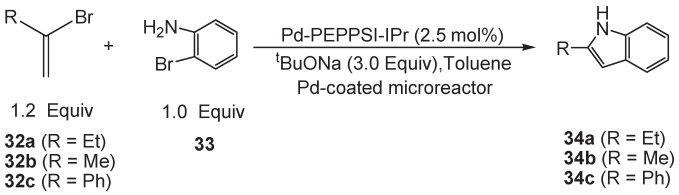


a) **b)** **c)**

Fig. 19 – *a) Metal-coated microreactor (ID = 1700 μm) residing inside the irradiation chamber of a dedicated microwave instrument b) thermal image of a metal-coated microreactor under microwave irradiation conditions. The image represents a partial reactor length of 3 cm (total length is 12 cm) inside the microwave chamber. Spo1 (352 °C) and Spo2 (474 °C) are the temperature readings at different points on the surface of the microreactor c) Scanning Electron Microscopy (SEM) image of developed Pd nanoclusters, obtained at x 30,000 magnification.*

Pd-coated microreactors were used initially to conduct extremely fast Suzuki-Miyaura and Heck cross-coupling reactions.[90f] Both reactions were complete within a 2-minute interval, being conducted in the absence of an external Pd catalyst as Pd^0 nanoclusters (of thin Pd film lining the inside of flow microreactors) provided the catalysis for both processes.

Other applications of Pd-coated microreactors include fast synthesis of Diels-Alder cycloadducts[90d] in one of the first ever examples of this methodology being conducted in flow and flow synthesis of substituted indoles **34** using an elegant 2-step (amination/Heck) cascade protocol for the reaction between bromoalkenes **32** and 2-bromoanilines **33** (Scheme 10).



Scheme 10

Inclusion of an external catalyst (Pd-PEPPSI-IPr) in this case presents a very interesting example of a homogeneous Pd catalyst working in tandem with heterogeneous Pd nanoclusters to catalyze this complex methodology.

Gold-coated microreactors were also used in a number of mechanistically-diverse, gold-catalysed organic transformations such as alkyne hydrosilylations and benzannulation reactions.

Firstly, the hydrosilylation of terminal alkynes was conducted in flow utilizing catalysis by thin Au films that proved very efficient[90c] in one of the first ever protocols to replace catalysis by benchmark catalysts such as Karsted's catalyst and Speier's catalyst with that of Au^0 thin films. This protocol not only tolerated a wide moiety of substrates, the *E* selectivity for the terminal silane product was always greater than 90 percent.

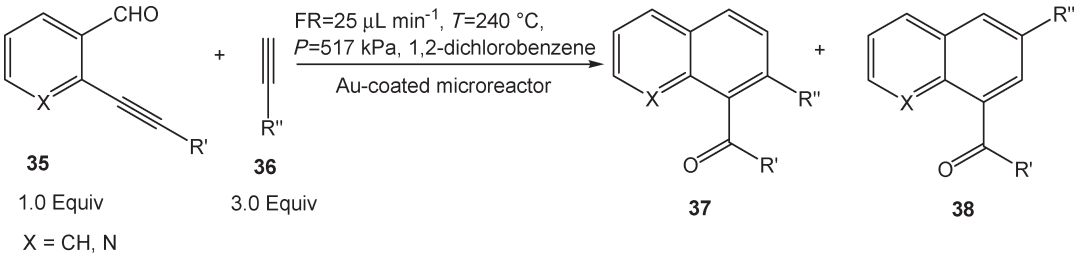
In mechanistically complex benzannulation reactions, alkynyl-substituted benzaldehyde derivatives **35** were flowed together with alkynes **36** in gold-coated microreactors in order to generate substituted naphthyl ketones **37** and **38**.[90b,g] Again, very good yields were obtained for a wide variety of products (Scheme 11).

In another original application, Cu-coated microreactors were used in the complex synthesis of propargyl amines **42** via a three-component reaction protocol.[90a,g] The thin Cu films provided the catalysis for the condensation process involving aldehydes **39**, amines **40** and alkynes **41** while the microwave irradiation of Cu films generated the necessary temperature for the process (Scheme 12).

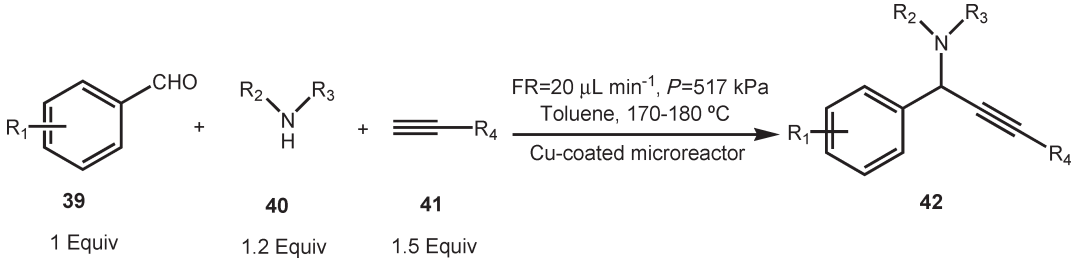
Ultrasonication as irradiation technique

Ultrasonication is another method that can be used for the remote transfer of energy into reaction medium including flowed processes. Initially used in the processing of liquids and slurries, ultrasonication offers great potential by improving the mixing and possibly reducing the reaction time in various applications.

The major phenomenon that may arise from the propagation of ultrasonic waves into a liquid is



Scheme 11



Scheme 12

called acoustic cavitation. This term refers to the formation, growth, oscillations and powerful collapse of gas bubbles into a liquid. During the rarefaction period of the sound wave, the local pressure decreases sufficiently below the vapor pressure and this generates gas bubbles by overcoming the static pressure and the cohesive forces. Bubbles will then oscillate, grow, and then collapse violently.[91a,b] The ensuing effects such as impinging liquid jets and strong hydrodynamic shear-forces are used for the deagglomeration of micrometer-size materials and mixing of reactants.

Another important fact is that the collapse of a vaporous cavity is more violent than a gas-filled one because when vapour is turned into liquid, there is no residual gas to cushion the collapse. Experimental results have shown that the impact of a collapsing cavitation bubble could last 10^{-7} s, reaching a local pressure up to 193 MPa.[91c] This could explain several phenomena involved in chemistry, biology, engineering etc., including why acoustic cavitation is believed to be the major effect of ultrasonic heat transfer enhancement: a bubble implosion near a solid-liquid interface can reduce thermal resistance by disrupting thermal and velocity boundary layers, and creating microturbulence. [91d]

Probably the main chemical application of ultrasonication technique today has been the reaction of transesterification of oils into biodiesel. Several protocols have been developed for this process in batch and flow-mode; however, flow applications of this process remain largely experimental. [91e,f]

Conclusions and perspective

The examples given in this review show that the departure from classical research platforms is necessary for rapid, continuous production of chemicals with minimum purification. As technological issues become an increasing part of daily chemical research, process and medicinal chemists alike are combining new methodologies and enabling technologies to create new synthetic platforms for conducting synthesis, including single as well as multistep catalytic transformations. Whatever chemists require, synthesis of few milligrams of a compound in drug discovery, or the preparation of kilogram quantities for clinical research, continuous flow processes can deliver for them.

Furthermore, continuous flow processes are considered a universal tool to allow the quick transition from laboratory research platforms to industrial research development, thus eliminating the time and material-consuming optimization from small-scale reactions to a full production scale. While the merits of flow synthesis, such as the ability to monitor reaction in real time and make instantaneous changes to reaction conditions, have long been recognized, the impact of this technology in the chemical sector is still small, primarily because of poor reaction kinetics during the brief time that reagents are flowed together in a flow reactor.

One of the greatest technical advancements for increasing the rate of chemical transformations is microwave heating, which, being considered today as an important enabling technology, has a major impact on many areas of preparative science and particularly on the area of synthetic chemistry. It is notable that this impact has probably been greater than many other technological developments; today numerous laboratories have commercial instruments, particularly as microwaves have genuinely become an acceptable and routinely applied method for synthesis.

After more than twenty years of applying microwave irradiation to small-scale batch synthesis, various microwave synthesizers today, ranging from single-mode to larger multimode instruments can perform the efficient multigram synthesis of materials without re-optimization steps. However, the scaling-up of microwave-assisted reactions leading to multi-kilogram products is necessary to extend the current scope of microwave-assisted synthesis. Because of the physical limitations of batch reactors, the most viable alternative toward the process and production scale-up will be microwave-assisted flow systems, mostly due to the unique ability of microwave irradiation to generate heat in-situ without the need and the cost of complex heat-exchange modules normally needed for conventionally heated flow reactors.

One of the main limitations of applying microwave-assisted flow chemistry lies in the handling of heterogeneous mixtures. More often than not, important synthetic organic reaction protocols involve insoluble reagents or catalysts that can not be substituted in all cases for soluble alternatives. The usually brief “residence time” (the time that a reaction plug spends inside the flow reactor, ranging from several seconds to several minutes) is another limitation as the temperatures achieved inside the flow reactor are often low and the heat thus generated is insufficient to drive reactions to completion. With respect to building larger flow reactors, many scientists in the field are questioning the use of costly microwave technology for heating, unless the clear benefits of this technique are evident.

From this perspective, we think that the Metals-in-Microwave approach offers a comfortable solution to all these problems. Not only does it solves the “thermal” and “non-thermal” heating effects on the reaction medium, it removes the uncertainty of

"penetration depth" of microwaves from the reaction medium, as the needed heat is now generated on the flow reactor and then conveniently conveyed inside to the reaction medium. This application clears the road ahead for the application of large-size flow reactors allowing the production of multi-kg quantities of product.

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