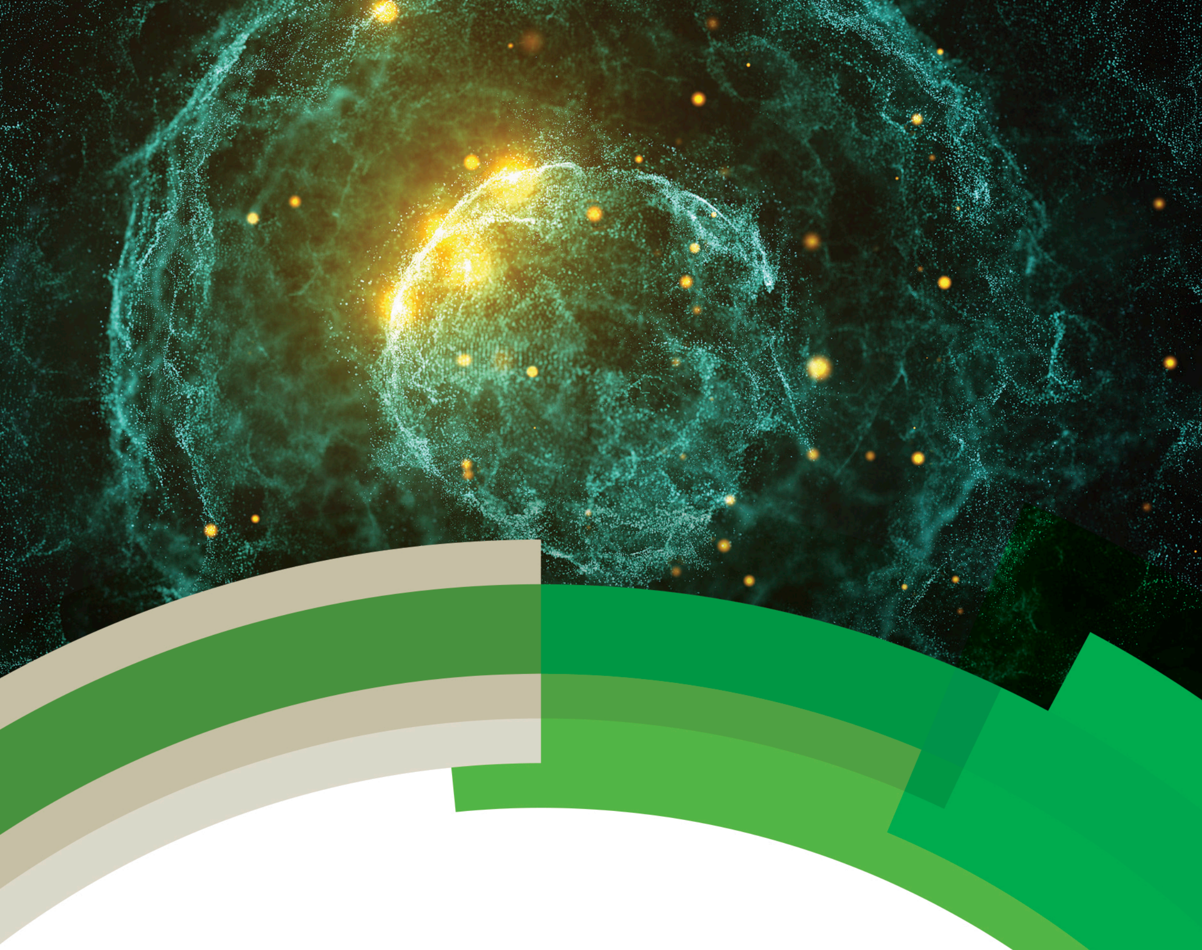

RSC Green Chemistry

# Alternative Energy Sources for Green Chemistry

Edited by Georgios Stefanidis
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# Alternative Energy Sources for Green Chemistry

# RSC Green Chemistry

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# *Preface*

The use of alternative energy sources, such as alternating electromagnetic fields at different operating frequencies, acoustic and hydrodynamic cavitation, magnetic fields, plasma and high gravity fields in chemical processing are some of the key approaches of process intensification to enable greener chemical processes and sustainable chemical manufacturing. Some of these technologies have already been commercialized for certain niches. However, the breadth of industrial implementation will depend on the production and operating costs, robustness, flexibility and safety. The progress in the development of alternative energy source-based processes in various disciplines of chemicals and materials manufacturing reported in the open and patent literature gives confidence that the above criteria will be met. In this book, world leading researchers demonstrate the potential of several alternative energy transfer technologies to enable greener chemical processing in different industries through attainment of resource- and energy-efficient reaction and separation processes. Rather than being comprehensive in a specific application area or technology, the book aims at highlighting the broad impact that the aforementioned technologies may have in various application areas.

In *Chapter 1*, the impressive impact of microwave irradiation in the field of organic chemistry is discussed. The ability of microwaves to deliver energy rapidly and selectively to those components of the reaction mixture that are strongly microwave-dissipative, whether a reagent, a catalyst or a solvent, can enable greener chemistry in terms of decreased process times, higher energy efficiency and processing under solvent-free or green solvent conditions.

*Chapter 2* presents different strategies for the application of microwaves to extract high value chemicals from plant matter. The volumetric heating of microwaves allows for their direct interaction with the plant matrix, intracellular water heating and vaporization, overpressure inside the plant matrix

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and, eventually, more effective cell wall rupture. This effect combined with rapid heating of a polar solvent may result in significantly faster extraction kinetics and improved materials efficiency, in terms of using less solvent and producing higher yields, compared to conventional heating.

*Chapter 3* places the focus on the potential use of microwave technology for low temperature (and thus energy efficient) decomposition of biomass and biomass constituents (cellulose, lignin, hemicellulose) to high value chemicals. Although most of the relevant work in this area has been carried out with lab-scale microwave equipment, microwave process upscaling possibilities are also discussed.

*Chapter 4* concludes the first part of the book devoted to microwave technology. The chapter discusses design aspects of different microwave applicator concepts suitable for chemical processing. The discussion extends beyond standard off-the-shelf monomode and multimode cavities to advanced non-cavity applicator types that can be used for efficient and tailored microwave activation of chemical reactors. In this context, an important suggestion put forward is that well-controlled and optimized microwave-assisted chemical processing requires transition from the current processing paradigm of chemical reactors activated by standing wave fields, as in conventional resonant cavity-based equipment, to chemical reactors activated by travelling electromagnetic fields.

*Chapter 5* gives an overview of applications of cavitational (ultrasonic and hydrodynamic) reactors to different reactive and separation processes and the associated benefits in terms of greener and intensified processing. Faster chemical syntheses, improved yields and selectivities and safer operation at ambient conditions, mostly due to radical formation and mass transfer intensification, are some of the benefits expected in reactive processes. Cavitation, in synergy with oxidants, can also enable effective decontamination of wastewater. Regarding separation processes, application of ultrasound to crystallization can affect the crystal size distribution and product polymorphism. Further, ultrasound can enable shorter extraction processes with improved recovery at milder temperatures and lower amounts of solvents, compared to conventional extraction. Ultrasound can also improve adsorbents' activity and enhance adsorptives' desorption. Finally, it has been reported that ultrasound can improve vapor–liquid mass transfer and possibly break azeotropes in distillation processes.

*Chapter 6* and 7 are concerned with magnetic fields. *Chapter 6* presents applications of magnetic fields to separation processes in the chemical and biotechnology industries. In particular, an overview of mechanical magnetic separations, magnetic separations involving magnetic solids with non-tailored surfaces and magnetic separations involving tailored and functionalized magnetic solids is presented.

*Chapter 7* introduces magnetic field-assisted mixing concepts. In most chemical reactive processes, the mixing rate determines the spatiotemporal distribution of the temperature and concentration fields, which in turn determine the reaction rates and product yield and distribution. Chapter 7 highlights intensification of mixing of fluids using magnetic fields in the context of ferrohydrodynamics and magnetohydrodynamics.

*Chapter 8* discusses past achievements and future trends in the field of heterogeneous photocatalysis for solar fuel synthesis and pollutant degradation. The chapter is organized in two parts. First, novel developments in catalyst design are presented with a special focus on the application of MOFs. Second, the current state-of-the-art and challenges in the design of photocatalytic reactors are discussed including alternative options for the light source to enhance efficiency.

*Chapter 9* reviews the most important reactor design concepts, which form building blocks for photocatalytic reactor designs aimed at wastewater treatment. The two popular performance indicators used in the literature to assess photocatalytic reactors are the photonic efficiency and the pseudo-first order rate constant. The former does not account for the total electricity consumption; the latter is process volume dependent. In this work, a new benchmark is introduced, the photocatalytic space-time yield, to address these limitations. The new benchmark has been demonstrated by comparing three different photocatalytic reactor designs, namely a microreactor, a membrane reactor and a parallel plate reactor. This comparative study points at a new direction in the research field of photocatalytic wastewater treatment. This is the efficient illumination of existing reactor geometries, instead of seeking new reactor geometries.

Plasma reactors are seen as an enabling technology for decentralized chemicals and fuels production and efficient utilization of renewable electricity generation from solar energy or wind. In this vein, *Chapter 10* summarizes and evaluates plasma-assisted nitrogen fixation reactions (NO, $NH_3$ and HCN synthesis) in different types of plasma reactors. Despite the current limitation in scalability of plasma reactors, non-thermal plasma processing in certain operating windows in combination with solid catalysts has the potential to enable energy efficient chemistries.

The last two chapters of the book give an overview of applications of high gravity fields to green intensified chemical processing through intensification of mixing, heat and mass transfer and the enablement of ideal flow patterns and short contact times. In this context, *Chapter 11* reviews the application of spinning disc reactors and rotating packed beds, including some novel recent versions of the latter, on polymerization, reactive-precipitation, catalytic and enzymatic transformation and adsorption processes. *Chapter 12* introduces the concept of rotating fluidized beds in static vortex chambers. The hydrodynamic aspects and design characteristics of the vortex chambers are discussed in detail based on experiments and CFD simulations. The technology can intensify various processes, including low temperature pyrolysis and gasification of biomass, and particle drying and coating, when compared to conventional fluidized beds.

Georgios D. Stefanidis
Andrzej I. Stankiewicz

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CHAPTER 1

# Microwave-Assisted Green Organic Synthesis

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## 1.1 Introduction

Due to the ability of some compounds (solids or liquids) to transform electromagnetic energy into heat, microwave (MW) radiation has been widely employed in chemistry as an energy source. Microwave irradiation has several advantages over conventional heating and these include homogeneous and rapid heating (deep internal heating), spectacular accelerations in reactions as a result of the heating rate (which frequently cannot be reproduced by classical heating) and selective heating. Consequently, microwave-assisted organic reactions produce high yields and lower quantities of side-products, purification of products is easier and, in some cases, selectivity is modified. Indeed, new reactions and conditions that cannot be achieved by conventional heating can be performed using microwaves. The use of microwaves in organic synthesis has been reviewed in numerous recent books, book chapters,[1] and reviews.[2]

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Absorption and transmission of microwave energy is completely different from conventional heating (Table 1.1). Conventional heating is a superficial heating process and the energy is transferred from the surface to the bulk by convection and conduction. This is an inefficient mode of heating because the surface is at a higher temperature than the bulk and the vessel must be overheated to achieve the desired temperature. In contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the bulk reaction mixture. The magnitude of the energy transfer depends on the dielectric properties of the molecules. As a guide, compounds with high dielectric constants tend to absorb microwave energy whereas less polar substances and highly ordered crystalline materials are poor absorbers. In this way, absorption of the radiation and heating can be very selective.

Considering the twelve principles of Green Chemistry reported by Anastas and Warner (Table 1.2),[3] the use of microwaves may be applicable to principle 6 (increased energy efficiency).

It has been reported that energy efficiency is higher with microwaves than with conventional heating.[4] Clark described an 85-fold reduction in energy demand on switching from an oil bath to a microwave reactor for a Suzuki reaction.[5] However, some reports consider that the relative "greenness" of microwave-assisted transformations is a complex issue in which numerous different factors must be considered. Firstly, the efficiency of the magnetron is low, with 65% conversion of electrical energy into electromagnetic radiation.

**Table 1.1** Characteristics of microwave and conventional heating.

| Microwave heating | Conventional heating |
|---|---|
| Energetic coupling | Conduction/convection |
| Coupling at the molecular level | Superficial heating |
| Rapid | Slow |
| Volumetric | Superficial |
| Selective (dependent upon the properties of the material) | Non-selective (independent of the properties of the material) |

**Table 1.2** The twelve principles of Green Chemistry[3]

1. Prevent waste
2. Maximize atom economy
3. Design less hazardous chemical syntheses
4. Design safer chemicals and products
5. Use safer solvents and reaction conditions
6. Increase energy efficiency
7. Use renewable feedstocks
8. Avoid chemical derivatives
9. Use catalysts, not stoichiometric reagents
10. Design chemicals and products to degrade after use
11. Analyze in real time to prevent pollution
12. Minimize the potential for accidents

Secondly, transformation of the electromagnetic radiation into heat could be low in apolar systems. The authors consider that it is highly questionable whether microwaves as a heating source should be labelled as being green, based on energy efficiency considerations.[6,7] Similarly, Ondrushka *et al.* reported energy efficiency data for a Suzuki–Miyaura reaction carried out under solvent-free conditions and determined that ball milling was more efficient than microwave irradiation.[8] However, Hessel *et al.* carried out a complete cost analysis on a production plant and they considered that integrated microwave heating and microflow processing led to a cost-efficient system on using a micropacked-bed reactor in comparison to wall-coated microreactor (Figure 1.1).[9]

Regardless of the considerations outlined above, it is clear that microwave irradiation is more efficient when using a substrate with a high loss tangent ($\tan\delta$), *i.e.*, a good microwave absorber that can easily transform microwave energy into heat.

In this chapter, we will review the applications of microwave irradiation related to Green Chemistry. In this regard, we will consider reactions that are performed under solvent-free conditions where radiation is absorbed

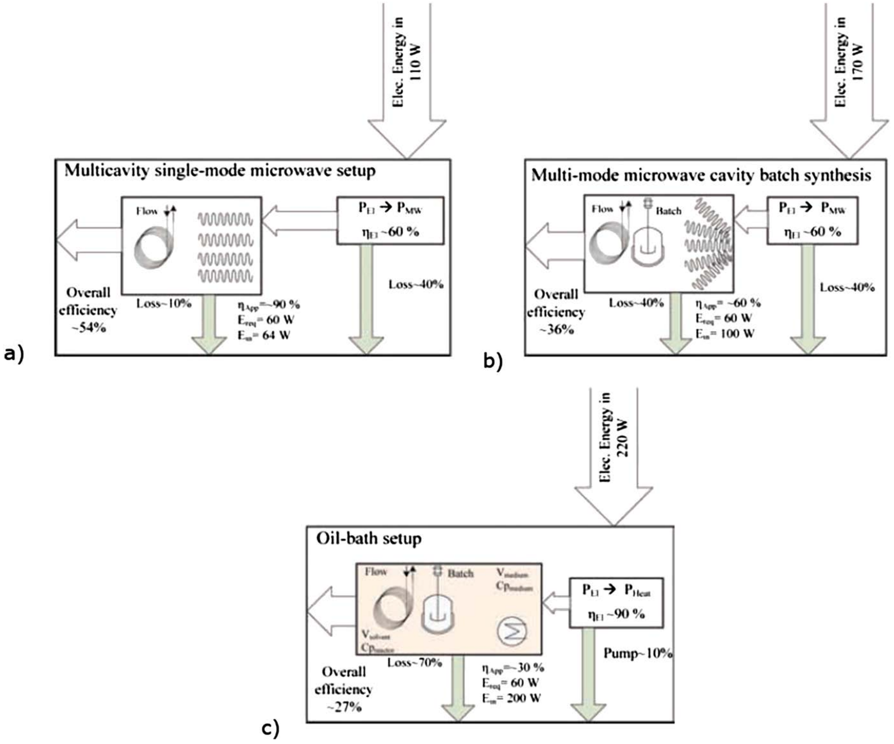


**Figure 1.1** Energy flow diagrams for (a) single-mode, (b) multimode microwave and (c) oil-bath heating. Reproduced from ref. 9 with permission.

directly by the reagents and, as a consequence, energy is not diffused in the solvent. The use of neoteric and green solvents that couple efficiently with microwaves will also be discussed. The synergic use of microwave irradiation with other non-conventional energy sources will not be considered in this chapter.

## 1.2 Solvent-Free Reactions

Although microwave irradiation is a safe source of heating, uncontrolled reaction conditions involving volatile reactants and/or solvents at high pressure may result in undesirable results. This problem has been addressed and organic syntheses have been made more sustainable processes through the use of open-vessel solvent-free microwave conditions.[10]

The absence of organic solvents in reactions leads to a clean, efficient and economical technology; safety is increased significantly, the work-up is simplified considerably, costs are reduced, larger amounts of reactants can be employed, the reactivity is enhanced and, in some cases, the selectivity is modified without dilution. In summary, the absence of solvent in conjunction with the high yields and short reaction times that are characteristic of microwave-assisted processes make these procedures very attractive for sustainable synthesis.

In solvent-free conditions, the radiation is directly absorbed by the substrates and not by the solvents, thus increasing the benefits of microwave irradiation. Energy savings are increased and the effects on yield and selectivity are more marked.

Loupy classified solvent-free microwave-assisted processes into three types:[10c] (i) reactions between neat reactants, needing at least one liquid polar molecule, where the radiation is absorbed directly by the reagents; (ii) reactions between supported reagents in dry media by impregnation of compounds on alumina, silica or clays; and (iii) phase transfer catalysis (PTC) conditions in the absence of organic solvent, with a liquid reagent acting both as a reactant and an organic phase.

In 1993, Loupy reported that potassium acetate can be alkylated in the absence of solvent in a domestic oven using equivalent amounts of salt and alkylating agent in the presence of Aliquat 336 (10% mol) (Scheme 1.1).[11] Yields are practically quantitative within 1–2 min regardless of the chain length, the nature of the halide leaving group and the scale (up to 500 mmol).

Quinolines are known not only for their important biological activities but also for the formation of conjugated molecules and polymers that combine enhanced electronic or nonlinear optical properties with good mechanical

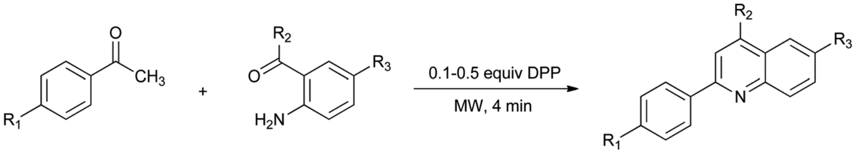
$$CH_3COO^-K^+ + R\text{-}X \xrightarrow[\text{MW}]{\text{Aliquat 336}} CH_3COOR + K^+X^-$$

**Scheme 1.1** Alkylation of potassium acetate under microwave irradiation in solvent-free conditions.

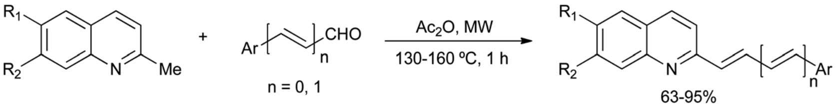
properties. Kwon described the preparation of a mini-library of 12 quinoline derivatives by Friedlander coupling condensation between an acetophenone and a 2-aminoacetophenone in the presence of diphenylphosphate (0.1–0.5 equiv.) within 4 min under microwave irradiation in the absence of solvent (Scheme 1.2).[12] This procedure afforded product yields of up to 85%, whereas the yield obtained with classical heating under similar conditions did not exceed 24%.

Styrylquinolines are valuable derivatives as imaging agents for β-amyloid plaques on human brain sections in Alzheimer patients. Menéndez reported a microwave-assisted solvent-free synthesis of 2-styrylquinolines by condensation of 2-methylquinolines with benzaldehydes or cinnamaldehydes in the presence of acetic anhydride (Scheme 1.3).[13]

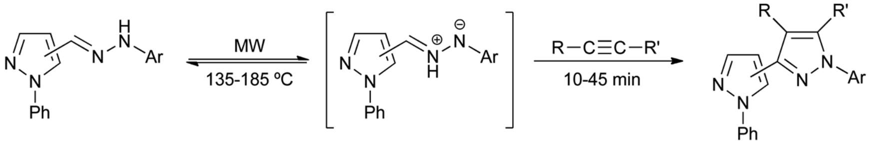
Thermal hydrazone/azomethine imine isomerization usually requires long reaction times (several hours or days) under reflux in high-boiling solvents (*e.g.* xylenes). However, this reaction can be easily promoted by microwave irradiation in the absence of solvent, as can the subsequent 1,3-dipolar cycloaddition with electron-deficient dipolarophiles. Thus, the use of pyrazolyl hydrazones led to valuable products such as bipyrazoles within a few minutes in 30–84% yields (Scheme 1.4).[14] The application of classical heating led to considerably lower yields and, indeed, several dipolarophiles did not react at all.



**Scheme 1.2** Preparation of quinoline derivatives under microwave irradiation in the absence of solvent.



**Scheme 1.3** Synthesis of 2-styrylquinolines under microwave irradiation in solvent-free conditions.



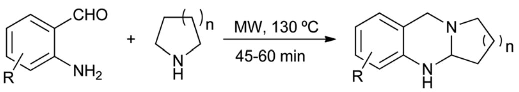
**Scheme 1.4** Preparation of bipyrazoles by microwave-induced hydrazone/azomethine imine isomerization in solvent-free conditions.

In 2008 Varma described the preparation of ring-fused aminals through microwave-assisted α-amination of nitrogen heterocycles in a high-yielding process that was solvent- and catalyst-free (Scheme 1.5).[15]

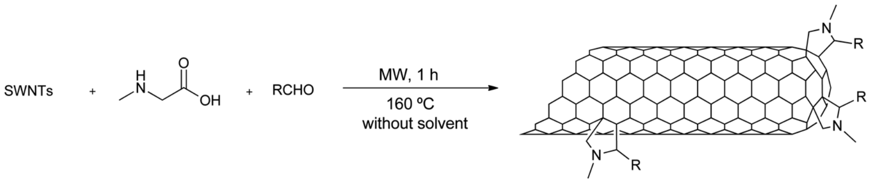
In the absence of solvents, carbon nanoforms (fullerenes, carbon nanotubes, graphene, *etc.*) absorb microwave radiation directly and it is possible to take full advantage of the strong microwave absorption characteristics of these structures. Very high temperatures are obtained in a few seconds, thus providing extremely time-efficient reactions and making new transformations possible. In 2002 Prato reported the azomethine ylide cycloaddition reaction on carbon nanotubes (CNTs).[16] This process required large amounts of DMF to disperse the CNTs and long reaction times (five days). On using microwave activation in solvent-free conditions the same reaction takes place in 1 h (Scheme 1.6).[17] This methodology has also been applied in the functionalization of carbon nanohorns (CNHs)[18] and to produce multifunctionalized nanostructures using a combination of this reaction and the addition of diazonium salts (in this case employing water as the solvent).[17*b*]

β-Enaminones and β-enaminoester derivatives are versatile synthetic intermediates for a wide range of bioactive heterocycles, pharmaceuticals and naturally occurring alkaloids. For this reason, several catalytic and non-catalytic methods have been applied for the synthesis of these compounds. In 2013 Das described the microwave-assisted synthesis of novel classes of β-enaminoesters within 5–10 min by reaction between ethyl 3-(2,4-dioxocyclohexyl) propanoate and different amines under solvent- and catalyst-free conditions (Scheme 1.7).[19] The reactions did not require work-up and clean product formation was achieved under milder reaction conditions, thus making this process in an environmentally benign method.

Recently, Jain reported an efficient and facile solvent-free peptide synthesis assisted by microwave irradiation using *N*,*N*′-diisopropylcarbodiimide



**Scheme 1.5** Solvent- and catalyst-free synthesis of ring-fused aminals under microwave induction (MWI).

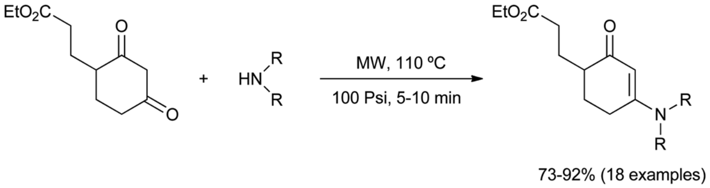


**Scheme 1.6** Microwave-assisted functionalization of CNTs in solvent-free conditions.

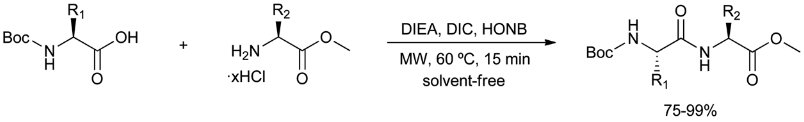
(DIC) as the coupling reagent and *N*-hydroxy-5-norbornene-*endo*-2,3-dicarbodiimide (HONB) as an auxiliary nucleophile (Scheme 1.8).[20] Peptides were obtained in 15 min at 60 °C in high yield and with high purity without racemization.

Difunctional triazinyl mono- and bisureas possess very interesting self-assembly properties that allow them to form supramolecular nanostructures as a result of non-covalent interactions in aqueous or hydrophobic environments. These abilities have resulted in applications such as ambipolar thin film devices and polyurea networks with 2D porous structures. de la Hoz reported an efficient and sustainable microwave-assisted solvent-free approach for the preparation of a wide range of 1,3,5-triazinyl mono- and bisureas.[21] Under these conditions non-reactive amino groups attached to the triazine ring are able to react with phenylisocyanate to yield selectively mono- and bisureas (Scheme 1.9). Products were obtained with a simple purification procedure, which simply involved washing with a solvent (diethyl ether or ethanol).

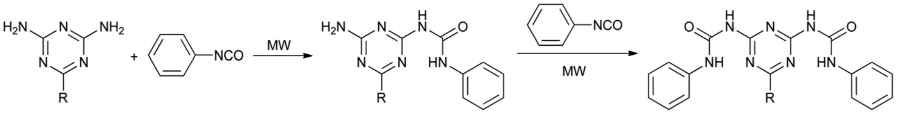
1,3-Diynes have received considerable attention in materials science due to their use for the construction of π-conjugated structures. The most widely used method for the synthesis of diynes involves the self-coupling of terminal acetylenes. Several palladium-free syntheses have been described in which copper salts are used as catalysts. However, these protocols require bases and/or additives as well as toxic and carcinogenic solvents.



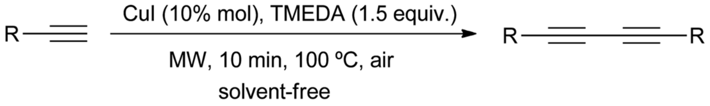
**Scheme 1.7** Solvent- and catalyst-free synthesis of β-aminoesters under MWI.



**Scheme 1.8** Synthesis of peptides under microwave irradiation in solvent-free conditions.



**Scheme 1.9** Synthesis of 1,3,5-triazinyl mono- and bisureas under microwave irradiation in dry media.



**Scheme 1.10** Microwave-assisted synthesis of 1,3-diynes in the absence of solvent.

Braga recently described a microwave-assisted synthesis of 1,3-diynes from terminal acetylenes catalysed by CuI and tetramethylenediamine, in the presence of air as the oxidant, at 100 °C for only 10 min under solvent-free conditions (Scheme 1.10).[22] The same protocol can also applied for the synthesis of unsymmetrical 1,3-diynes.

## 1.3 Microwave Susceptors

The nature of the radiation means that non-polar substances are poorly heated by microwaves. In other cases, the reaction requires very high temperatures that cannot be achieved by the absorption of the reagents. These problems can be overcome by the use of a susceptor, an inert compound that efficiently absorbs microwave radiation and transfers the thermal energy to other compounds that are poor radiation absorbers or to the reaction medium.

### 1.3.1 Graphite As a Microwave Susceptor

Most forms of carbon interact strongly with microwaves. Powdered amorphous carbon and graphite rapidly (within 1 min) reach very high temperatures (>1000 °C) upon irradiation and, for this reason, graphite has been widely employed as a microwave susceptor. The amount of graphite can be varied. In some cases, a catalytic amount of graphite (10% or less than 10% by weight) is sufficient to induce rapid and strong heating of the reaction medium. However, in most cases the amount of graphite is at least equal to or greater than the amount of reagents, thus resulting in a graphite-supported microwave process.[23]

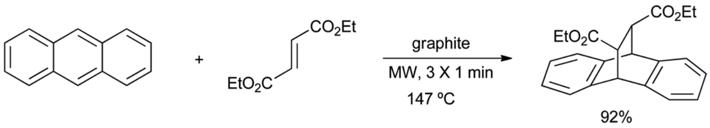
In 1996, Dubac described the Diels–Alder cycloaddition between anthracene and diethyl fumarate supported on graphite in a dry medium (Scheme 1.11).[24] Sequential irradiation (irradiation with “battlements”) at moderate power, 3 × 1 min at 30 W, allowed the reaction temperature to be controlled and avoided the retro-Diels–Alder process, which would diminish the product yield of unstable adducts. On applying classical heating, a reaction time of 60 h in refluxing dioxane was required to achieve a similar yield.

The efficiency of the graphite-supported process is all the more noteworthy because reagents are frequently volatile, but the adsorption power of graphite retains these components and this enhances the reaction. For example, the cycloaddition reaction between isoprene and ethyl glyoxylate affords 73% yield within 10 × 1 min (final temperature 146 °C) whereas only 10% can be obtained by classical heating (Scheme 1.12).[25]

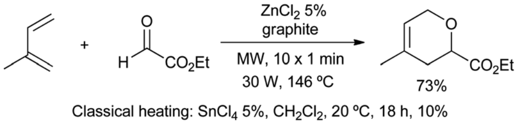
Besson reported that a quinazolin-4-one ring can be fused onto a benzimidazo[1,2-*c*]quinazoline skeleton by a modified Niementowski reaction. Thermal heating of the two reagents at 120 °C or in refluxing butanol for 48 h gave only 50% of the target compound. The reaction time was reduced to 6 h in a microwave-assisted process, albeit without an improvement of the yield. However, irradiation of the quinazoline derivative and an excess of anthranilic acid (6 equiv.), absorbed on graphite, led to the desired product in 1.5 h with 95% yield (Scheme 1.13).[26] Furthermore, the fact that by-products were not detected allowed the easy purification of the product.

The thiazole and benzothiazole rings are present in various natural compounds. Likewise, indolo[1,2-*c*]quinazoline and benzimidazo[1,2-*c*]quinazoline skeletons are often present in potent cytotoxic agents. For these reasons, Besson described the fusion of these two systems under microwave irradiation in the presence of graphite as a sensitizer (10% by weight) and the expected products were obtained in good yields and in short reaction times (Scheme 1.14).[27]

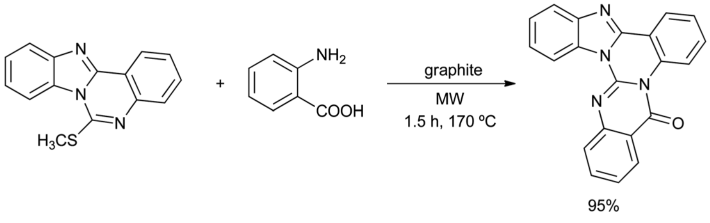
Graphene is a one atom-thick two-dimensional carbon structure that has attracted considerable attention due to its amazing properties and potential applications in material science. In 2011 Kim described the fabrication of high quality graphene nanosheets within 1 min by solid-state microwave



**Scheme 1.11** Microwave-assisted cycloaddition between anthracene and diethyl fumarate supported on graphite in a dry medium.



**Scheme 1.12** Microwave-assisted cycloaddition between isoprene and ethyl glyoxylate adsorbed on graphite.



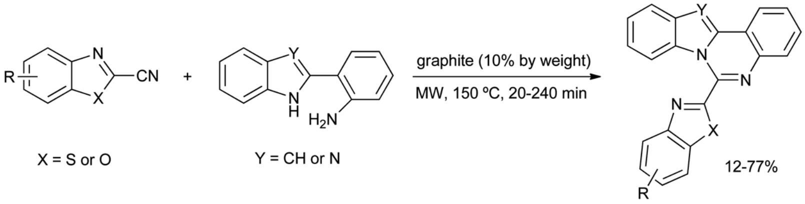
**Scheme 1.13** Preparation of polyheterocyclic derivatives under microwave irradiation in conjunction with graphite.

irradiation of a mixture of graphite oxide and graphene nanosheets (10 wt%) under a hydrogen atmosphere.[28] The graphene nanosheets in the mixture acted as a microwave susceptor providing sufficiently rapid heating for the effective exfoliation of graphite oxide (Figure 1.2). The hydrogen atmosphere plays an important role in improving the quality of the graphene nanosheets by promoting the reduction of graphite oxide and preventing the formation of defects.

Carbon nanotubes can act as microwave susceptors in the curing of epoxy polymers. The presence of carbon nanotubes (0.5 or 1.0 wt%) within an epoxy matrix has proven to shorten the curing time, which decreased as the carbon nanotube concentration was increased (Figure 1.3).[29] Substantial changes were not observed in the mechanical behaviour of the carbon nanotube-reinforced polymers. However, the energy saving was quantified to be at least 40% due to the reduction in the curing time.

## 1.3.2 Silicon Carbide (SiC) As a Microwave Susceptor

It is well known that silicon carbide (SiC) is thermally and chemically resistant (melting point *ca.* 2700 °C) and that it is a strong microwave absorber. The use of SiC as a microwave susceptor has been reported in materials and ceramics science.[23] Sintered SiC has a very low thermal expansion coefficient and no phase transitions that would cause discontinuities in thermal



**Scheme 1.14** Preparation of quinazoline derivatives under microwave irradiation using graphite as a sensitizer.

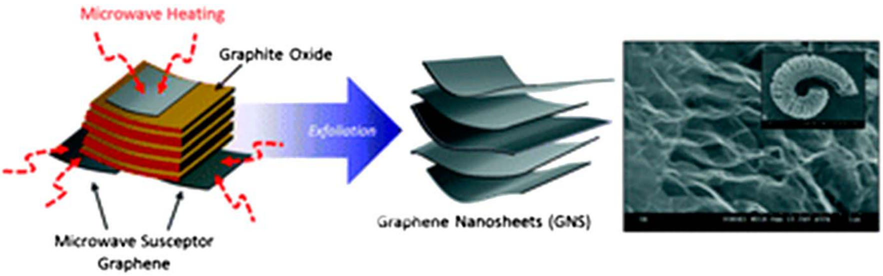


**Figure 1.2** Preparation of graphene nanosheets under microwave irradiation using graphene as a susceptor. Reproduced from ref. 28 with permission from the Royal Society of Chemistry.

expansion. Thus, SiC cylinders sintered at 2000 °C, which are stable to corrosion and temperatures up to 1500 °C, have been developed for use as microwave susceptors in organic processes (Figure 1.4).[30]

Non-polar solvents can be rapidly and deeply heated by microwave irradiation in the presence of SiC as a susceptor, and chemical transformations can

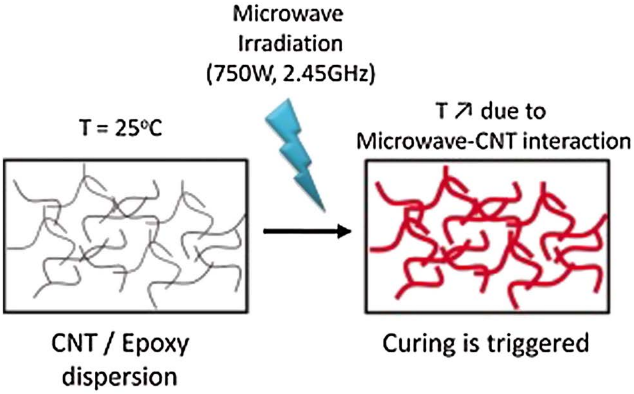


**Figure 1.3** Carbon nanotubes as a microwave susceptor in the curing of epoxy polymers. Reproduced from I. Fotiou *et al.*, *J. Appl. Poly. Sci.* with permission from John Wiley and Sons. Copyright © 2013 Wiley Periodicals, Inc.[29]

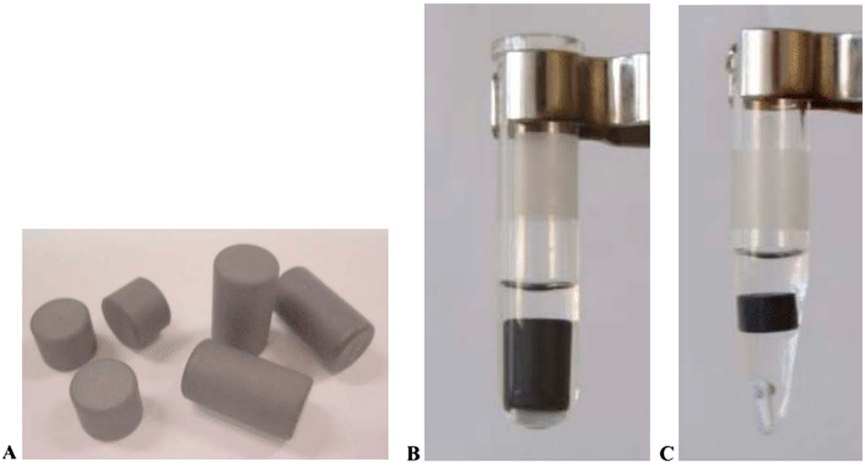


**Figure 1.4** (a) SiC cylinders: 10 × 8 mm (1.94 g) and 10 × 18 mm (4.35 g). (b) SiC cylinder (10 × 18 mm) inside a standard 10 mL microwave vial used in single-mode microwave apparatus, solvent volume 2 mL. (c) SiC cylinder (10 × 8 mm) inside a standard 5 mL conical microwave vial, solvent volume 2 mL. Reproduced with permission from J. M. Kremsner and C. O. Kappe, *J. Org. Chem.* 2006, **71**, 4651–4658. Copyright (2006) American Chemical Society.[30]

be performed at temperatures as high as 300 °C (Table 1.3).[30] These passive heating elements are compatible with any solvent or reagent, they are virtually indestructible and they can be re-used indefinitely without loss of efficiency.

Kappe described the use of SiC in several transformations. Michael addition of methyl acrylate and piperazine in toluene as the solvent afforded the bis-Michael adduct in 98% yield within 10 min at 200 °C (Scheme 1.15).[30] However, despite the presence of piperazine the microwave absorbance of the reaction mixture was not sufficient: after 7 min of irradiation at 300 W the maximum temperature was 170 °C and very low conversion to the final product was observed. Full conversion to the product at room temperature in toluene required 2 days.

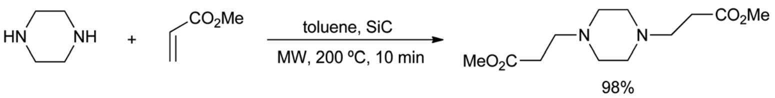
In another example, Kappe studied the high-temperature rearrangement of a heterocyclic derivative bearing a nucleophilic free amino group. Since ionic liquids cannot be used as microwave susceptors owing to the presence of a nucleophilic group, SiC was employed as a heating element. Thus, the thermal Dimroth rearrangement was performed within 30 min at 220 °C and the product was isolated in 68% yield (Scheme 1.16).[23] The reaction did not proceed at all in the absence of SiC (maximum temperature after 4 min: 140 °C).

**Table 1.3** Microwave-induced temperatures of non-polar solvents in the presence and absence of SiC as a microwave susceptor.[a]

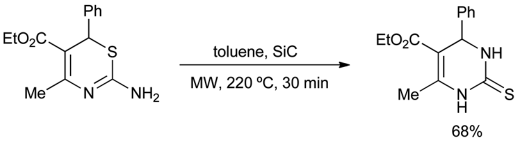
| Solvent | T without SiC (°C) | T with SiC (°C) | Time[b] (s) | B.p. (°C) |
|---|---|---|---|---|
| $CCl_4$ | 40 | 172 | 81 | 76 |
| Dioxane | 41 | 206 | 114 | 101 |
| Hexane | 42 | 158 | 77 | 69 |
| Toluene | 54 | 231 | 145 | 111 |
| THF | 93 | 151 | 77 | 66 |

[a] 150 W constant magnetron output power, 2 mL solvent, sealed 10 mL quartz (pure solvent) or Pyrex (solvent with SiC) reaction vessel, magnetic stirring.

[b] Time until the maximum pressure limit of the microwave apparatus employed by the researchers (20 bar). Significantly higher solvent temperatures can be obtained using different instrumentation with higher pressure limits.



**Scheme 1.15** Michael addition of methyl acrylate and piperazine in the presence of SiC as a microwave susceptor.



**Scheme 1.16** Dimroth rearrangement of a 2-amino-1,3-thiazine using SiC as a microwave susceptor.

It is noteworthy that chemical transformations using SiC cylinders as heating elements generally require only a fraction of the magnetron output power (30–70%), which represents a significant energy saving.

In order to facilitate the penetration of radiation into the reaction mixture, microwave vessels are typically made from materials that have low microwave absorption or are microwave transparent (Pyrex, quartz or Teflon™). However, these useful materials do have some drawbacks, which include lack of stability under extreme reaction conditions (very high temperature or pressure, or aggressive chemical media). In an effort to solve these problems a sintered SiC ceramic reaction vessel with the exact same geometry as a standard 10 mL Pyrex vial has been produced (Figure 1.5).[31]

Kappe studied 21 selected chemical transformations and compared the results obtained in microwave-transparent Pyrex vials with experiments carried out in SiC vials at the same reaction temperature.[31] As an example, SiC vials were used to carry out microwave-assisted aliphatic fluorine–chlorine exchange reactions using trimethylamine trihydrofluoride (TREAT-HF, $Et_3N{\cdot}3$ HF) as a reagent in benzene at 250 °C (Scheme 1.17).[31] Since TREAT-HF can release hydrogen fluoride at high temperatures, a significant level of corrosion of standard Pyrex vials was observed in the vapour space above the reaction mixture. This corrosion represents a serious safety risk as the pressure rating of the heavy-walled Pyrex vials (20–30 bar) cannot be maintained. In contrast, the SiC vial was completely resistant to TREAT-HF even at 250 °C for prolonged periods.

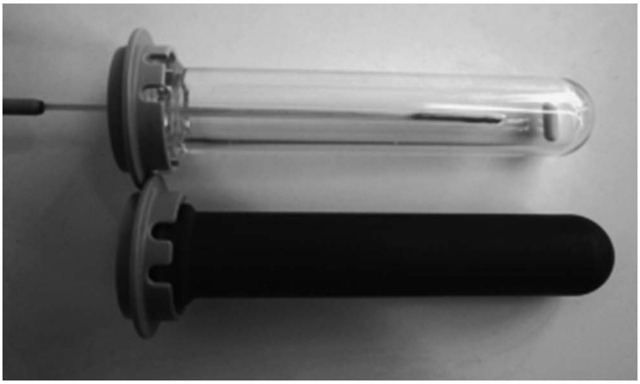
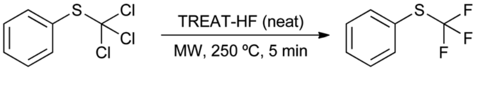


**Figure 1.5** Reaction vial made from sintered SiC (lower). For comparison a standard 10 mL Pyrex vial with a snap cap, internal FO probe and a magnetic stirrer bar is also included (upper). Reproduced from B. Gutmann, *Chem. Eur. J.*, with permission from John Wiley and Son. Copyright © 2010 WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim.[31]



**Scheme 1.17** Microwave-assisted aliphatic fluorine–chlorine exchange in a SiC vial.

Parallel microwave synthesis has received a great deal of attention in recent decades due to the benefits of these two technologies. The most important issue in this application was to achieve a uniform temperature distribution in all of the plates. This problem was addressed by developing deep-well plates made of Weflon™ (Teflon™ doped with 10 wt% graphite). However, a significant limitation of all early microtiter plate systems is that is was impossible to perform microwave chemistry under sealed-vessel conditions in a pressure range similar to those operating in single-mode reactors (20–30 bar). In 2007 the first sealed microtiter plate system made from SiC for use in a dedicated multimode microwave instrument was described.[32] At present, these systems allow high-speed microwave chemistry to be carried out in a highly parallelized and miniaturized format (0.02–3.0 mL) at a maximum temperature and pressure limit of 200 °C and 20 bar, respectively. Up to 192 reactions can be performed depending on the specific plate and rotor configuration (Figure 1.6).[33]

### 1.3.3 Other Microwave Susceptors

Other substances that are strong microwave absorbers have also been used as microwave susceptors. Metal particles (Fe or Ni) were employed in microwave-assisted pyrolysis processes that require temperatures of up to 1200 °C.[34] The use of ionic liquids to reach high temperatures in microwave-assisted reactions is described in Section 1.4.2.

In 1996 Díaz-Ortiz described the microwave-assisted 1,3-dipolar cycloaddition of nitriles with nitrones or nitrile oxides in solvent-free conditions using an alumina–magnetite ($Fe_3O_4$) (5 : 1) bath as an external microwave susceptor.[35] The product yields decreased significantly in the absence of a microwave susceptor or when using classical heating.

A few years later our research group demonstrated the reproducibility and scalability of solvent-free microwave-assisted reactions from domestic

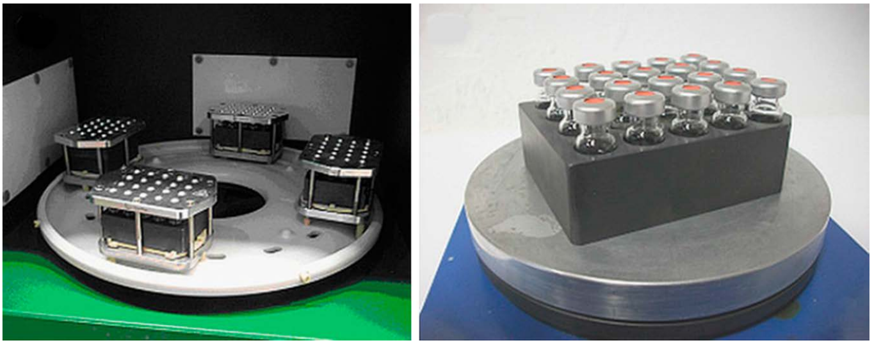


**Figure 1.6** Fully equipped systems with SiC well plates commercialized by Anton Paar GmbH. Reprinted from Molecular Diversity, Parallel Microwave Chemistry in Silicon Carbide Microtiter Platforms: A Review, 16, 2011, C. O. Kappe, with permission from Springer.[33]

ovens to a dedicated microwave apparatus. In this study the 1,3-dipolar cycloaddition between nitriles and nitrile oxides was selected and 24 reactions were carried out in a multiwell plate (Scheme 1.18).[36] The reactions were performed in a Weflon™ multiwell plate. This system not only acted as a microwave susceptor to raise the reaction temperature, but it ensured identical conditions for each individual reaction.

## 1.4 Reactions in Solution

The vast majority of reactions in organic synthesis, on both the industrial and laboratory scales, are performed in solution.

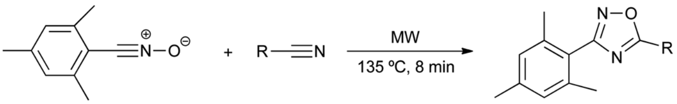
The use of solvents allows the following:

- Obtaining an efficient mixture of reagents at the molecular level.
- Placing in contact the reagents at the appropriate concentrations to achieve a suitable reaction rate.
- Transporting reagents and/or products and facilitating the dosage for introduction into the reactor.
- Controlling the temperature of the reaction.
- In endothermic processes, increasing the temperature within the limit of the boiling point of the solvent.
- In exothermic processes, absorbing excess heat and controlling the temperature by reflux of the solvent or by cooling the solvent directly.

However, the use of solvent does present several problems and is not environmentally friendly. Solvents are used in large excess, *i.e.*, 10–100 times the quantity of reagents, and most of them are volatile (VOC's). Solvents are used not only during the reaction but also in the separation, purification (recrystallization, chromatography) and, possibly, in a final separation (evaporation, distillation, decantation, filtration or centrifugation) to obtain the final product.

On the other hand, solvents are the most likely contaminants amongst the auxiliary products because of their volatile and fluid nature. Solvents may have occupational toxicity, ecotoxicity, flammability or carry the risk of explosion and they may have drawbacks such as persistent contamination and pollution. Moreover, solvents may increase the greenhouse effect and contribute to the destruction of the ozone layer.

Water is an obvious choice in green chemistry to replace common organic solvents but it is hardly used because of the low solubility of organic



**Scheme 1.18** Microwave-assisted 1,3-dipolar cycloaddition between nitriles and nitrile oxides.

compounds at room temperature. The development of neoteric solvents, supercritical fluids, ionic liquids and fluorous solvents has led to the development of a new sustainable chemistry. All of these systems have been used in efficient processes under microwave irradiation.

### 1.4.1 Reactions in Water

Water is considered as a paradigm green solvent. Water is readily available and is non-toxic and non-flammable. The use of water in organic synthesis has been hampered by the low solubility of organic compounds, however, new strategies have been designed to overcome this problem, for instance the use of an organic cosolvent, the exploitation of hydrophobic effects (chemistry "on-water") and the use of water at high temperatures. The latter conditions can be exploited easily under microwave irradiation. Water at elevated temperatures, close to the critical point, has unique properties that are very different from those observed at room temperature (Table 1.4).[37]

High temperature near-critical water (NCW) shows interesting properties for applications in organic synthesis. The dielectric constant of water changes from 78.5 at 25 °C to 27.5 at 250 °C (similar to acetonitrile at 25 °C) and 20 at 300 °C (similar to acetone at 25 °C). This means that at these temperatures water can be considered as a pseudo-organic solvent. In addition to the advantages of using water, the isolation of materials is simplified as pure products could be obtained by crystallization on cooling the aqueous solution.

The ionic product of water increases by 3 orders of magnitude from room temperature to 250 °C. As a consequence, at this temperature water can be used as a strong acid and a strong base, thus avoiding the use of mineral acids and bases which have to be neutralized when the reaction is complete.

The reactions studied under microwave irradiation in water include palladium-catalysed coupling reactions, heterocycle synthesis, multicomponent reactions, nucleophilic substitutions, cycloadditions, decarboxylations, hydrolyses and radical reactions. These reactions have recently been reviewed.[38]

**Table 1.4** Properties of water under different conditions[37]

| Fluid | Ordinary water, $T < 150$ °C, $p < 0.4$ MPa | Near-critical water (NCW), $150 < T < 350$ °C, $0.4 < p < 20$ MPa | Supercritical water (SCW), $T > 374$ °C, $p > 25$ MPa | Steam |
|---|---|---|---|---|
| Temp (°C) | 25 | 250 | 400 | 400 |
| Pressure (bar) | 1 | 50 | 250 | 1 |
| Density (g cm$^{-3}$) | 1 | 0.8 | 0.17 | 0.0003 |
| Dielectric constant, $\varepsilon'$ | 78.5 | 27.1 | 5.9 | 1 |
| $pK_w$ | 14 | 11.2 | 19.4 | — |

In this chapter some representative examples will be highlighted.

Leadbeater and Marco[39] described a Suzuki coupling in water under microwave irradiation (Scheme 1.19). The addition of TBAB as a phase transfer agent facilitated the reaction because it enhances the solvation of the organic substrate in water and increases the rate of the coupling reaction through the formation of a complex with the boronate. The authors reported that the reaction can be performed without the use of a palladium catalyst.

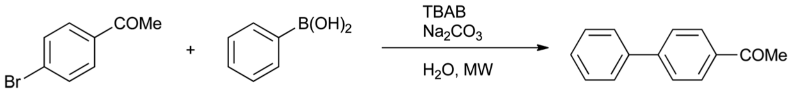
In a second paper it was reported that ultralow levels of palladium (50 ppb) found in the sodium carbonate base were responsible for the reaction.[40] In all cases, a clear reduction in the reaction time was observed on using microwave irradiation (from 120 to 5 min). Finally, an *in situ* Raman detection system was employed to show that the reaction had reached completion after 135 s.[41]

Ericsson and Engman reported the microwave-assisted group-transfer cyclization of organotellurium compounds in a radical reaction performed in different solvents including water (Scheme 1.20).[42]

It was found that the reaction was substantially improved under these conditions. The reaction time was shortened and the process could be performed in water without additives and in the absence of toxic tin mediators. The only drawback was the loss of diastereoselectivity due to the higher temperatures used.

Baran reported the total synthesis of the antiviral marine alkaloid ageliferin from sceptrin by a tautomerization/ring expansion.[43] The reaction was only successful in water under microwave irradiation and was complete in 1 min to give 40% yield (Scheme 1.21). Longer reaction times or the use of conventional heating led to decomposition of this unstable compound.

Reactions in near-critical water are scarce but they have especially been used for hydrolysis and degradative purposes. The first reactions were reported by Strauss[44] with the MBR microwave reactor developed at the CSIRO in Australia.



MW, 100 W, 150°C, 5 min 100%
CH, 150°C, 120 min 94%

**Scheme 1.19** Suzuki reaction in water.

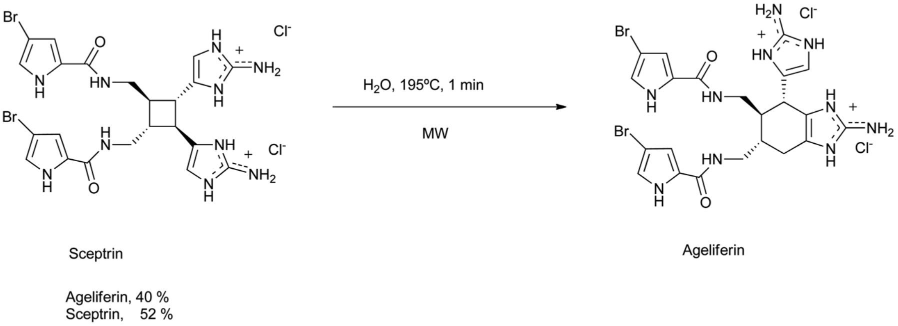
R = Bn, Ethyleneglycol, 250 °C, 6 min 74%, endo/exo, 1/1,8
Water, 180°C, 10 min <10%, endo/exo, 1/2,4

**Scheme 1.20** Group transfer cyclization of organotellurium compounds.

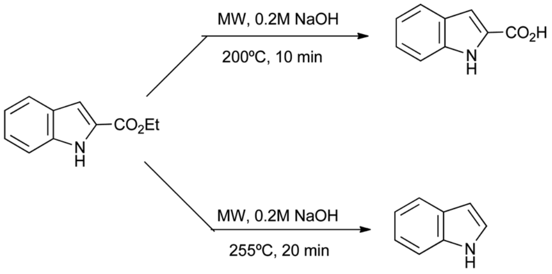
As an example, degradative hydrolysis of an indole 2-carboxylic ester was carried out in which, by controlling the temperature, it was possible to control the hydrolysis and the subsequent decarboxylation (Scheme 1.22).

Kremsner and Kappe performed a proof-of-concept study that involved a wide range of reactions in water at temperatures up to 300 °C and pressures up to 80 bar in a dedicated multimode microwave reactor (Scheme 1.23).[45] They concluded that microwave–NCW technology is ideally suited to perform organic synthesis in this high-temperature region as it combines the advantages of both techniques.

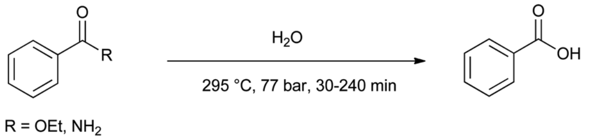
Santra and Andreana reported an Ugi/Michael/aza-Michael cascade reaction in aqueous media at high temperature to obtain azaspiro tri- and tetracyclic compounds.[46] The process generates a quaternary centre, four stereogenic centres and six contiguous bonds, and provides good to excellent yields and regioselectivities with appreciable diastereoselectivity (Scheme 1.24).



**Scheme 1.21** Microwave-assisted transformation of sceptrin into ageliferin.



**Scheme 1.22** Hydrolysis of indole 2-carboxylic ester in water.



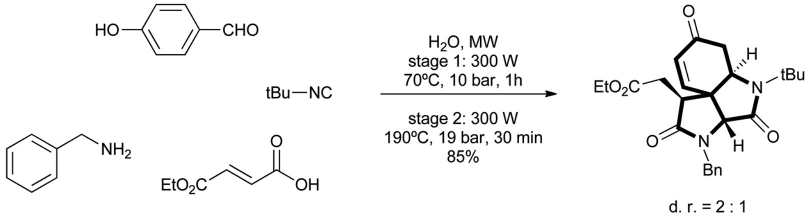
**Scheme 1.23** Hydrolysis of benzoic esters and amides in subcritical water.

Finally, the Tour reaction of single-walled carbon nanotubes (SWCNTs) in water under microwave irradiation was described as a green process for the functionalization of CNTs.[47] Pristine SWCNTs were dispersed in water with aniline derivatives in a microwave glass vessel. After sonication for a few minutes, isoamyl nitrite was added and a condenser was attached. The mixture was irradiated for 90 min at 80 °C in a focused microwave reactor (Scheme 1.25). TGA showed the presence of one functional group for each 68 carbon atoms approximately.

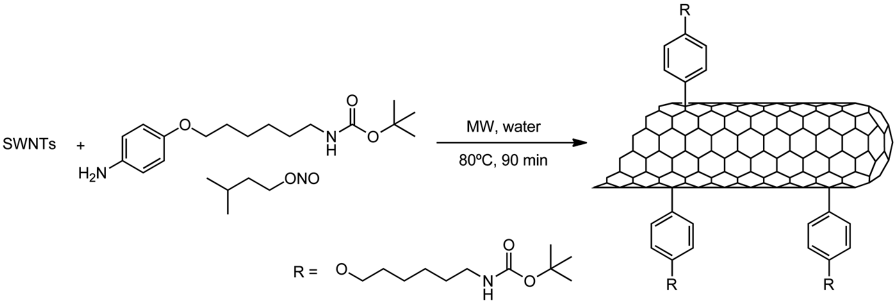
## 1.4.2 Reactions in Ionic Liquids (ILs)

Ionic liquids (ILs) are an excellent green alternative to VOCs. ILs are organic salts that remain liquid at room temperature. The properties of ILs that make them suitable for applications in synthesis are:

- Non-volatility: ILs present negligible vapour pressure over a wide range of temperatures.
- High thermal and chemical stability.
- Broad solubility range: ILs can dissolve a wide variety of organic, inorganic and organometallic compounds. They are also miscible with several organic solvents.
- Low combustibility: ILs are considered to be non-flammable compounds.



**Scheme 1.24** Microwave-assisted cascade reactions in water.



**Scheme 1.25** Tour reaction of CNT in water.

- Catalytic properties: ILs can act as catalysts, for example as Lewis acid catalysts.
- Large electrochemical window and relatively high electrical conductivity.

The main mechanisms for the transformation of electromagnetic radiation into heat are dipolar rotation and ionic conduction. Due to their ionic character, ILs absorb microwave irradiation very efficiently and transfer energy quickly by ionic conduction. As a result, ILs can reach very high temperatures in very short times. The ionic conduction mechanism produces superheating of an ionic substance due to the motion generated by an electric field. The transfer of energy becomes more efficient as the temperature increases. However, for organic reactions performed in ionic liquids under consecutive microwave irradiation, overheating is an inevitable problem because of the non-volatile nature of these solvents.

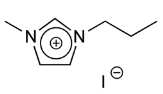
The combination of ILs and microwave irradiation in organic synthesis has been reviewed.[48] A number of representative examples of the advantages of the IL–MW combination are discussed in this section.

Leadbeater and Torrenius investigated the effect of the addition of a small quantity of ionic liquid in apolar solvents (hexane and toluene). They showed that these solvents can be heated above their boiling points in sealed vessels by adding just 2 mmol of IL for each 1 mL of solvent. This technique permitted the use of solvents with very low loss tangents in microwave-assisted reactions (Table 1.5).[49]

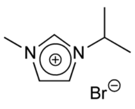
**Table 1.5** The microwave heating effects on adding a small quantity of **1** and **2** to hexane, toluene, THF, and dioxane.[a,d]

| Solvent used | Ionic liquid added | Temp attained (°C) | Time taken (s) | Temp without ionic liquid[b] (°C) | Boiling point[c] (°C) |
|---|---|---|---|---|---|
| Hexane | **1** | 217 | 10 | 46 | 69 |
| | **2** | 228 | 15 | | |
| Toluene | **1** | 195 | 150 | 109 | 111 |
| | **2** | 234 | 130 | | |
| THF | **1** | 268 | 70 | 112 | 66 |
| | **2** | 242 | 60 | | |
| Dioxane | **1** | 264 | 90 | 76 | 101 |
| | **2** | 246 | 90 | | |

[a] Experiments run using a microwave irradiation power of 200 W.
[b] Temperature attained during the same microwave irradiation time but without any ionic liquid added.
[c] Boiling point of the solvent used (for comparison purposes).
[d]



**1**



**2**

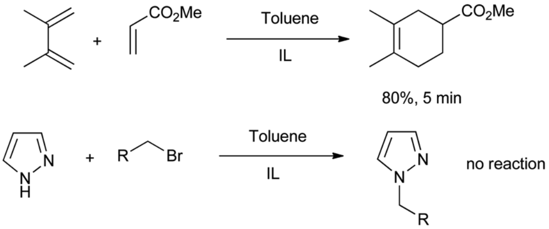
These solvent mixtures were used in Diels–Alder reactions, Michael additions and alkylation reactions. Improvements were observed in most reactions on using this protocol, with the exception of the alkylation reactions. The alkyl halide must react with the IL at the elevated temperatures used in the reaction and this leads to decomposition of the IL (Scheme 1.26).

Microwaves have shown significant benefits in the preparation of ILs. Conventional methods require several hours at high temperatures to afford acceptable yields. Under microwave irradiation, however, reactions can be performed in solvent-free conditions in short reaction times. The first example was reported by Varma for the synthesis of 3-methylimidazolium halides by alkylation of imidazoles in solvent-free conditions (Scheme 1.27).[50]

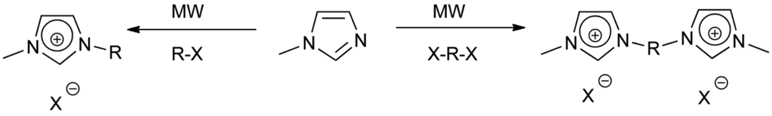
Task-specific ionic liquids (TSIL) have been used successfully under microwave irradiation. Applications include the use of solid-supported ILs and grafted ILs as substrates for the liquid-phase combinatorial synthesis of small molecules and as matrices for multicomponent reactions.

Bazureau described a microwave-assisted Knoevenagel condensation and Schiff base formation using a TSIL prepared by esterification of 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate (Scheme 1.28).[51]

The use of deep eutectic solvents (DES) under microwave irradiation is rare. These systems consist of a mixture of compounds that has the lowest melting point. Depression of freezing point is related to the strength of interactions between the two components. Many components are inexpensive, non-toxic, non-flammable, biodegradable and versatile. As such they are



**Scheme 1.26** Microwave-assisted reactions in toluene with addition of ionic liquids.



**Scheme 1.27** Microwave-assisted alkylation of imidazoles in solvent-free conditions.

considered to be green solvents and they have properties related to those of ILs. However, DES materials show unusual solvent properties:

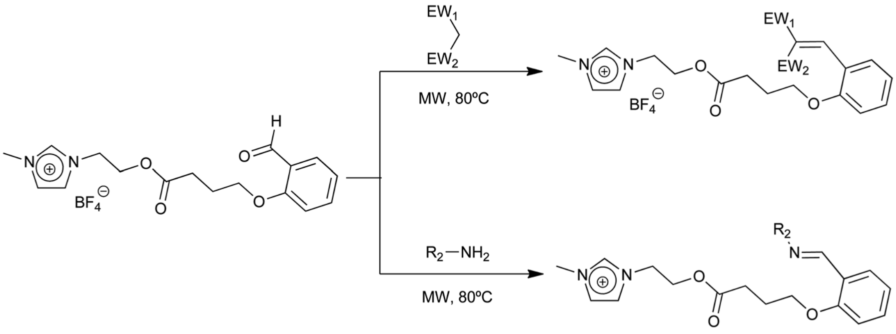
- They dissolve a wide range of solutes, *e.g.* salts, polar organics, metal oxides, amino acids, enzymes and surfactants.
- Solvent properties can be markedly changed by altering the hydrogen bond donor (HBD).

The most common DES is a mixture of choline chloride and urea.

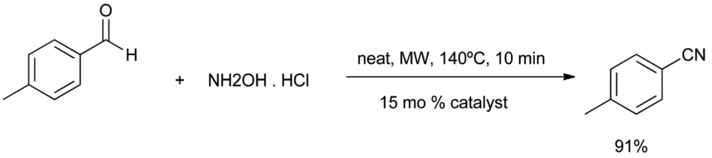
These materials have been used in combination with microwave irradiation, particularly for extraction processes,[52] and there are only a few examples in which organic synthesis has been carried out such media. For example, Nagarkar described the use of a deep eutectic mixture of choline chloride and urea (1 : 2) in the synthesis of nitriles from aldehydes under microwave irradiation in solvent-free conditions.[53] The eutectic mixture was used as an eco-friendly catalyst (Scheme 1.29).

## 1.4.3 Fluorous Chemistry

The chemistry of highly fluorinated compounds has grown significantly since its inception in 1994. This type of chemistry is related to the characteristics of highly fluorinated materials, molecular fragments or solvents and it is based on carbon with a $sp^3$ hybridization. This area also concerns fluorous media or solvents, fluorous separation techniques, fluorous tags and



**Scheme 1.28** Reactions with task-specific ionic liquids (TSIL).



**Scheme 1.29** Microwave-assisted reaction with a deep eutectic mixture as catalyst.

fluorous reagents and substrates. In this way, fluorous reactions and fluorous chemistry can be defined as concerning those materials in which a highly fluorous component is used in the reaction or synthesis.

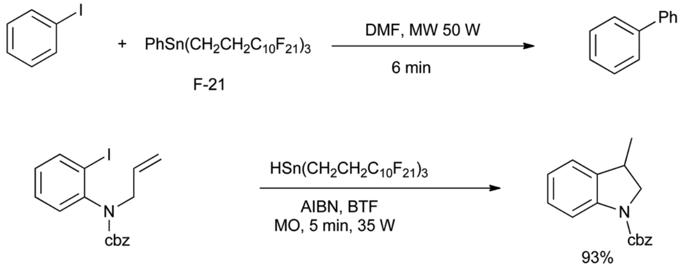
The green character of fluorous chemistry is associated with the solvophobicity to aqueous and organic solvents at room temperature, a property that is exploited in the development of new phase-tag-based separation techniques. In many cases, a simple extraction can be employed to obtain the pure products, thus avoiding the use of distillation, recrystallization or chromatography, and this advantage leads to significant savings in energy and solvents.

However, it should be noted that fluorous solvents have debatable toxicological properties; many perfluorocarbons are environmentally persistent and the low boiling point of perfluorocarbons is believed to be responsible for ozone depletion and global warming.[54]

Fluorous solid-phase extraction (F-SPE) increases the synthetic efficiency and reduces the amount of solvent required for purifications. Because of their solvophobic and fluorophilic nature, fluorous molecules can be retained in fluorous silica gel cartridges when eluted with a fluorophobic solvent. After separation of the non-fluorous molecules, the fluorous component is washed out from the cartridge with a stronger solvent.[54]

Microwave-assisted fluorous chemistry combines the advantages of microwave irradiation during the reaction and the advantages of F-SPE, since microwave irradiation has a strong influence on the reaction but not on the separation and purification steps.

Curran and Hallberg reported the first example of fluorous chemistry under microwave irradiation.[55] They described a series of coupling reactions, reductions, cyclizations and additions using tin derivatives with an F-21 tag. The high reaction rate under microwave irradiation and the subsequent easy purification makes this procedure an interesting alternative for use in combinatorial chemistry. The use of microwave irradiation makes compounds with F-21 an alternative to F-13. The corresponding tin derivatives with the F-21 tag are highly insoluble in organic solvents, thus facilitating their purification on silica gel or by liquid–liquid extraction (Scheme 1.30).



**Scheme 1.30** Microwave-assisted Stille coupling and radical cyclizations with fluorous reagents.

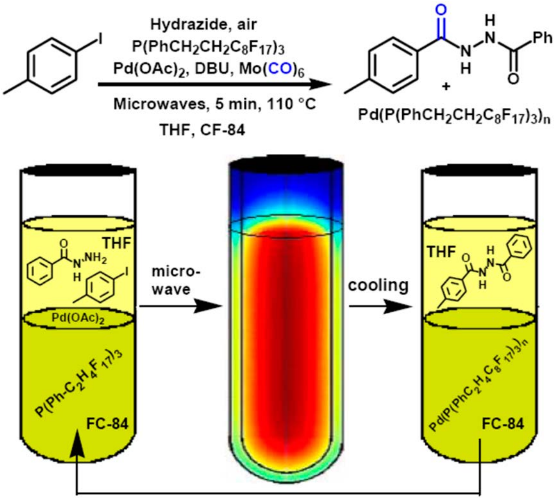


**Figure 1.7** Synthesis of diacylhydrazines with a fluorous phosphine. Reproduced from ref. 56 with permission © Georg Thieme Verlag KG.

Larhed described the synthesis of diacylhydrazines by *in situ* carbonylation of aryl iodides using $Mo(CO)_6$ as the carbon monoxide source. A fluorous phosphine ligand was used and the authors demonstrated that the catalytic system can be recycled up to six times (Figure 1.7).[56]

## 1.5 Flow Chemistry

The synergistic combination of microwave irradiation and flow chemistry is an interesting approach to solve the problems associated with the scale-up of reactions under microwave irradiation and this will further enhance the synthetic possibilities.

Microwave irradiation is a volumetric limited heating process. At the typical microwave frequency (2.45 GHz), the penetration depth is of the order of a few centimetres depending on the dielectric properties of the material. The composition and consequently the polarity of the reaction medium changes during the reaction and this determines the penetration depth and the total absorption of the microwave energy. Therefore, the ability to scale-up a reaction is always dependent on the reaction conditions. These characteristics have prevented the scale-up of microwave reactions in batch to a few litres and prevent their use in the production of compounds on a large scale.

An excellent review of microwave reactions under continuous flow conditions has been published[57] and in this section a selection of some key systems are discussed.

Synergy between microwave irradiation and flow was described by Strauss *et al.*,[58] who developed a continuous microwave flow reactor (CMR) that enabled a complete range of parameters to be controlled (temperatures to

200 °C, pressures up to 14 bar and flow rates of 15–20 mL $\text{min}^{-1}$). The application of these conditions with a residence time of 1–2 min allowed the processing of 1 L of reaction mixture in 1 h (Figure 1.8).

They described a series of reactions that included esterification, elimination, substitution and oxidation amongst others (Scheme 1.31).

Today microwave vendors provide commercially available flow systems (pumps, reactors, injection systems, *etc.*) that can be attached to the standard microwave systems – both single-mode and multimode.

However, several flow systems have been designed in-house for particular applications.

Haswell described a microreactor for the continuous-flow Suzuki reaction using a palladium catalyst and a gold bed.[59] Use of microwave irradiation enabled the localized heating of the catalyst.

Two reactors shown in Figure 1.9 were designed, the first reactor had a catalyst channel that was 1.5 mm wide, 0.08 mm deep and 15 mm long. The

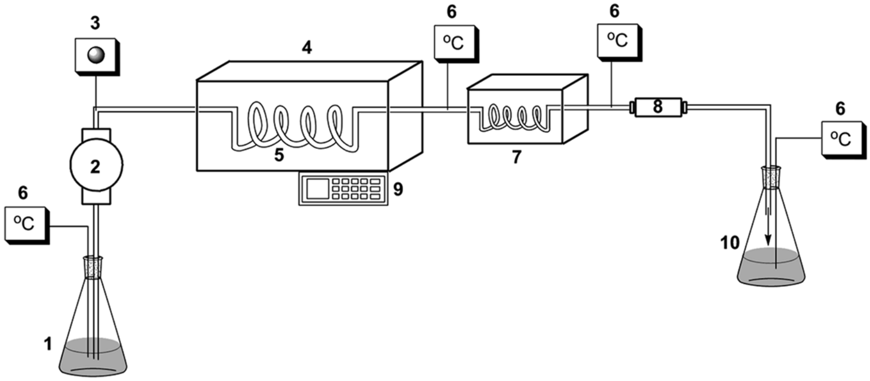
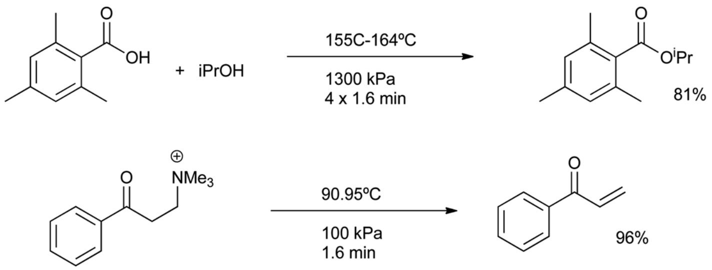


**Figure 1.8** Schematic illustration of the CMR. 1. Reaction mixture, 2. Pump, 3. Pressure sensor, 4. Microwave cavity, 5. Reaction coil, 6. Temperature sensor, 7. Heat exchanger, 8. Pressure control valve, 9. Electronic key pad and display and 10. Product mixture. Reproduced with permission from T. Cablewski, A. F. Faux and C. R. Strauss, *J. Org. Chem.* 1994, **59**, 3408–3412. Copyright (1994) American Chemical Society.[58]



**Scheme 1.31** Examples of microwave reactions in flow with the CMR reactor.

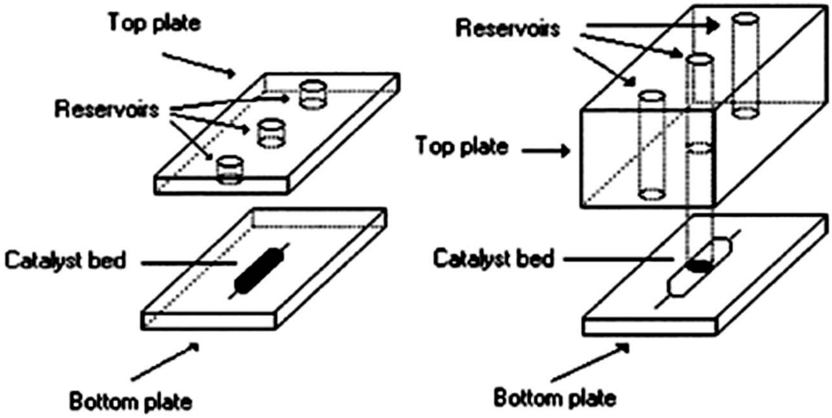


**Figure 1.9** Continuous-flow Suzuki coupling in microchannels. Reproduced from ref. 59 with permission from the Royal Society of Chemistry.

catalyst is introduced as a monolayer with a thickness of 45–63 mm. The efficiency of the catalyst is reduced after the first cycle but in the next four cycles the loss of activity is very low. The main problem encountered with this system was the difficulty in measuring the temperature with an IR sensor.

Organ described a microreactor for microwave-assisted organic synthesis using microcapillaries.[60] The internal diameter of the capillary was 200–1200 mm and the flow rate varied from 2 to 40 mL $min^{-1}$, which corresponds to an irradiation time of 4 min. Capillaries were impregnated internally with a thin layer of Pd(0) and the system showed a great acceleration in coupling reactions such as the Suzuki reaction (Figure 1.10). Reagents can be injected into the capillary system and mixing and reaction occurs without the usual laminar flow problems that occur in microreactors. The authors described the impregnation with other metal catalysts and developed a multireactor, which can be applied to the preparation of libraries of compounds (Figure 1.10).

Bagley described a flow reactor to be used with supports.[61] In this system a standard pressure-rated glass tube (10 mL) was fitted with a custom-built steel head. The flask was filled with sand (10 g) between two drilled frits (Figure 1.11) to minimize dispersion and effectively create a lattice of microchannels. The system was charged with solvent (5 mL), sealed using PTFE washers and connected to an HPLC flow system with a back-pressure regulator. Reagents were introduced in the bottom of the vessel and they flowed to the top of the reactor. An IR detector in the bottom of the reactor was used to determine the reaction temperature. The authors tested the system in two previously reported reactions and they observed a significant improvement in yield and demonstrated the ease of scale-up.

Ley described the use of polyurea microencapsulated palladium (PdEnCat) as a catalyst for the microwave-assisted Suzuki reaction described in