



A continuous-flow resonator-type microwave reactor for high-efficiency organic synthesis and Claisen rearrangement as a model reaction

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Abstract

We have developed a single-mode microwave reactor for continuous-flow synthesis with various methods of operation. This device measures the resonant frequency and modulates the oscillation frequency accordingly to maintain the maximum electric field intensity in the cavity. It can be operated either using constant applied irradiation power or using new programs which change the electric power (E-GRA) and change the flow rate (FI-GRA), in order to rapidly screen various reaction conditions. As a model reaction, the Claisen rearrangement reaction of allyl 1-naphthyl ether **1** was rapidly optimized in this device, affording the desired product 2-allylnaphthalen-1-ol **2** in high (91%) yield and up to 20 g/h productivity.

Keywords Continuous flow · Microwave · Single-mode microwave reactor · Flow synthesis · Claisen rearrangement

Introduction

Conventionally, organic reaction systems are heated by external heaters such as oil baths. However, over the last 30 years microwave (MW) heating has been utilized [1, 2] due to its advantages such as non-contact heating (which reduces the overheating of material surfaces), energy transfer instead of heat transfer (penetrative radiation) and material selectivity. Moreover, MW heating has the ability to rapidly heat or cool mixtures, where and heat transfer can benefit from the transport of heat from the interior of the reactor outward, instead of the transport of heat from the surface of reactor inward [3]. MW heating often gives higher yields and purities of products

in shorter time periods than conventional heating [4]. Hence, the number of reports on organic synthesis using MW heating has grown in the past decades [5, 6].

The MW oscillator is either a magnetron or a solid-state device, which differ in their profile of emitted frequencies and output power. Whilst the magnetron is capable of several hundred watts of MW power, it emits numerous MW frequencies over a broad distribution and the frequency cannot be controlled. Regarding MW-assisted chemical reactions, magnetron oscillators have typically been utilized. The cavity which accepts the MW irradiation is either a multimode or single-mode cavity. Multimode cavities work by accepting the broad range of MW frequencies emitted by the magnetron at various orientations (modes) and allowing them to distribute randomly within the cavity [7, 8]. Single-mode cavities work by generating a definable MW waveform [7–11]. Compared to multimode cavities, single-mode cavities have higher energy efficiency and well-defined electromagnetic fields which can be matched to the reactor vessel geometry and position.

Several batch reaction-type MW reactors have been commercially available since 1997 [12–15]. These reactors use a magnetron oscillator to irradiate a load within either a multimode or a single-mode cavity. Under multimode irradiation, it is difficult to control local temperature distribution due to the unknown and uneven distribution of the MW intensity. In some cases, MW energy does not propagate through the load and is instead reflected and converted into undesired

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forms of energy. On the other hand, single-mode irradiation harnesses a greater proportion of the energy distribution and in a well-designed reaction vessel, energy can be efficiently propagated. In either case, however, it is difficult to scale up MW-mediated syntheses from laboratory scale to production scale simply by using a larger reactor. This is because (1) the penetration depth of microwaves into the absorbing target is restricted and (2) if the reaction is carried out under high pressure, there can be a significant danger of the reaction vessel undergoing malfunction and/or rupture. Notably, a continuous-flow approach bypasses both problems.

Continuous-flow processing has shown benefits over batch processing mode in terms of environmental impact, efficiency and safety [16]. By combining a continuous-flow system with MW heating, it is possible to scale up MW chemistry without necessarily increasing the size of the reaction vessel. The synergy of MW heating and flow chemistry was pioneered by Strauss et al. [17, 18] and Wang et al. [19] almost three decades ago. Initial efforts used a commercially available MW oven fitted with a reaction tube for flow. Such systems were expected to become powerful tools in organic synthesis [18]. Indeed, there have been several reports on organic synthesis in this context such as Pd-catalyzed C-C bond formations [20–24], biodiesel synthesis [25–29] and others [30–33], using a flow-type MW device. Flow-type MW heating in a microcapillary reactor has also been utilized in various reactions [34–37]. Recently, several reactions were demonstrated on gram/h scale by placing a custom-made flow cell within a commercially available MW device [38–43]. Commercially available MW flow reactors are also available [15, 44]. However, the distribution of electromagnetic field in these commercial devices is poorly characterized, so the irradiation distribution is hard to define. If the distribution of the electromagnetic field within the cavity is known, it is possible to efficiently and reproducibly irradiate a reaction vessel at the same position with the same MW power in order to realize the reproducibility of the target reaction.

We previously reported a single-mode MW device for continuous-flow synthesis (MW flow reactor), with a resonator in which the electric field is well-amplified and well-characterized [45]. The MW generator is a solid-state device which generates a uniform electromagnetic field within the cavity. Tuning of the irradiation frequency uses a technology which adjusts the frequency for detected electric power in the resonator to be maximized. Moreover, the reactor can tolerate high pressures (MPa) and allow the straightforward and safe operation of reactions at temperatures above the boiling point at normal pressure. We previously demonstrated the syntheses of carbazole derivatives [45] and the Diels-Alder reactions of fullerenes with indene derivatives [46] using this apparatus. Ley et al. have used it in the syntheses of β -lactams [47]. Very recently, further applications of this device to other classes of reactions have been disclosed [48–52]. These reactions all required elevated

conditions of temperature and pressure and were ideally suited to scale-up in the aforementioned MW flow reactor.

Compared to conventionally-heated stainless-steel coil flow reactors [53–55], the MW flow reactor benefits from 1) faster data acquisition toward optimization, by virtue of the ability to rapidly heat or cool mixtures under MW irradiation [46] and 2) negligible thermal expansion (even up to 270 °C) due to the lower coefficient of thermal expansion of reactor material (Duran) combined with engineering controls [46]. Thermal expansion has been shown to result in up to ca. 40% larger collected reaction mixture volume than expected when operating at elevated temperatures (up to 300 °C) in a stainless-steel coil flow reactor [56]. Moreover, reports of thermal and non-thermal MW heating effects [5] which benefit reaction conversion may be realized in this device.

The Claisen rearrangement is another class of reaction which generally requires high temperature and has previously benefitted from conventionally-heated flow reactors [57–59]. Herein, we report the incorporation and application of new operation programs into this MW flow reactor, which either 1) hold the flow rate constant and vary the applied MW power (E-GRA) or 2) hold the MW power constant and vary the flow rate (FI-GRA). Thus, many reaction conditions can be rapidly screened in a short time allowing optimum reaction conditions to be quickly identified. The Claisen rearrangement of an allyl 1-naphthyl ether *I* was chosen as a model reaction for this study [60].

Results and discussion

The MW flow reactor is composed of a power supply, MW irradiation unit and cavity (TM₁₁₀ type rectangular resonant cavity: 79 mm × 81 mm × 100 mm), a pumping unit capable of flow rates up to 2 × 9.9 mL/min and a personal computer (PC) controlling the device (for an image of the complete setup, see Supporting Information, SI-1). A helical tubular borosilicate glass reactor (o.d. 4.0 mm, i.d. 2.4 mm, length: 100 mm internal volume in the resonant cavity: 1.0 mL, see Fig. 1a) is placed within the TM₁₁₀ type rectangular resonant cavity. In order to bring the resonance frequency within operational range of the ISM band, a tube of borosilicate glass (o.d. 20 mm, i.d. 17.6 mm, length 140 mm) was installed around the reaction tube.

This device has a built-in resonance frequency measurement system and a solid-state oscillator controlled by an algorithm that modulates the resonance frequency, so that the electromagnetic wave intensity in the cavity is maintained at the maximum. The exit temperature of the reaction solution is directly measured using a thermocouple installed at the outlet of the flow channel, set at a position which does not interact with the microwaves in the cavity. In summary, the present device can monitor and control the MW irradiation power, the reflected power, the electric field in the cavity, the pressure of

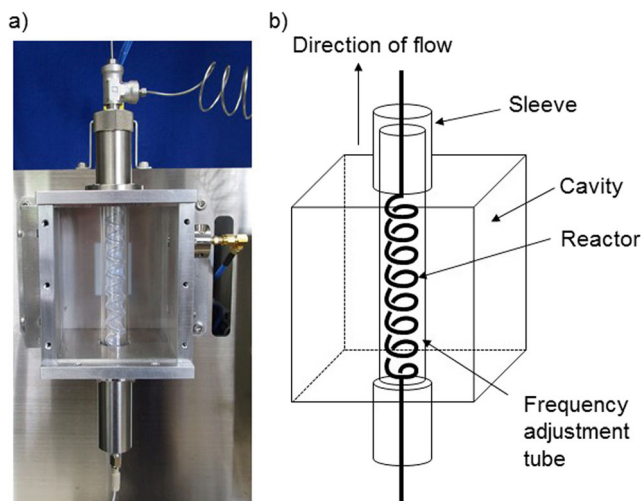


Fig. 1 a) Photograph and b) schematic of the helical tubular borosilicate glass tube reactor set in the resonant cavity

the reaction solution and the exit temperature of the reaction solution at the outlet of the flow channel in real time.

First, the resonant frequencies and electric power reflectances of the cavity containing the helical tubular flow channel filled with various solvents were measured at room temperature by the MW flow reactor's in-built 'Peakfinder' function. Solvents measured included those of high-polarity like dimethyl sulfoxide to those of low-polarity like decahydronaphthalene. The results in Table 1 show all measured resonance frequencies within the 2.40 to 2.50 GHz operational range of the MW flow reactor. The difference in electric power reflectance is caused by dielectric loss, ϵ_r'' of the solvents. A small ϵ_r'' value corresponds to high reflectivity. The electric power propagation was efficient across the board, even for *o*-xylene which gave 27.8% reflectance.

CPME is an acyclic ether solvent that can be used as a replacement for diethyl ether in a wide temperature range from $-140\text{ }^\circ\text{C}$ to $106\text{ }^\circ\text{C}$ [61]. It is easy to remove due to its low latent heat of evaporation, has a high ability to solubilize various organic substances and has high stability without producing peroxide. The $\epsilon_r' - j\epsilon_r''$ value of CPME at 2.45 GHz was $4.38 - j0.17$ and the reflectance in this system was 17.5%. Hence, CPME is a low polarity solvent whose MW heating is challenging due to low MW absorption. Therefore, heating of CPME was attempted using this device.

The measured temperature profile of CPME by MW heating is shown in Fig. 2. The heating was carried out under a constant flow rate and constant applied power (ISO method). The volume of the flow channel is 1.0 mL, resulting in a residence time of ($R_T =$) 1 min when the flow rate is 1.0 mL/min. After eight residence times, ($8 \times R_T$) at 45 W MW irradiation, the temperature stabilized at $208.1\text{ }^\circ\text{C}$. The boiling of CPME was prohibited by the back pressure regulator set to 2.5 MPa.

Next, to control the temperature of the flow channel, heating was carried out under a constant flow rate and stepped applied power (E-GRA method). The temperatures at each applied power are shown in Fig. 3. When the power increase of each step was from 20 to 80 W in 5 W steps, the temperature increase was ca. $17\text{ }^\circ\text{C}$ and the temperature became steady after 3 min without overheating (see Supporting Information, SI-2-1).

As the applied power of the MW increased, the temperature of the CPME first increased almost proportionally, reaching about $270\text{ }^\circ\text{C}$ at 60 W. At higher applied MW powers, the temperature was almost steady and is presumed to be the boiling point of CPME at 2.5 MPa [62]. The above data show that CPME can be heated to very high temperatures ($270\text{ }^\circ\text{C}$)

Table 1 Resonant frequencies and reflectances of various solvents measured by the MW flow reactor's in-built 'Peakfinder' function^a

Solvent ^b	$\epsilon_r' - j\epsilon_r''$	Resonant frequency (GHz)	Reflectance (%)
DMSO	$44.2 - j 11.1$	2.405	8.8
DMF	$36.9 - j 5.2$	2.410	1.1
Acetonitrile	$35.4 - j 1.8$	2.410	6.9
MEK	$18.6 - j 1.1$	2.425	14.1
Ethanol	$7.5 - j 7.0$	2.435	3.4
EA	$7.25 - j 0.2$	2.439	18.9
THF	$6.2 - j 0.3$	2.439	20.4
CPME	$4.38 - j 0.17$	2.444	17.5
<i>o</i> -Xylene	$2.70 - j 0.08$	2.459	27.8
Toluene	$2.5 - j 0.1$	2.448	20.3
Decalin	$2.14 - j 0.001$	2.448	21.9

^a A borosilicate glass pipe was placed around the helical tubular spiral-shaped flow channel in order to adjust the frequency

^b DMSO, dimethylsulfoxide; DMF, *N,N*-dimethylformamide; MEK, methyl ethyl ketone; EA, ethyl acetate; THF, tetrahydrofuran; CPME, cyclopentyl methyl ether

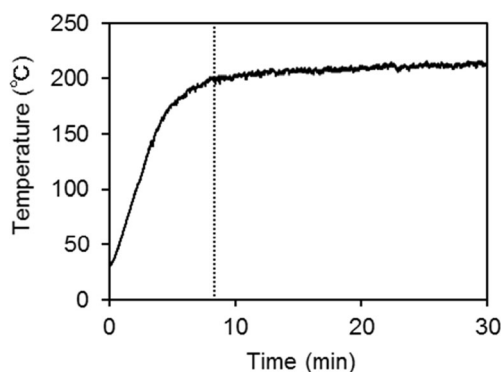


Fig. 2 Heating curve of CPME when irradiated with MW in the ISO method for up to 30 min. Flow rate: 1.0 mL/min, back pressure: 2.5 MPa, applied power: 45 W

at only 60 W using the MW flow reactor, with a flow rate of 1.0 mL/min and under back pressure of 2.5 MPa.

The throughput of a flow reactor can be increased by increasing the flow rate, in principle increasing the productivity with a fixed reactor size. However, at high flow rates, a temperature decrease can accompany the increased throughput, which may decrease conversion of the reaction. To balance the throughput and conversion, heating was carried out under constant applied power (50 W) and stepped flow rate (decreasing from 2.4 to 0.6 mL/min by 0.2 mL/min every 10 min, FI-GRA method) under a back pressure of 2.5 MPa. The stabilized temperatures at each flow rate are shown in Fig. 4 (see Supporting Information SI-2-2). As the flow rate declined, the temperature of CPME in the flow channel increased. The rate of temperature change was small because heat dissipation was very fast at such high temperatures.

Next, we tested the Claisen rearrangement of allyl 1-naphthyl ether **1** as a model reaction using this system (Scheme 1) [63, 64]. The Claisen rearrangement of an allyl aryl ether generally requires an elevated temperature for an extended reaction time [57–59]. The current system was envisaged to efficiently heat the reaction solution to a high temperature in a short time by using direct MW heating. The

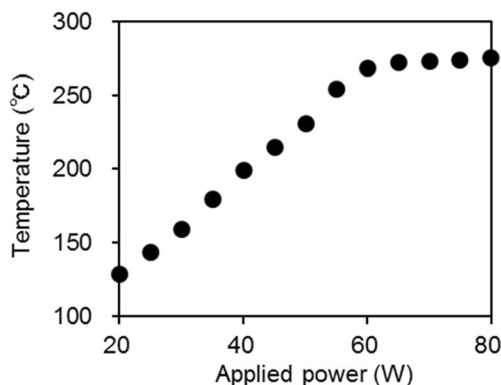


Fig. 3 Temperature of CPME at each applied power in the E-GRA method. MW power increased in 5 W steps within the range of 20–80 W, at a flow rate of 1.0 mL/min and under back pressure of 2.5 MPa

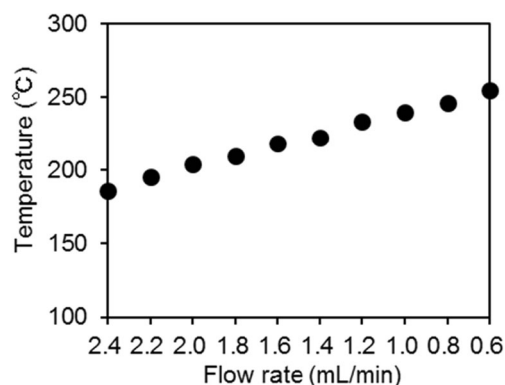


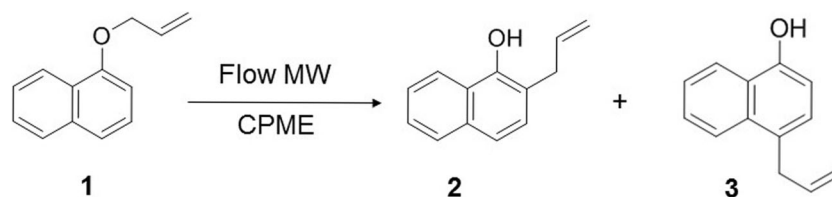
Fig. 4 Temperature of CPME at each flow rate by FI-GRA method. Flow rate: from 2.4–0.6 mL/min stepwise by 0.2 mL/min every 10 min, applied power: 50 W, back pressure: 2.5 MPa

benefits of this machine towards rapid screening and identification of optimal reaction conditions have been highlighted by recent studies [45, 46, 50, 51].

First, the E-GRA method was used to identify a suitable reaction temperature. A CPME solution of **1** (50 mM) was heated by MW with the applied power increasing from 34 to 60 W in 2 W steps, under the flow rate of 1.0 mL/min and a back pressure of 2.5 MPa. As the applied power increased, the conversion of **1** increased as the stabilized temperature gradually increased from 163.5 °C to 263.5 °C. The stabilized temperature and the yields of compounds **1–3** at each step are shown in Fig. 5 (see Supporting Information SI-5-1).

With an applied power of 60 W, the temperature of the solution reached 264 °C and the conversion of **1** was 98.7%, indicating that the reaction proceeded almost quantitatively at the corresponding residence time ($R_T = 1$ min). Traces of unreacted **1** (1.3%), in addition to the *o*-Claisen rearrangement product 2-allyl-1-naphthol (**2**) (86.3%) and a small amount of *p*-Claisen rearrangement product 4-allyl-1-naphthol (**3**) (3.3%) were observed in the reaction mixture. In Claisen rearrangements of allyl aryl ethers, the *o*-Claisen rearrangement product often undergoes enolization to give an *o*-allyl phenol derivative [65, 66]. Moreover, it is known that the *p*-Claisen rearrangement product occurs for allyl aryl ethers with substitution at the *o*-position via Cope rearrangement of the enol intermediate [67]. A previous study showed that the reaction of **1** produces both **2** and **3** [67].

In the E-GRA experiment, 14 reaction conditions at different temperature were examined within only 3.5 h and the effect of temperature on the yields of **1**, **2** and **3** was successfully investigated. The yield of **2** increased as the temperature of the solution increased. On the other hand, the yield of **3** first gradually increased with the temperature, reaching a maximum value at 227.4 °C and then declined. Access to intermediate **5** would involve dearomatization of the two aromatic rings instead of one, thus it is proposed that rearrangement via intermediate **4** takes precedence. Subsequent enolization proceeded rapidly and *ortho*-rearranged **2** was obtained as the



Scheme 1 Claisen rearrangement of **1**

main product. As the temperature increases, the rearrangement of intermediate **4** to intermediate **6** increases the amount of product **3** to a certain threshold (227.4 °C). However, under higher temperatures, the mass balance remains relatively constant and the increasing yield of **2** cannot be explained solely by the conversion of substrate **1** and is accompanied with a decreasing yield of **3**. Presumably, this is due to the known reversibility of this reaction [61] giving rise to **2** as the thermodynamic product. In this reaction, it was found that the production amount of **3** varies depending on the reaction temperature (Scheme 2).

Subsequently, we investigated the influence of the flow rate on the Claisen rearrangement of **1** using the FI-GRA method. The CPME solution of **1** (50 mM) was irradiated under an applied MW power of 50 W and a back pressure of 2.5 MPa whilst the flow rate was decreased from 2.2–0.6 ml/min in steps of 0.2 mL/min. The yields of **1–3** at each step are displayed in Fig. 6. As the flow rate decreased, the temperature of the solution gradually increased from 163.5 °C to 263.5 °C (see Supporting Information SI-5-2).

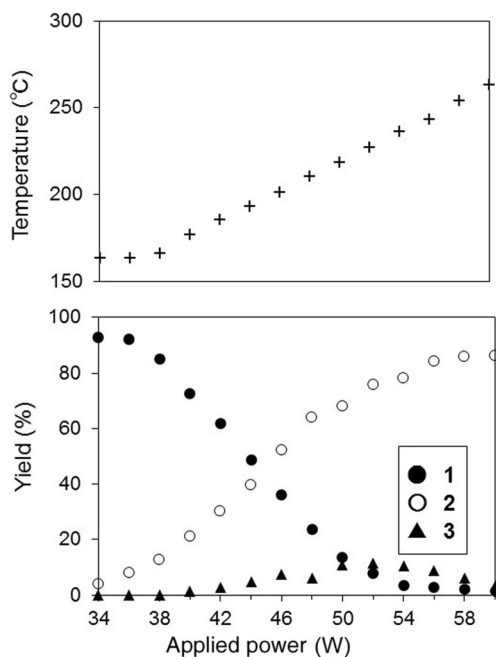
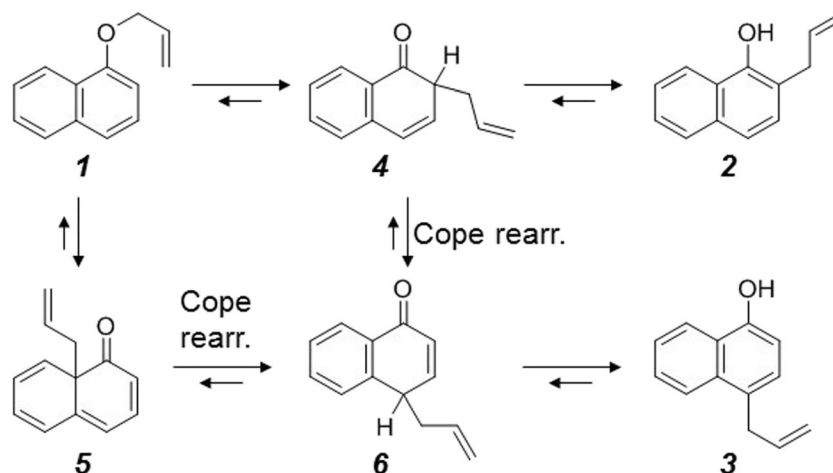


Fig. 5 Temperature of the reaction solution and the yields of **1–3** at each applied power (34–60 W) at a flow rate of 1.0 mL/min and under back pressure of 2.5 MPa. Yields are calculated by ¹H NMR spectroscopic analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene (1.0 eq.) as an internal standard

As the flow rate decreased, both the residence time of the solution and the temperature increased. Therefore, the conversion of **1** and the yield of **2** increased as the solution temperature rose (Table SI-5). On the other hand, the yield of **3** at its maximum at the flow rate of 1.0 mL/min (225 °C) and decreased at flow rates slower than 1.0 mL/min (and higher temperatures than 225 °C). This is the same trend as the E-GRA method, which gave the maximum yield of **3** at the same specific temperature (ca. 226 °C). When the residence time was longer, the reaction selectivity favoured **2**. At the lowest flow rate of 0.6 mL/min, the temperature became ca. 232 °C and **1** reacted completely. We found that the reaction was accelerated by the temperature rises as a result of (and possibly in addition to) the longer residence times employed.

Next, the concentration of **1** in the solution was increased from 0.05 to 2.0 M in order to increase the g/h productivity. The other conditions were: an applied MW power of 50 W, a flow rate of 1.0 mL/min and a back pressure of 2.5 MPa in ISO mode. As the concentration of **1** increased, the temperature of the solution increased slightly as shown in Fig. 7 (see Supporting Information SI-5-3). Furthermore, the conversion of **1** and the yield of **2** increased, while the yield of **3** decreased. At a concentration of 2.0 M, the temperature reached was 232.8 °C and the yield of **2** was 96.3%.

To explain the observed influence of reactant concentration, the ϵ'' values of the solutions were measured. As shown in Table 2, an increasing concentration of **1** leads to an increasing $\tan \delta$ at 2.45 GHz (at 2.0 M, the $\tan \delta$ is similar to that of H₂O). This suggests that a more concentrated reaction solution exhibits stronger MW absorption which explains the observed temperature increase with higher concentration of **1** in Fig. 7, despite identical irradiation power. Such behavior demonstrates the selective heating of molecules of **1** over CPME; at the same overall reaction temperature, the substrate molecules experience a greater proportion of the heating. This highlights the advantage of MW heating toward large-scale operations, where larger tube diameters and faster flow rates (for example, using laminar flow) would suffer inferior heat transfer from conventional heating [68, 69]. Toward industrial-scale applications, larger version MW-flow reactors are available, with 2 pumps capable of delivering up to 50 mL/min flow rates (100 mL/min in total) through a 6.0 mL helical tube reactor. Systems capable of 250 W MW input power are currently in development. Scale-up becomes possible by increasing the flow rate for a given residence time. Extension of



Scheme 2 *o*- and *p*-Claisen rearrangement products of **1**.

the residence time can be achieved by lengthening or widening the reaction tube within the MW cavity. Due to the MW intensity distribution being maximized at the center of the cavity, increasing the winding density of the coiled reactor tube would be an effective method. An additional increase in channel volume can be realized by increasing the cavity length or by stacking multiple cavities in series.

Based on the above findings, the operation time for the Claisen rearrangement of **1** was extended under the appropriate conditions (2.0 M, 50 W, flow rate 1.0 mL/min, back pressure 2.5 MPa). A solution containing 11.1 g of **1** was processed over 30 min at 259.9 °C. The crude yields of **2** and **3** were 91.3% and

2.6%, translating to productivities of 20.26 g/h and 0.29 g/h, respectively. The isolated yields of **2** and **3** after purification were 9.17 g (82.6%) and 0.29 g (2.6%), respectively. Thus, scalability of the Claisen rearrangement of **1** was demonstrated in the MW flow applicator as well as the ability to safely execute the process at a temperature > 100 °C higher than the b.p. of the solvent (CPME) over an extended operation time. Regarding scalability, the g/h productivity and employed flow rate of the MW flow Claisen rearrangement herein are similar to (or superior to) previously reported Claisen rearrangements in conventionally-heated flow reactors [57–59].

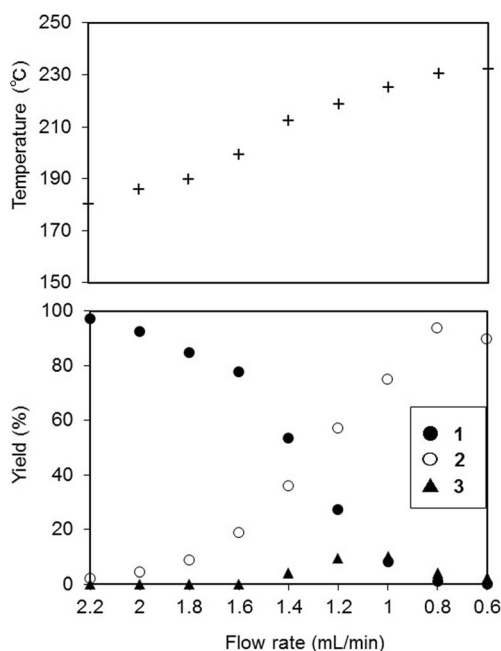


Fig. 6 Temperature of the reaction solution and the yields of **1–3** at each flow rate (2.2–0.6 mL/min) under the applied power of 50 W at a back pressure of 2.5 MPa. Yields are calculated by ^1H NMR spectroscopic analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene (1.0 eq.) as an internal standard

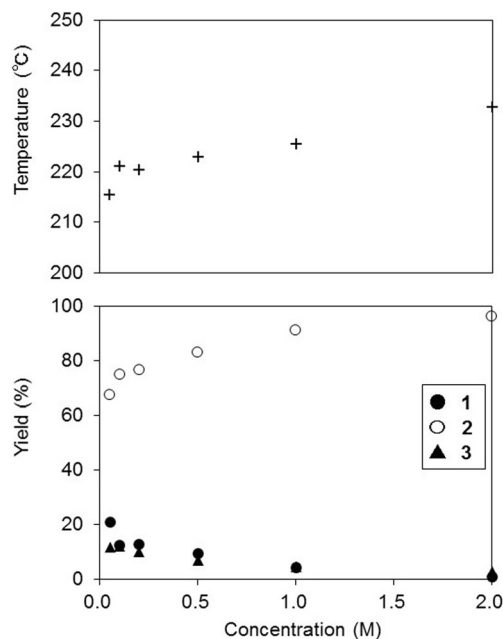


Fig. 7 Temperature and yield versus solution concentration of **1**. Flow rate: 1.0 mL/min, solution concentration: 0.05–2.0 M, applied power: 50 W, back pressure: 2.5 MPa. Yields are calculated by ^1H NMR spectroscopic analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene (1.0 eq.) as an internal standard

Table 2 Relationship between concentration of **1**, complex permittivity ϵ and $\tan \delta$

Concentration of 1	ϵ_r' @ 2.45 GHz ^a	ϵ_r'' @ 2.45 GHz ^a	$\tan \delta$ @ 2.45 GHz
CPME only	4.38	0.17	0.039
0.05 M	4.40	0.16	0.036
0.1 M	4.39	0.18	0.042
1.0 M	4.28	0.26	0.062
2.0 M	4.25	0.36	0.085

^a Estimated by the coaxial probe method at room temperature

Conclusion

A continuous-flow MW device (MW flow reactor) was developed with adjustable applied MW power and flow rate, which was applied to the Claisen rearrangement reaction of allyl 1-naphthyl ether as a model reaction. The effects of MW power, flow rate and reactant concentration on the yield and productivity were examined. By virtue of the ability to rapidly change reaction temperature by MW heating, combined with the ability of continuous-flow to quickly screen different reaction conditions, the optimal reaction temperature was swiftly identified by screening 14 different temperatures in just 3.5 h. Prolonged continuous operation was performed under the determined optimum reaction conditions, to demonstrate scalability and viability toward production. Finally, whilst it is generally thought that solvents with poor MW absorption (low ϵ_r') are unsuitable for MW reactions, our system successfully heated CPME solvent up to 260 °C in a safe manner in continuous-flow. Application of this device to other organic reactions, as well as the influence of substrate-selective heating detected herein on the reaction conversion are topics currently under investigation.

Experimental section

General information

All reagents and solvent are commercially available and were used without further purification. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE III 400 MHz using tetramethylsilane (TMS) as internal standard in chloroform-*d* (CDCl₃). The purification of reaction mixture was performed by recycling gel permeation (GPC) chromatography (chloroform as eluent, Japan Analytical Industry Co., Ltd.).

Synthesis of **1**

Compound **1** was prepared according to a literature procedure [70]. To a mixture of 1-naphthol (M.W. = 144.17, 15.0 g, 104.0 mmol) and allyl bromide (M.W. = 120.98, 15.0 g, 124.0 mmol) in acetone (200 mL), 7.0 g of KOH (M.W. =

56.11, 124.8 mmol) was added under nitrogen. The mixture was stirred at 60 °C for 2 h and then filtered. The filtrate was concentrated in vacuo and the residue was purified by using GPC to afford **1** in chloroform as a colorless oil (20.1 g, 95% yield); ¹H NMR (400 MHz, CDCl₃) δ 8.33–8.30 (m, 1 H), 7.81–7.78 (m, 1 H), 7.50–7.44 (m, 2 H), 7.42 (d, J = 8.2 Hz, 1 H), 7.35 (t, J = 7.7 Hz, 1 H), 6.80 (d, J = 7.5, 1H), 6.22–6.12 (m, 1 H), 5.52 (d, J = 22.7 Hz), 5.33 (d, J = 12.4 Hz), 4.71 (dt, J_1 = 5.1 Hz, J_2 = 1.5 Hz, 2 H); ¹³C NMR (400 MHz, CDCl₃) δ 154.2, 134.5, 133.3, 127.4, 126.3, 125.7, 125.7, 125.1, 122.1, 120.3, 117.2, 105.0, 68.8 ppm. ¹H and ¹³C NMR data are consistent with the literature.

Configuration of a flow type microwave reactor

The output power of this system is 10 to 100 W where microwaves can be irradiated continuously. The flow system is equipped with a back pressure regulator after the reactor and a cooling coil, so that the pressure of the flowing solution can be set between 1.0–3.0 MPa. When the pressure was below 1.0 MPa, MW irradiation was stopped in order to prevent bumping of the solution. The upper and lower-limits of the settable flow rate were 0.1 to 9.99 mL/min.

Measurement of resonance frequency and reflectance

The resonance frequency and reflectance of each solvent at room temperature were measured as follows. The helical tubular reactor was filled with solvent, plugged in the upper and lower entrances and set at the center of the cavity. In order to adjust the resonance frequency, a cylindrical borosilicate (Duran) tube (outer diameter: 20 mm, inner diameter: 17.6 mm, length: 140 mm) was placed around the helical reactor. Then, the resonance frequency and reflectance were measured using the 'Peakfinder' function of the flow-type MW reactor.

Microwave irradiation of CPME using ISO method

The applied power, flow rate and back pressure were set to 45 W, 1.0 mL/min and 2.5 MPa, respectively. After filling the flow path with CPME, the flow was started and the back

pressure was increased to 2.5 MPa. Then, MW irradiation was carried out for 30 min.

Microwave irradiation of CPME using E-GRA method

After filling the flow path with CPME, CPME was flowed at a rate of 1.0 mL/min and a back pressure of 2.5 MPa. The MW was applied with the initial power setting (20 W). The E-GRA test was started upon reaching stable temperature. Under this method, the power of the MW irradiation was increased stepwise by 5 W every 15 min from 20 to 80 W.

Microwave irradiation of CPME using FI-GRA method

After filling the flow path with CPME, CPME was flowed at an initial flow rate of 2.4 mL/min under an output electric power of 50 W and a back pressure of 2.5 MPa. After the MW application was started and the temperature stabilized, the FI-GRA method was carried out. In this method, the flow rate was decreased from 2.4 to 0.6 mL/min in steps of 0.2 mL/min every 10 min.

Microwave irradiated reaction of **1** in CPME solution using E-GRA method

The reactant **1** (M.W. = 184.23, 2.763 g, 15.0 mmol) was dissolved in CPME (300 mL) to prepare a 50 mM solution of **1**. After the flow path was filled with CPME only, CPME was flowed at a rate of 1.0 mL/min and a back pressure of 2.5 MPa. The MW was applied with the initial power setting (20 W). After the temperature stabilized, the flow path was switched to CPME solution of **1** (50 mM) and was discarded for the same volume as the entire flow path (ca. 8 mL) before the E-GRA mode was started. The power of MW irradiation was increased stepwise by 5 W every 15 min from 34 to 60 W. After each change in the applied power and reaching stable temperature, the initial 9 mL reaction solution was discarded and then 5 mL of subsequent solution was collected and used for yield determination. To these 5 mL aliquots collected at different temperatures were added 0.5 mL aliquots of 1,3,5-trimethoxybenzene solution in acetonitrile (500 mM) as an internal standard to match the initial material (1 eq.) and then the solvent was removed in vacuo. The recovery ratio of **1** and the yields of **2** and **3** were calculated by the ^1H NMR spectrum of the crude reaction mixture.

Microwave irradiated reaction of **1** in CPME solution using FI-GRA method

The reactant **1** (2.763 g) was dissolved in 500 mL of CPME (50 mM). The flow rate was decreased from 2.2 to 0.6 mL/min stepwise by 0.2 mL/min every 10 min using the FI-GRA method. The flow path was filled with pure CPME, then

CPME flow was started at the set initial flow rate of 2.4 mL/min and back pressure of 2.5 MPa. MW irradiation was started at an applied power of 50 W. After the temperature stabilized, the liquid was switched to CPME solution of **1** (50 mM). After each change in the applied power, the initial 9.5 mL of the reaction solution was discarded and then 5 mL of solution was collected and used for yield determination. To these 5 mL aliquots collected at different temperatures were added 0.5 mL aliquots of 1,3,5-trimethoxybenzene solution in acetonitrile (500 mM) as an internal standard to match the initial material (1 eq.) and the solvent was removed in vacuo. The recovery ratio of the starting material **1** and the yields of **2** and **3** were calculated by the ^1H NMR spectrum of the crude reaction mixture.

Microwave irradiation of CPME solutions of **1** at various concentrations using ISO method

The reactant solutions (**1** in CPME at 50 mM, 100 mM, 200 mM, 500 mM, 1.0 M and 2.0 M) were prepared with a volume of 50 mL each. The reaction conditions all used MW power of 50 W, ISO mode, a flow rate of 1.0 mL/min and a back pressure of 2.5 MPa. CPME was flowed and irradiated until constant temperature was achieved. Then, the flow of CPME solution of **1** was started and was discarded for the same volume as the entire flow path (ca. 8 mL) and then 5 mL of subsequent solution was collected. To these 5 mL aliquots collected at different temperatures were added 0.5 mL of 1,3,5-trimethoxybenzene solution in acetonitrile (500 mM) as an internal standard to match the initial material (1 eq.) and the solvent was removed in vacuo. The recovery ratio of the starting material **1** and the yields of **2** and **3** were calculated by the ^1H NMR spectrum of the crude reaction mixture.

Microwave irradiation of CPME solution of **1** for 30 min using ISO method

The solution of **1** in CPME was prepared (2.0 M, 80 mL). The reaction conditions used MW power of 50 W, ISO mode, a flow rate of 1.0 mL/min and a back pressure of 2.5 MPa. CPME was flowed and the 50 W MW irradiation was used to achieve constant temperature. Then, the flow of a CPME solution of **1** was started and was discarded for the same volume as the entire flow path (ca. 8 mL). Then, 30 mL of the reaction solution was collected over 30 min. To this 30 mL aliquot was added 1,3,5-trimethoxybenzene solution in acetonitrile (500 mM) as an internal standard so as to match the initial material (1 eq.) and then the solvent was removed in vacuo. The recovery ratio of the starting material **1** and the yields of **2** and **3** were calculated by the ^1H NMR spectrum of the crude reaction mixture. The crude reaction mixture was then purified by GPC to determine the isolated yields of compounds **1–3**.

Measurement of permittivity

A network analyzer (Rohde & Schwarz ZVB14, 10–14 GHz) was used to determine the permittivity of samples. The complex relative permittivity (ϵ_r^*) was determined by the coaxial probe method using the ϵ_r and $\tan \delta$ measurement system (Keycom Corp.). The real and imaginary parts of ϵ_r^* are equivalent to ϵ_r' and ϵ_r'' , respectively. The dielectric and the dielectric loss ($\tan \delta$) is estimated by ϵ_r''/ϵ_r' .

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References

- Gedye R, Smith F, Westaway K, Ali H, Baldisera L, Laberge L, Rousell J (1986) The use of microwave ovens for rapid organic synthesis. *Tetrahedron Lett.* (3):279–282
- Giguere RJ, Bray TL, Duncan SM, Majetich G (1986) Application of commercial microwave ovens to organic synthesis. *Tetrahedron Lett.* (41):4945–4948
- Bogdal D (2005) Microwave-assisted organic synthesis one hundred reaction procedure. *Tetrahedron Org Chem. Ser.* 25:vii
- de la Hoz A, Loupy A (2012) *Microwaves in organic synthesis* 3rd edn. Wiley-VCH, Weinheim
- Chen P-K, Rosana MR, Dudley GB, Stiegman AE (2014) Parameters affecting the microwave-specific acceleration of a chemical reaction. *J Org Chem* 79:7425–7436
- Jennifer TR, Kremsner M, Kappe CO (2008) Investigating the existence of nonthermal/specific microwave effects using silicon carbide heating elements as power modulators. *J Org Chem* 73:6321–6329
- Chandrasekaran S, Ramanathan S, Basak T (2012) Microwave material processing—a review. *AIChE J.* 58:330–363
- Kappe CO, Stadler A, Dallinger D (2013) *Microwaves in organic and medicinal chemistry*, chapter 3.3–3.5. Wiley-VCH, Weinheim
- Kappe CO (2004) Controlled microwave heating in modern organic synthesis. *Angew. Chem. Int. Ed.* 43:6520–6284
- Metaxas AC, Meredith RJ (1983) *Industrial microwave heating*. Peter Peregrinus Ltd., London, pp 146–185
- Leonelli C (2017) in *Microwave Chemistry*. (Eds.: G. Cravotto, D. Camaroglio). Walter de Gruyter GmbH & Co. KG, pp. 39–45
- Biotage Co. Ltd., Initiator, <http://www.biotage.com>. (Last accessed: April 8, 2018)
- CEM CO. Ltd., Discover, <http://cem.com/en/>. (Last accessed: April 8, 2018)
- J-Science Lab Co., Ltd., Green Motif, <http://www.j-sl.com>. (Last accessed: April 8, 2018)
- Sairem Co. Ltd., LABOTORON, <https://www.sairem.com/microwave-radio-frequency-rf-products/microwave-chemistry/> (Last accessed: April 8, 2018)
- Kobayashi S (2016) Flow “fine” synthesis: high yielding and selective organic synthesis by flow methods. *Chem. Asian J.* 11:425–436
- Strauss CR (1990) A continuous microwave reactor for laboratory-scale synthesis. *Chem. Aust.* 186
- Cablewski T, Faux AF, Strauss CR (1994) Development and application of a continuous microwave reactor for organic synthesis. *J Org Chem* 59:3408–3412
- Chen S-T, Chiou S-H, Wang K-T (1990) Preparative scale organic synthesis using a kitchen microwave oven. *J. Chem. Soc. Chem. Commun.*:807–809
- Znidar D, Hone CA, Inglesby P, Boyd A, Kappe CO (2017) Development of a continuous-flow sonogashira cross-coupling protocol using propyne gas under process intensified conditions. *Org. Process. Res. Dev.* 21:878–884
- Konda V, Rydfjord J, Savmarker J, Larhed M (2014) Safe palladium-catalyzed cross-couplings with microwave heating using continuous-flow silicon carbide reactors. *Org. Process. Res. Dev.* 18:1413–1418
- Ohmgren P, Fardost A, Russo F, Schanche JS, Fagrell M, Larhed M (2012) Evaluation of a nonresonant microwave applicator for continuous-flow chemistry applications. *Org. Process. Res. Dev.* 16:1053–1063
- He P, Haswell SJ, Fletcher PDI, Kelly SM, Mansfield A (2011) Scaling up of continuous-flow, microwave-assisted, organic reactions by varying the size of Pd-functionalized catalytic monoliths. *Beilstein J. Org. Chem.* 7:1150–1157
- Glasnov TN, Findenig S, Kappe CO (2009) Heterogeneous versus homogeneous palladium catalysts for ligandless Mizoroki-heck reactions: a comparison of batch/microwave and continuous-flow processing. *Chem. Eur. J.* 15:1001–1010
- Tangy A, Pulidindi IN, Perkas N, Gedanken A (2017) Continuous flow through a microwave oven for the large-scale production of biodiesel from waste cooking oil. *Bioresour. Technol.* 224:333–341
- Tesfaye M, Katiyar V (2016) Microwave assisted synthesis of biodiesel from soybean oil: effect of poly (lactic acid)-oligomer on cold flow properties, IC engine performance and emission characteristics. *Fuel* 170:107–114
- Encinar JM, Gonzalez JF, Martinez G, Sanchez N, Pardo A (2012) Soybean oil transesterification by the use of a microwave flow system. *Fuel* 95:386–393
- Terigar BG, Balasubramanian S, Lima M, Boldor D (2010) Transesterification of soybean and rice bran oil with ethanol in a continuous-flow microwave-assisted system: yields, quality, and reaction kinetics. *Energy Fuel* 24:6609–6615
- Muley P, Boldor D (2013) Scale-up of a continuous microwave-assisted transesterification process of soybean oil for biodiesel production. *Trans. ASABE* 56:1847–1818
- Barekati-Goudarzi M, Muley PD, Clarens A, Nde DB, Boldor D (2017) Continuous microwave-assisted in-situ transesterification of lipids in seeds of invasive Chinese tallow trees (*Triadica sebifera* L.): kinetic and thermodynamic studies. *Biomass Bioenergy* 107: 353–360
- Baxendale IR, Hayward JJ, Ley SV (2007) Microwave reaction under continuous flow conditions. *Comb Chem high Thr Scr* 10: 802–836. Glasnov TN, Kappe CO (2007) Microwave-assisted synthesis under continuous-flow conditions. *Macromol Rapid Comm* 28:395–410
- Sauks JM, Mallik D, Lawryshyn Y, Bender T, Organ MA (2014) Continuous-flow microwave reactor for conducting high-temperature and high-pressure chemical reactions. *Org. Process. Res. Dev.* 18:1310–1314
- Sklingshaug B, Rydfjord J, Savmarker J, Larhed M (2016) Microwave heated continuous flow palladium(II)-catalyzed desulfurative synthesis of aryl ketones. *Org. Process. Res. Dev.* 20:2005–2011

34. He P, Haswell SJ, Fletcher PD (2004) Microwave heating of heterogeneously catalysed Suzuki reactions in a micro reactor. *Lab Chip* 4:38–41
35. Comer E, Organ MG (2005) A microreactor for microwave-assisted capillary (continuous flow) organic synthesis. *J. Am. Chem. Soc.* 127:8160–8167
36. Shore G, Morin S, Organ MG (2006) Catalysis in capillaries by Pd thin films using microwave-assisted continuous-flow organic synthesis (MACOS). *Angew. Chem. Int. Ed.* 45:2761–2766
37. Comer E, Organ MG (2005) A microcapillary system for simultaneous, parallel microwave-assisted synthesis. *Chem. Eur. J.* 11: 7223–7227
38. Wilson NS, Sarko CR, Roth G (2004) Development and applications of a practical continuous flow microwave cell. *Org. Process. Res. Dev.* 8:535–538
39. Saaby S, Baxendale IR, Ley SV (2005) Non-metal-catalysed intramolecular alkyne cyclotrimerization reactions promoted by focussed microwave heating in batch and flow modes. *Org Biomol Chem* 3:3365–3368
40. Baxendale IR, Griffiths-Jones CM, Ley SV, Tranmer GK (2006) Microwave-assisted Suzuki coupling reactions with an encapsulated palladium catalyst for batch and continuous-flow transformations. *Chem. Eur. J.* 12:4407–4416
41. Savin KA, Robertson M, Gernert D, Green S, Hembre EJ, Bishop J (2003) A study of the synthesis of triazoles using microwave irradiation. *Mol. Divers.* 7:171–174
42. Bagley MC, Lenkins RL, Lubinu MC, Mason C, Wood R (2005) A simple continuous flow microwave reactor. *J Org Chem* 70:7003–7006
43. Glasnov TN, Vugts DJ, Konigstein MM, Desai B, Fabian WMF, Orru RVA, Kappe CO (2006) Microwave-assisted Dimroth rearrangement of thiazines to dihydropyrimidinethiones: synthetic and mechanistic aspects. *QSAR Comb. Sci.* 26:509–518
44. Sairem Co., Ltd., MiniFlow, <https://www.sairem.com/microwave-radio-frequency-rf-products/microwave-chemistry/microwave-assisted-synthesis-laboratory/> (Last accessed: April 8, 2018)
45. Yokozawa S, Ohneda N, Muramatsu K, Okamoto T, Odajima H, Ikawa T, Sugiyama J, Fujita M, Sawairi T, Egami H, Hamashima Y, Egi M, Akai S (2015) Development of a highly efficient single-mode microwave applicator with a resonant cavity and its application to continuous flow syntheses. *RSC Adv.* 5:10204–10210
46. Barham JP, Tanaka S, Koyama E, Ohneda N, Okamoto T, Odajima H, Sugiyama J, Norikane Y (2018) Selective, scalable synthesis of C₆₀-fullerene/indene monoadducts using a microwave flow applicator. *J Org Chem* 83:4348–4354
47. Musio B, Mariani F, Sliwinski EP, Kabeshov MA, Odajima H, Ley SV (2016) Combination of enabling technologies to improve and describe the stereoselectivity of Wolff-Staudinger cascade reaction. *Synthesis* 48:3515–3526
48. Ichikawa T, Mizuno M, Ueda S, Ohneda N, Odajima H, Sawama Y, Monguchi Y, Sajiki H (2018) A practical method for heterogeneously-catalyzed Mizoroki–Heck reaction: flow system with adjustment of microwave resonance as an energy source. *Tetrahedron Lett.* 74:1801–1816
49. Egami H, Sawairi T, Tamaoki S, Ohneda N, Okamoto T, Odajima H, Hamashima Y (2018) (E)-3-[4-(Pent-4-en-1-yl)oxy]phenyl]acrylic acid. *Molbank*:M996
50. Vámosi P, Matsuo K, Masuda T, Sato K, Narumi T, Takeda K, Mase N (2018) Rapid optimization of reaction conditions based on comprehensive reaction analysis using a continuous flow microwave reactor. *Chem. Rec.* <https://doi.org/10.1002/tcr.201800048>
51. Egami H, Tamaoki S, Abe M, Ohneda N, Yoshimura T, Okamoto T, Odajima H, Mase N, Takeda K, Hamashima Y (2018) Scalable microwave-assisted Johnson–Claisen rearrangement with a continuous flow microwave system. *Org. Process. Res. Dev.* 22:1029–1033
52. Barham JP, Tamaoki S, Egami H, Ohneda N, Okamoto T, Odajima H, Hamashima Y (2018) C-Alkylation of N-alkylamides with styrenes in air and scale-up using a microwave flow reactor. *Org Biomol Chem* 16:7568–7573
53. Carneiro PF, Gutmann B, de Souza ROMA, Kappe CO (2015) Process intensified flow synthesis of 1H-4-substituted imidazoles: toward the continuous production of Daclatasvir. *ACS Sustain Chem Eng* 3:3445–3453
54. Parida D, Serra CA, Garg DK, Hoarau Y, Bally F, Muller R, Bouquay M (2014) Coil flow inversion as a route to control polymerization in microreactors. *Macromolecules* 47:3282–3287
55. Gage JR, Guo X, Tao J, Zheng C (2012) High output continuous nitration. *Org Process Res Dev* 16:930–933
56. Martin RE, Morawitz F, Kuratli C, Alker AM, Alanine AI (2012) Synthesis of annulated pyridines by intramolecular inverse-electron-demand hetero-Diels–Alder reaction under superheated continuous flow conditions. *Eur. J. Org. Chem.*:47–52
57. Rincón JA, Barberis M, G-Esguevillas M, Johnson MD, Niemeier JK, Sun W-M (2011) Safe, convenient ortho-Claisen thermal rearrangement using a flow reactor. *Org. Process. Res. Dev.* 15:1428–1432
58. Kobayashi H, Driessen B, van Osch DJGP, Talla A, Ookawara S, Noël T, Hessel V (2013) The impact of novel process windows on the Claisen rearrangement. *Tetrahedron* 69:2885–2890
59. Razzaq T, Glasnov TN, Kappe CO (2009) Continuous-flow microreactor chemistry under high-temperature/pressure conditions. *Eur. J. Org. Chem.*:1321–1325
60. Mathew NT, Khaire S, Mayadevi S, Jha R, Sivasanker S (2005) Rearrangement of allyl phenyl ether over Al-MCM-41. *J Catal* 229: 105–113
61. ZEON, <http://www.zeon.co.jp/content/200121075.pdf#search=%27CPME+physical+value%27>
62. Science of Petroleum II (1938) 1281
63. Ollevier T, Mwene-Mbeja TM (2006) Bismuth triflate catalyzed Claisen rearrangement of allyl naphthyl ethers. *Tetrahedron Lett.* 47:4051–4055
64. Schünemann K, Furkert DP, Connelly S, Fraser JD, Sperry J, Brimble MA (2014) Synthesis and biological evaluation of 7-deoxy analogues of the human rhinovirus 3C protease inhibitor thysanone. *Eur J Org Chem.* <https://doi.org/10.1002/ejoc.201301515>
65. Castro AMM (2004) Claisen rearrangement over the past nine decades. *Chem. Rev.* 104:2939–3002
66. Rhoads SJ, Raulines NR (1975) The Claisen and cope rearrangements. *Org React* 22:1–252
67. Wipf P, Rodriguez S (2002) Water-accelerated Claisen rearrangements. *Adv. Synth. Catal.* 344:434–440
68. de la Hoz A, Diaz-Ortiz A, Moreno A (2005) Microwaves in organic synthesis. Thermal and non-thermal microwave effects. *Chem Soc Rev* 34:164–178
69. Herrero MA, Kremsner JM, Kappe CO (2008) Nonthermal microwave effects revisited: on the importance of internal temperature monitoring and agitation in microwave chemistry. *J Org Chem* 73: 36–47
70. Reich SH, Melnick M, Pino MJ, Fuhry MAM, Trippe AJ, Appelt K, Davies II JF, Wu B-W, Musick L (1996) Structure-based design and synthesis of substituted 2-Butanols as Nonpeptidic inhibitors of HIV protease: secondary amide series. *J Med Chem* 39:2781–2794