

# Impact of Microwaves on Organic Synthesis and Strategies toward Flow Processes and Scaling Up

Katia Martina, Giancarlo Cravotto,\* and Rajender S. Varma\*



Cite This: <https://doi.org/10.1021/acs.joc.1c00865>



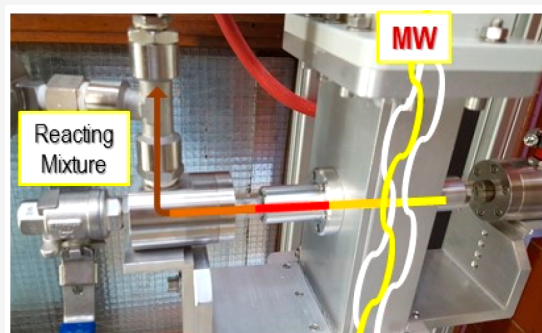
Read Online

ACCESS |

Metrics & More

Article Recommendations

**ABSTRACT:** Microwave-assisted organic synthesis has been widely studied and deliberated, opening up some controversial issues as well. Nowadays, microwave chemistry is a mature technology that has been well demonstrated in many cases with numerous advantages in terms of the reaction rate and yield. The strategies toward scaling up find an ally in continuous-flow reactor technology comparing dielectric and conductive heating.



In the more than 30 years of microwave (MW) chemistry, many green protocols in organic synthesis have been reported, showing significant advantages compared to the conventional heating. Selective, volumetric dielectric heating has resulted in time and energy savings, enabled the deployment of safer solvents or solvent-free processes, selective catalysis in fewer steps, and generally attaining higher selectivity and yields.<sup>1</sup> Although in the beginning, an improper temperature measurement sometimes overestimated the positive effect on the reaction rate, a fast and efficient energy transfer was demonstrated; however, for years, MW applications in organic synthesis were limited to the laboratories of a limited number of experts. The paucity of data available pertaining to the dielectric properties of materials as a function of temperature and frequency generated an empirical approach. In the meantime, the design of MW reactors was mainly focused on applications in analytical chemistry because of the rapid diffusion in sample mineralization. The lack of dedicated equipment often led to scarcely reproducible results and varying kinetics, which limited scaling-up studies for the industrial applications.

Despite the evident production efficiency under dielectric heating, the interest in industrial processing was delayed by the demand for safer equipment and plants.<sup>2</sup> The candidates for further development were the most efficient and reproducible protocols.

However, continuous-flow synthetic processes were shown to be less flexible when working with different reactions. After the optimization of the residence time, mixing, and flow rate, the reaction could be easily scaled up with parallel reactors or in bigger size. In all cases, the main goal was to preserve the reaction kinetics.<sup>3</sup>

Aiming to improve heat and mass transfer, a progressive transition from batch to continuous processing is expected, which is a mandatory condition for exploiting the MW energy in industrial production. MW-assisted continuous-flow organic synthesis (MACOS) has been successfully investigated in a plethora of organic reactions (e.g., heterocycle synthesis and metal-catalyzed chemistry) and, in particular, for the semi-industrial preparation of aromatic compounds.<sup>4</sup> Numerous studies on MW-assisted synthesis have nowadays revealed the possibility of transferring the methodology from the MW batch mode to a conventionally heated or MW-heated flow mode.

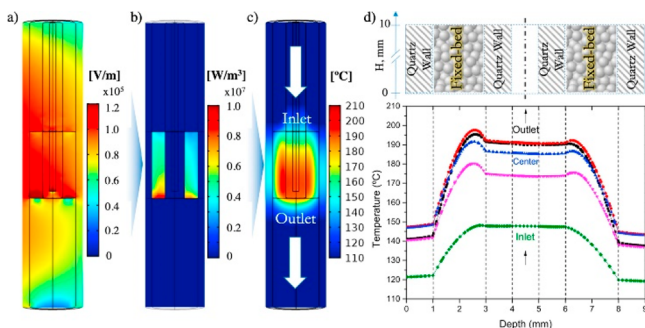
Because this field of research has been previously reviewed and a number of publications have reported the advances in MW-assisted organic synthesis (MAOS) in batch and in continuous flow mode,<sup>5–10</sup> this Perspective has focused on recent studies with an emphasis on the advantages and limitations of MW heating. In this regard, synthetic protocols aimed at scaling up of the process and the comparison between different approaches directed to large-scale synthesis have been selected to provide a comprehensive picture of the state of the art. Recent advancements in stereoselective MAOS are included as well.

**Special Issue:** Enabling Techniques for Organic Synthesis

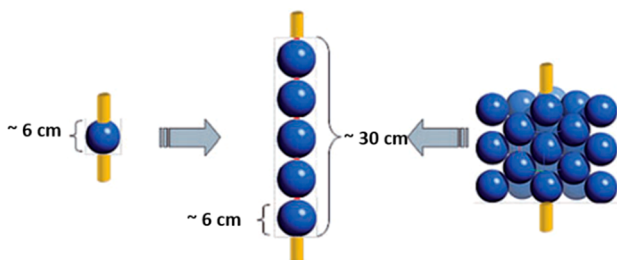
**Received:** April 14, 2021

## RECENT ADVANCES IN MICROWAVE TECHNOLOGY

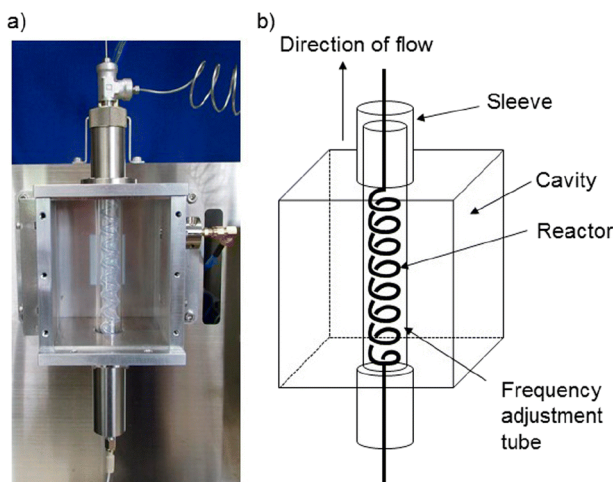
The use of alternative energy sources to improve mass or heat transfer has tremendous potential for chemical reactions, and



**Figure 1.** Simulated view of the quartz tube fixed bed of NaY zeolite and its corresponding (a) electric field, (b) power, and (c,d) spatial temperature distribution at steady state. Reproduced with permission from ref 13. Copyright 2019 Elsevier.



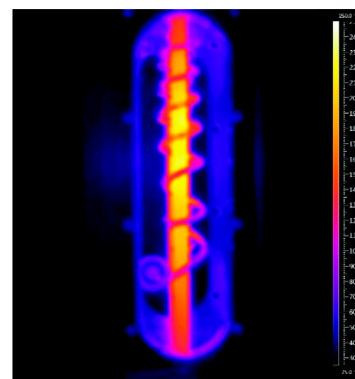
**Figure 2.** MW resonator flow concept obtained by combining mono- and multimode technologies. Reproduced with permission from ref 22. Copyright 2012 Walter de Gruyter.



**Figure 3.** Photograph and schematic representation of the resonant-type MW tubular reactor. Reproduced with permission from ref 25. Copyright 2018 The Authors.

dielectric heating may strongly enhance the reaction rate. Scrutinizing the chemical engineering advancements to intensify synthetic protocols under MW irradiation, special attention is being paid to the design of the MW cavities that provides a homogeneous field and uniform heating.<sup>11</sup>

Single-mode MW instruments have higher energy efficiency when compared to multimode counterparts, as the reactor vessel



**Figure 4.** IR camera image of a continuous oxidative Heck reaction in DMF (200 °C set temperature). The reactor is heated by the helical antenna. Reproduced with permission from ref 26. Copyright 2012 American Chemical Society.

geometry and position enable a well-defined field. A monomodal MW instrument is well suited for the mechanism study of the chemical reaction, but only relatively small vial diameters may receive/adsorb significant power.<sup>12</sup>

A recent study reported a fixed bed of 200 mg of NaY zeolite in a monomode rectangular resonant cavity wherein a temperature gradient was correlated to the nonuniform electric-field distribution.<sup>13</sup> As presented in the Figure 1, the region at the higher temperature corresponds to the higher electric field region, and almost 60% of the sample has a temperature from 160 to 197 °C.

The attenuation of the electromagnetic wave, measured at a small penetration depth of the most adsorbing solvent, is another limitation of MW irradiation when large-scale synthesis is studied. Different approaches have been pursued to overcome this limitation, and the combination of MW irradiation with acoustic waves (ultrasound) may help generate an increase in the penetration depth beyond intensifying the mixing and mass transfer.<sup>14,15</sup> The mechanical stirring would yield volumetric heating, and an example of a large-scale MW batch reactor devoted to synthesis has been described.<sup>16</sup>

Understanding how the MW deployment can enhance the reaction rates in organic synthesis requires a good background with knowledge of MW interactions with matter and other fundamentals. Moreover, a strict control of the applied energy with suitable hardware and software and reliable tools for temperature and pressure measurement is necessary. A rational balance of the pros and cons of MW energy deployment is relevant in deciding when and where MW irradiation can replace other energy input sources, and for this purpose, a study by Mase et al. reported a method that combines experimental design and 3D surface approximation for the rapid optimization of reaction conditions.<sup>17</sup> The principles behind and the factors determining the successful scale-up of MW-assisted technology are the frequency, power, penetration depth, and energy consumption; thus studies in this field are collected in this comprehensive review focused on instrument design and reactor configuration.<sup>18–20</sup>

Modern MW technology can finely tune the electromagnetic radiation at high field strength and frequency, leading to fast and safe heating. MW heating can, a priori, be independent of the macroscopic temperature; MW penetrability is dependent on the frequency. National and international institutions allow only a few frequencies for laboratory, industry, and medical (ISM) applications. The main frequency bands for commercially

available equipment are 2.45 GHz (most common), 915 MHz (USA), and 896 MHz (U.K.). Although equipment at 5.8 GHz is presently being created, an industrial setup requires further developmental work. MW irradiation at 5.8 GHz displays a shorter penetration depth but a better energy conversion. The selected frequency impacts the dielectric constants and the dissipation factors ( $\tan \delta$ ). Apart from MW reactors working at 2.45 GHz, all other devices require ad hoc designs because they are not available from commercial suppliers.<sup>21</sup>

Relevant advances in the “kilolab” continuous-flow MW mode have been reported by Morschhäuser et al. using a transmission-line short-circuited waveguide unit, combining the features of mono- and multimode systems.<sup>22,23</sup>

The new generation of MW reactors have come a long way in terms of efficiency and compatibility with the continuous-flow systems; they can promote chemical reactions at varying temperatures up to 300 °C and pressures up to 200 bar with safety as a priority and excellent parameter controls.<sup>24</sup> The combination of several modes in the direction of the reaction flow allows a homogeneous field distribution in resonator cavities, therefore, the continuous reactions have advantages related to MW irradiation and flow chemistry (Figure 2).

Two examples of the evaluation of MW applicators for flow synthesis are represented in Figures 3 and 4. A resonator-type MW reactor for continuous flow mode is depicted in Figure 3. The system comprises a rectangular MW cavity equipped with a helical tubular borosilicate glass reactor with an internal volume of 1.0 mL.<sup>25</sup> In Figure 4, another example of an MW tubular reactor heated by means of an Al–Cu helical antenna is represented and, in particular, the IR camera image that represents the temperature is shown.<sup>26</sup> The temperature is rather homogeneous, and lower temperatures are registered at the top and bottom of the reactor, which correspond to the entrance and exit of the flow.

Large laboratory MW units have been produced to achieve the kilogram scale in loop, in stopped flow or continuous flow, and with parallel vessels; nevertheless, these systems have a few inherent limitations.<sup>27</sup>

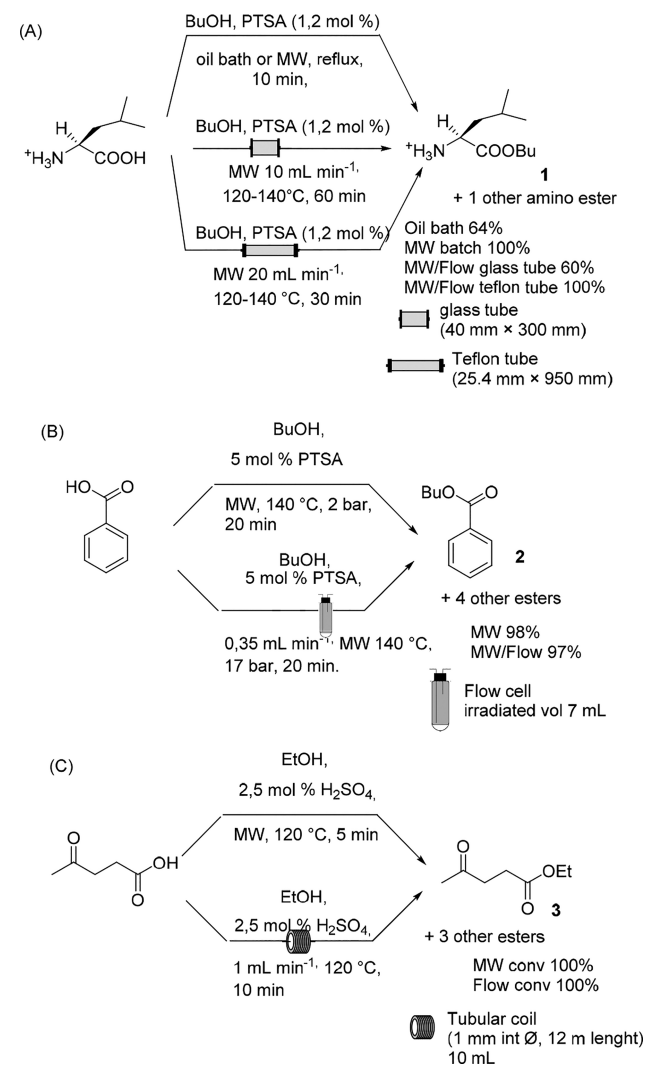
The industry is adopting strict strategies to minimize risks and to avoid batch failures, thus moving toward the continuous-flow synthetic processes. Proper modeling and simulation tools are fundamental for the design of safe and efficient reactors. This would help to get rid of bottlenecks that currently prevent scaling up. In addition to the reaction behavior during the reaction course, modern MW reactors should strictly monitor all of the parameters. Several variables affect the output of MW reactor and its scale, reflecting that MW technology cannot be implemented in a straightforward manner like classic conductive heating.

Industrial MW installations have been developed by specialized companies on the basis of the chemical conversion and the productivity required. Equipment manufacturers, who offer on-demand specifications (reactor geometry, frequency, power, etc.), can then make recommendations and offers.

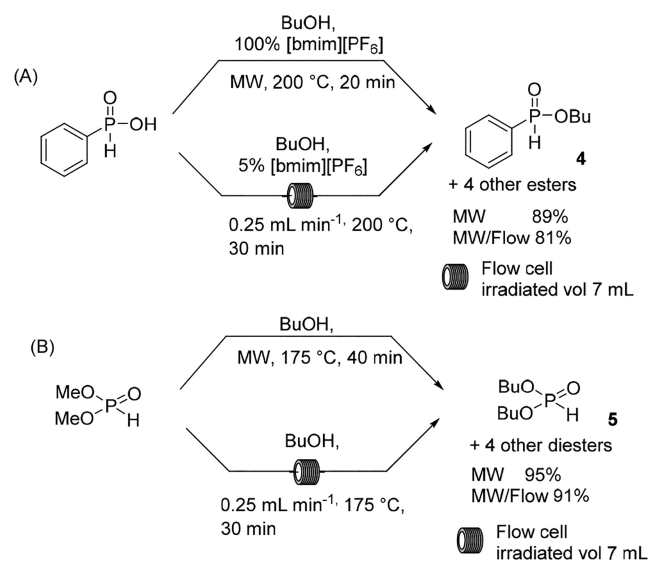
## ■ IMPACT OF HIGH TEMPERATURE AND PRESSURE ON HOMOGENEOUS ORGANIC SYNTHESIS

Recent examples of batch and continuous MW organic synthesis take advantage of modern instruments in which the temperature and pressure are controlled. Esterification, aromatic nucleophilic substitution, and Claisen rearrangement, among others, have been optimized under high pressure and consequently at higher temperature.

## Scheme 1. Fischer Esterification Reaction

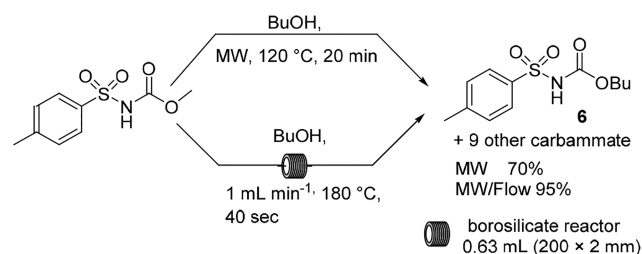


## Scheme 2. Organophosphorus Transformations

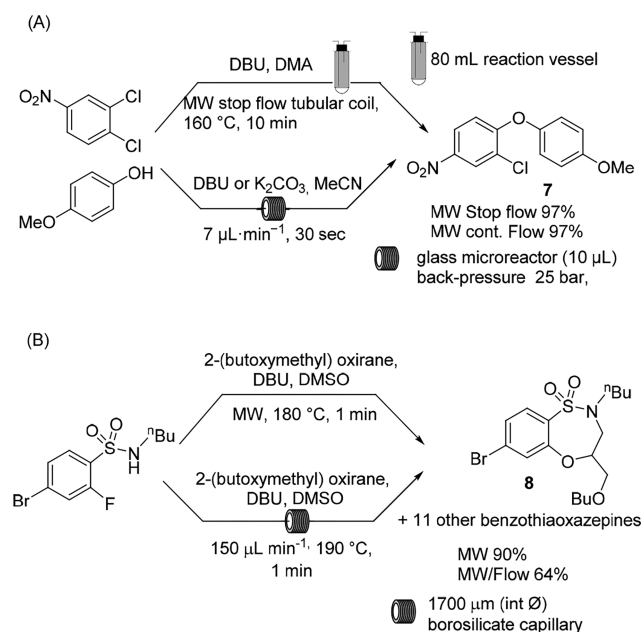


An investigation of Fischer esterification evidenced the importance of heating the solvent above the atmospheric boiling point, and for this reason, the flow reactor under pressure has

Scheme 3. Transcarbamylation/Transesterification of Sulfonyl Carbamate



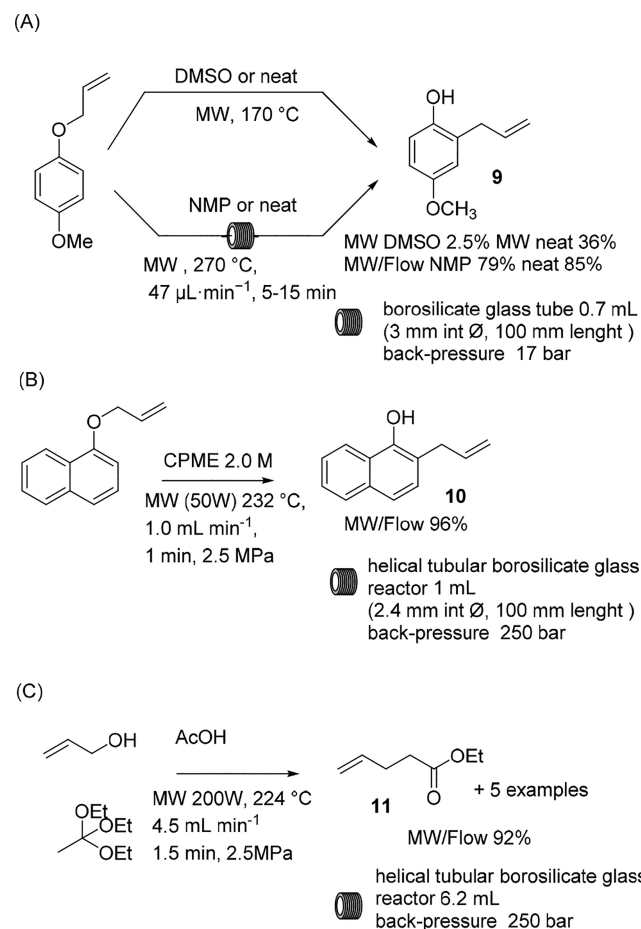
Scheme 4. Scaling up of MW-Assisted SNAr



been successfully exploited.<sup>28</sup> Comparing different studies also underlined the importance of the MW reactor design, and the depth of the MW irradiation has sometimes been measured. The typical limitations due to MW absorbance and its conversion have been largely centered on continuous operations with a thinner reaction cell, tube, or tubular coil.

In 2017, the esterification of leucine with PTSA (*p*-toluene sulfonic acid) and butanol was efficiently performed in an MW reactor (Scheme 1A, compound 1).<sup>29</sup> The authors compared the Fischer–Speier esterifications performed in a round-bottomed flask or in two types of tubular reactors of different inner diameters and lengths. By means of the in situ measurement of the dielectric properties of the reaction mixture in methanol, the penetration depth was calculated (~13 mm), and the reaction was therefore performed in MW batch mode and continuous-flow mode with an MW oven equipped with tubular reactors made of glass or Teflon with varying dimensions (Scheme 1A). In the case of a large-scale reaction with a Teflon tube deployment, the authors observed that the highest impact on the reaction conversion was correlated to the inner diameter of the reactor. With a 40 mm internal diameter, the beneficial effect of flow was apparent, but the reaction was not complete. As depicted in Scheme 1A, the full conversion was attained when the MW batch reaction was performed at reflux with a thinner tubular reactor heated to 120–140 °C. Esterification that was performed in a conventional batch mode gave only 64% conversion. Furthermore, this study demonstrated that the MW-

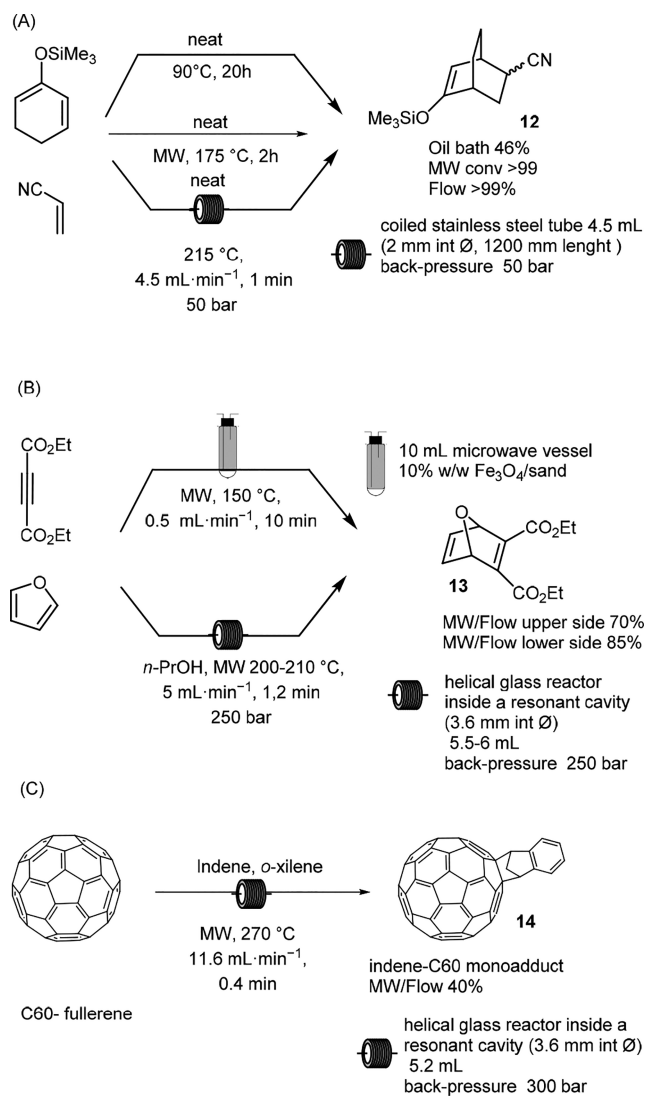
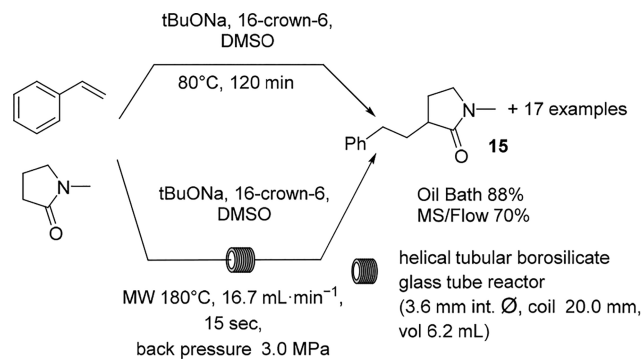
Scheme 5. Claisen Rearrangement



assisted flow reaction could be successfully scaled up to a tubular system of a ~600 mL inner volume with a flow of 20 mL·min<sup>-1</sup> at an elevated temperature of 140 °C, but an optimal reactor tube was necessary to secure the highest yield.

The esterification of benzoic acid under MW irradiation has been proven to be fast and efficient, and a few studies reported this reaction in the presence of acid catalysts.<sup>30</sup> The most recent protocol of the continuous MW-assisted esterification of benzoic acid in the presence of PTSA was optimized at 140 °C on the basis of an MW-assisted protocol studied in a batch mode.<sup>31</sup> On the basis of the order of reactivity of alcohols (*n*BuOH, *i*BuOH > *n*PrOH, *n*PentOH, *i*OctOH > EtOH > *i*PrOH), the authors accomplished the reaction in flow mode with a variable residence time of 20 to 30 min (Scheme 1B). The reaction was performed in a CEM Discover focused MW synthesizer equipped with a CEM 10 mL flow-cell accessory (irradiated volume 7 mL), wherein 35 mmol of benzoic acid was converted to its ester form in >95% yield. Another example of the esterification of levulinic acid using sulfuric acid or PTSA as the catalyst in MW batch mode and in conventional flow mode performed above the atmospheric boiling point of the solvent has been described.<sup>32</sup> MW heating provided complete conversion at 120 °C in 5 min with catalyst loading of 2.5 mol % and a levulinic acid–ethanol ratio of 1:10 (Scheme 1C). To mimic the batch reaction conditions in conventional flow mode, two solutions of acid and of levulinic acid in ethanol were pumped in a 10 mL perfluoroalkoxy alkane (PFA) coil that could operate at up to 150 °C. When the reaction was performed with 2 mL/min flow, a conversion of 78% was observed; therefore,

## Scheme 6. MW-Assisted Diels–Alder Reaction

Scheme 7. C-Alkylation of *N*-Alkylamides

reducing the flow rate to 1 mL/min was found to be necessary to attain complete conversion in one pass.

Large interest in organophosphorus transformations has garnered the attention of the MW-assisted protocol, and the esterification of phenyl-*H*-phosphinic acid took advantage of the high temperature, namely, in the alcoholysis of dimethyl *H*-phosphonate.<sup>33–35</sup> Both MW reactions were performed and scaled up in MW/flow in a flow cell housed in a CEM MW

reactor. The esterification was promoted by the addition of [bmim][PF<sub>6</sub>], which exhibited activity as an enhancer of MW irradiation, whereas transesterification generally did not require catalyst addition (Scheme 2A). Butanol reacted at 175–200 °C in 30 min in an MW flow cell of 10 mL, and the authors showed that roughly the same conversion was obtained in both the batch and flow modes (Scheme 2B).

The investigation of the transcarbamylation/transesterification of sulfonyl carbamate evidenced that the MW flow procedures shortened the reaction time when compared to the MW procedure performed at the boiling point of the solvent. The reaction was shortened from 20 min to 40 s when butanol was heated from 120 °C in MW batch mode to 180 °C in MW flow mode (Scheme 3).<sup>36,37</sup>

The S<sub>N</sub>Ar reaction has been extensively studied by means of MW irradiation in a preliminary attempt to scale up the aromatic nucleophilic substitution of chloroarenes. The MW batch procedure could be adapted to a stop-flow continuous MW protocol.<sup>38</sup> The reaction was performed between 1,2-dichloro-4-nitrobenzene and 4-methoxy phenol in an 80 mL reaction vessel (50 mL of operating volume) in the presence of an organic base (DBU) in DMA, and the vessel was filled and emptied along different lines (Scheme 4A, reaction conditions above). The automated repetition of the small-batch MW protocol ensured the large-scale production of product 7. In 2011, the Watts group translated the methodology to a continuous-flow microreactor, enabling a reduction in the reaction time from 10 min to 60 s by means of a glass microreactor of 10 μL volume (Scheme 4A, reaction conditions below).<sup>39</sup> Other advantages of the microreactor have been exploited because under pressure, a high-boiling solvent such as DMA could be replaced with MeCN. This could speed up the reaction outcome and the product isolation.

To extend the scope of MW continuous-flow S<sub>N</sub>Ar, a two-step procedure via an epoxide opening/S<sub>N</sub>Ar cyclization was reported by Organ et al. for the synthesis of benzofused sultams (Scheme 4B).<sup>40</sup> The optimal protocol in batch mode was performed under MW irradiation in DMSO at 180 °C in 1 min, and DBU and *t*BuOK were selected as the optimal bases. Scaling up in continuous-flow mode by means of a single-mode Biotage Smith Creator synthesizer equipped with a 1700 μm (int Ø) borosilicate capillary allowed the production of 12 derivatives on a 2 to 3.5 g scale in a 55% average yield. To avoid clogging, the reactions were performed in the presence of DBU.

Claisen rearrangement is accelerated under high-temperature and high-pressure conditions, and the efficacy of MW irradiation to enhance the reaction conversion has been exploited in continuous MW synthesis. Horikoshi et al. studied the influence of MW irradiation on the conversion of 1-allyloxy-4-methoxybenzene (Scheme 5A, reaction conditions above),<sup>41</sup> as they observed that no significant improvement could be discerned when the reaction was performed under conventional conditions or under MW heating in DMSO. Neat conditions enabled the increase in the yield from 2.5 to 36%, and a two-fold yield improvement was observed compared to the reaction heated in an oil bath. A similar study was reported by Larhed et al. to access the applicability of a nonresonant MW system for the continuous MW/flow chemistry.<sup>26</sup> As depicted in the Scheme 5A (reaction conditions below), the reaction has been performed in *N*-methyl-2-pyrrolidone (NMP) and neat at 270 °C, proving the efficacy of higher temperature conditions. In 5 to 15 min, the 2-allyl phenol was obtained in 78 to 85% yield,

respectively, with a calculated throughput of 13.6 and 15.0 mmol/h.

Another study focused on a resonator-type MW reactor in which a helical tubular borosilicate glass reactor was placed within a rectangular resonant cavity where the electromagnetic wave intensity was maintained at the maximum. The Claisen reaction of allyloxy naphthalene was tested as a model reaction, and a detailed evaluation of the effects of the MW power, concentration, and flow rate were described by Koyama et al.<sup>25</sup> An extremely efficient protocol was described in cyclopentyl methyl ether (CPME) with the substrate dissolved at an optimal concentration of 2.0 M in the presence of a back pressure of 2.5 MPa. The solution was heated to 232 °C and flowed at 1 mL/min with a residence time of 1 min to obtain the desired product in >95% yield (Scheme 5B). The scaling up of the reaction was validated with 11 g of starting material that reacted in 30 min, and a productivity of 20.26 g/h was attained.

The Johnson–Claisen rearrangement has been demonstrated to be a suitable option for the MW continuous-flow protocol. Allyl alcohol and triethyl orthoacetate can be converted to ethyl pent-4-enoate with an excellent productivity of 89.5 g/h (Scheme 5C). The desired product was collected in high purity with a residence time of ~1.5 min. 10 to 25 mol % acetic acid was necessary to obtain the product in good yield while the reaction temperature was maintained at 224 °C.

Many examples of the Diels–Alder reaction have been reported in MW irradiation and in flow mode. The beneficial effect of MW irradiation was exploited to optimize the protocol and then was applied to the conventional flow mode. In 2012, Abele et al. reported the Diels–Alder reaction of (cyclohexa-1,5-dien-1-yloxy)trimethylsilane with acrylonitrile and observed that under MW irradiation the side reaction of acrylonitrile polymerization was highly reduced when compared to the conventional oil bath (Scheme 6A).<sup>42</sup> Because the polymerization of acrylonitrile leads to microreactor clogging, the optimization of MW irradiation was performed at different temperatures up to 175 °C, and the authors observed that in 2 h, at 175 °C, acrylonitrile was completely consumed, but 6–8 mol % of dienophile was still present. Therefore, they decided to translate the procedure in flow mode in the presence of excess flow. Working with a coiled stainless-steel tube of 4.5 mL, the reaction was scaled up in flow under solvent-free conditions. The reaction temperature was increased to 30 °C, and the reaction time was decreased to 2 min. When 2 equiv of dienophile was used, in 1.25 min, the reaction was complete, and no precipitation was observed. The conventional continuous flow was performed at 215 °C with a residence time of 60 s to generate 164 g of compound **12** in 45 min in 95% recovery.

The Diels–Alder cycloaddition between furan and diethyl acetylenedicarboxylate has been reported as a model reaction to assess the performance of two different continuous MW equipment setups. Two recent studies reported the reaction performed on meso scale. A 10 mL MW vessel tapered to a threaded inlet was used as a reactor in one case, whereas the other case exploited a helical tubular borosilicate glass reactor of 5.5 to 6.0 mL placed in the resonant cavity (Scheme 6B).<sup>43,44</sup> In the first case, the reaction was performed at 150 °C for 10 min under neat conditions, which revealed that the MW/flow reaction yield was lower when compared with the conventional batch reaction. The 10 mL flow cell was therefore packed with a strong MW adsorber (10% w/w Fe<sub>3</sub>O<sub>4</sub>/sand) to increase the sample temperature, and an increase in the reaction yield from 60 to 70% was observed, but it was still lower than the reaction

conventionally performed batch mode in the absence of the matrix (Scheme 6B, reaction conditions above).<sup>43</sup> The second study reported the optimization of an MW-assisted flow Diels–Alder reaction in a resonant cavity. The optimal reaction conditions were obtained by varying the flow rate, the MW power, and the concentration of reagent.<sup>44</sup> The highest yield of 85% was obtained with a short residence time (1.2 min) at the highest concentration of 4 M in *n*-PrOH at 200–210 °C measured as the exiting temperature (Scheme 6B, reaction conditions below). The authors observed that the advantages of continuous flow in this reaction were correlated to the rapid heating with a residence time shorter than 1.5 min as well as the rapid cooling to reduce the impact of the retro Diels–Alder reaction, which affects the reaction at an elevated temperature.

Furthermore, the Diels–Alder reaction has been successfully studied in the chemical derivatization of graphene and fullerene, and MW irradiation has been shown to improve its efficiency (Scheme 6C). A recent example includes the synthesis of an indene-C60 monoadduct and an indene-C60 bis-adduct. Because of their high open cell voltages, these products are used in polymer solar cells, and the scaling up of their synthesis is highly desirable. To achieve maximum productivity, the authors optimized the reaction at a temperature of up to 270 °C with the highest concentration of indene in *o*-xylene. The flow rate was maintained at 11.6 mL/min (residence time of 0.4 min), and the productivity was found to be 1.07 g/h.<sup>45</sup>

With the aim to secure arylbutanamides on a large scale, a pharmaceutically relevant substructure, the C-alkylation of dimethylacetamide with styrene has been studied using MW irradiation and scaled up in MW continuous flow mode (Scheme 7).<sup>46</sup> Interestingly, an optimized protocol allowed the use of *t*-BuOK instead of a stronger base such as BuLi with superb results in the synthesis of a large array of derivatives. When the reaction was scaled up in flow mode in a resonant MW cavity, excellent results were obtained, and the reaction could be scaled up to reach a productivity of almost 65 g/h. A high selectivity of mono- versus dialkylated product was obtained (10:1 mono/dialkylated).

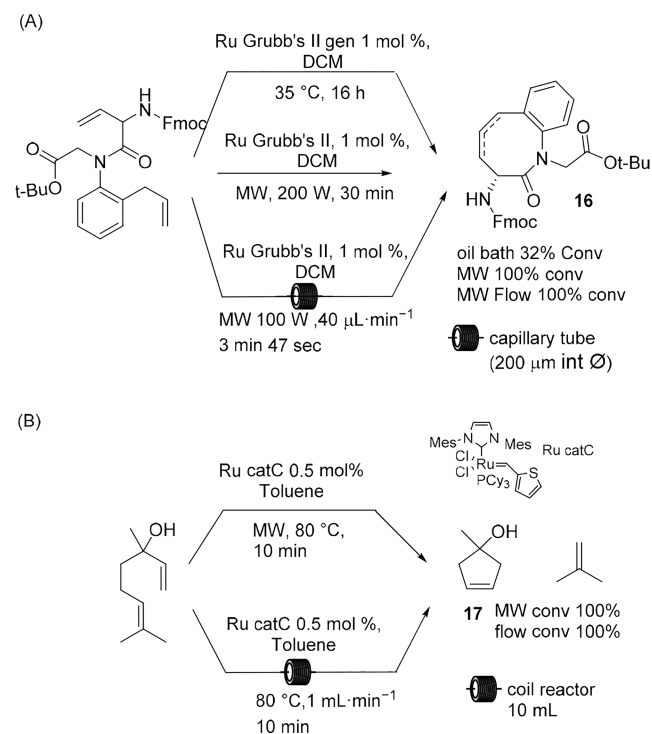
## ■ APPLIED HOMOGENEOUS AND HETEROGENEOUS CATALYSIS

MW-assisted synthesis has been largely applied to organometallic reactions,<sup>47–50</sup> including a review in 2019 on the continuous-flow Suzuki–Miyaura and Mizoroki–Heck reactions describing the efficacy of MW heating in scaling up of the reaction protocols in continuous mode.<sup>51</sup> In addition to palladium-catalyzed synthesis, a few examples of homogeneous organometallic catalysis with other metals have been scaled up under MW continuous flow mode, and several examples have documented the attempts to optimize the scalable processes in MW batch synthesis.

Ru-catalyzed metathesis has been reported under MW irradiation,<sup>52,53</sup> and an example of the scalable procedure was proposed by Grella et al. with the aim to contribute to the scaling up of the synthesis of Apremilast, an orally active drug for the treatment of psoriatic arthritis and psoriasis; nevertheless, the reaction has been reported on only a small scale.<sup>54</sup>

An example of the nonconventional scaling up of ring-closing metathesis (RCM) was proposed by Organ et al.<sup>55</sup> The generation-II Grubbs catalyst was tested, and the authors compared the conventional conditions, MW batch irradiation, and continuous flow irradiation with a capillary-based flow system in the synthesis of compound **16**. As depicted in Scheme

## Scheme 8. Ruthenium-Catalyzed Ring-Closing Metathesis



8A, interestingly, the reaction was performed in DCM, an MW transparent solvent ( $\tan \delta$  0.040); nevertheless, the study showed that MW irradiation showed higher conversion when compared with the conventional conditions, suggesting a direct

## Scheme 10. Large-Scale Cu(0) Nanoparticle-Catalyzed Reduction of Nitrobenzene in Conventional and in MW Batch Mode

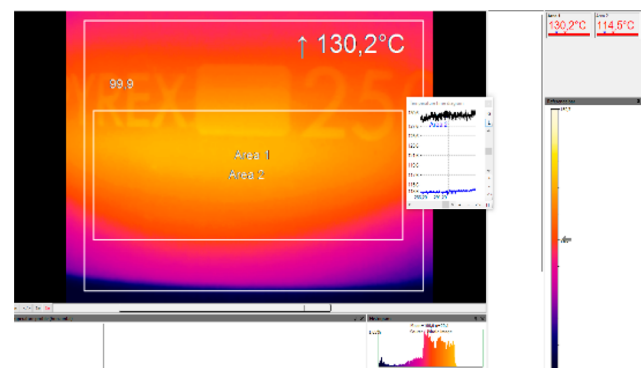
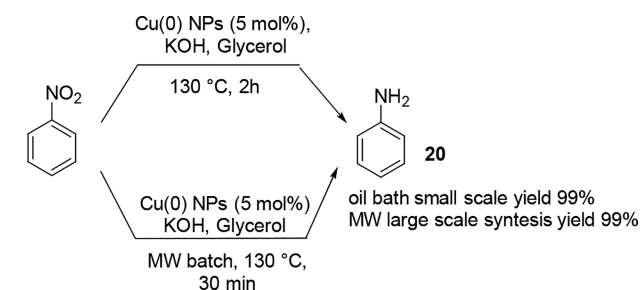


Figure 5. Density of temperature recorded by an IR camera in an MW-irradiated reduction of nitrobenzene Cu(0) nanoparticles cat. Reproduced with permission from ref 70. Copyright 2020 The Authors.

## Scheme 9. Macrocyclization

