

Evaluation of a Nonresonant Microwave Applicator for Continuous-Flow Chemistry Applications

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Supporting Information

ABSTRACT: The concept of a nonresonant microwave applicator for continuous-flow organic chemistry is introduced and evaluated. The frequency of the incident microwave radiation can be adjusted between 2.4 and 2.5 GHz to optimize the energy absorbance. The temperature of the reaction is monitored by five IR sensors, and their signals can be used to automatically adjust the power output from the microwave generator. The heating of several different solvents up to 20 °C above the standard boiling point has been explored. Several different organic reactions have been successfully carried out using a 200 mm × Φ 3 mm tubular borosilicate reactor and a flow between 47 and 2120 μ L/min. The microwave heating pattern was visualized with an IR camera. The transformations include palladium-catalyzed coupling reactions (oxidative Heck and Suzuki reactions), heterocyclic chemistry (oxathiazolone and Fischer indole synthesis), rearrangement (Claisen), and a Diels–Alder cycloaddition reaction. A scale-out to 57 mmol/h was performed with the Fischer indole reaction.

■ INTRODUCTION

A new way of heating organic chemistry reactions was presented some 25 years ago with the introduction of microwave-assisted organic synthesis (MAOS). The instrumentation for MAOS applications has undergone rapid development from domestic microwave ovens used in the mid 1980s^{1,2} to the highly dedicated and safe single- and multimode equipment commonly used for small-scale batch MAOS today.^{3–6} The introduction of MAOS has provided a new way to rapidly heat organic reactions remotely.^{7–10} Rapid heating, reduced reaction times, and in many cases, increased yields have made MAOS a commonly used tool, especially for the preparative medicinal chemist.^{5,10–12} Additionally, microwave (MW) heating often generates a more uniform in situ heating profile than conductive heating, and many of the problems originating from wall effects can be avoided in microwave systems.⁵ However, since microwaves have a limited penetration depth, the possibility of scaling up reactions using microwaves is somewhat limited. Large multimode applicators^{3,13,14} or flow/stop approaches^{3,11} are some of the alternatives that have been used to circumvent this problem.

Parallel with the development of MAOS has been the introduction of continuous-flow (CF) systems for performing organic chemical reactions in a standard laboratory environment.^{15,16} CF synthesis, especially in microflow systems, has led to impressive results, mainly due to the large surface-to-volume ratio, allowing relatively fast heating.^{17–19} Since only a small volume of the reaction mixture is processed at a time, the CF approach is also beneficial from a safety perspective, e.g. when using explosive substrates or performing highly exothermic reactions. However, most commercial CF systems available today still utilize conductive heating by heated oil,²⁰ heated air,²¹ electric resistance,²² or induction.^{23,24}

The shortened reaction times offered by microwave heating indicate that additional benefits could be obtained from an energy-saving perspective by exploiting this technology even further.^{25–28} However, when increasing the reaction scale in a multimode microwave batch applicator, both the time required to reach the desired reaction temperature and the time required for cooling will be increased, thus canceling out some of the energy benefits.²⁷ Thus, the energy efficiency can only be exploited by maintaining the small reaction volume in small-scale MW batch applicators. One of the main advantages of a combined CF-MAOS setup is that organic transformations can be optimized rapidly due to the possibility of adjusting the temperature in the heated zone in real time. A second advantage of low-volume MW applicators is reduced dead volumes that considerably reduces the consumption of stock solutions during an optimization process. Performing a scale-out, rather than a scale-up, using the combination of CF and MAOS should allow excellent control of the temperature, higher power density in the reactor (and thus increased flow), shorter reaction times, and rapid cooling.²⁸ Such an approach will also allow direct and safe transition from small- to larger-scale synthesis with little or no need for time-consuming reoptimization of the reaction conditions.

The first combination of CF and MAOS was presented by Strauss et al. in 1994.^{29,30} They were followed by many others, often utilizing a dedicated batch microwave applicator cavity, modified to serve as the heating unit of a CF system,^{31–33} or a stop/flow system.^{11,31} The CF-MAOS equipment described so

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far has been based on helical-type flow cells of borosilicate glass,³⁴ U-formed borosilicate glass loops,^{35,36} standard 10-mL vials filled with sand,³⁷ glass bead reactors,³⁸ or microcapillary flow cells.³⁹

Herein, we describe a new, nonresonant CF-MAOS prototype instrument designed for performing organic synthesis.⁴⁰ A range of solvents (high and low microwave absorbers) were tested in an initial study, illustrating the excellent control and heating capacity of the microwave applicator and the uniform heating of the tubular flow reactor.

We also report on the usefulness of the system in different types of relevant chemical organic reactions, including metal-catalyzed Heck and Suzuki couplings, the synthesis of heterocyclic compounds, a Claisen rearrangement, and a Diels–Alder cycloaddition. These applications exhibited throughputs of up to 57 mmol/h and residence times as short as 20 s using a 200 mm × Φ 3 mm tubular borosilicate reactor.

THE CF-MAOS SYSTEM

The newly designed CF-MAOS system consists of a microwave generator, an applicator to transfer the microwave energy to the reaction mixture, and a tubular borosilicate reactor in which the reaction mixture passes through the applicator (Figure 1).

The Generator. The microwave generator consists of a transistor-based two-stage microwave amplifier, powered by a 32 V, 20 A power supply, and a controller unit that is connected to a computer and the IR temperature sensors in the applicator. The power supply can be run from 110 or 240 V AC mains. The generator also contains an active cooling module using liquid coolant (tap water or circulated coolant) and temperature sensors to prevent the amplifier from overheating.

The first stage of the amplifier generates the microwave power output and microwave frequency set in the software. The second stage amplifies the signal to the determined level. The system is able to generate from 0–150 W of output in a frequency range from 2.4 to 2.5 GHz, which is within the allowed range for public use in microwave instruments. The possibility to vary the frequency during the reactions could, to some extent, compensate for the temperature change, $\tan \delta$. The microwaves are transmitted through a magnetic circulator, through a coaxial connector to the microwave applicator via a microwave-transmitting coaxial cable consisting of a nonmagnetic, high-temperature, shielded, 50- Ω solid-core material. Nonabsorbed microwaves are reflected back through the coaxial cable and deflected in the circulator to generate heat which is removed by the active coolant.

The Applicator. The microwave applicator is illustrated in Figure 1. The microwaves are applied to the reaction mixture in the tubular reactor by means of a helical antenna made of an Al–Cu material. The axial-field microwave applicator is based on a novel design using a nonresonant structure that suppresses mode patterns (standing waves) in the applicator, thus avoiding hot and cold spots. As opposed to single- and multimode applicators, the axial field applicator is not based on the cavity resonator principle. In the axial field applicator the microwave field is generated in a coil surrounding the flow reactor, allowing the microwave field to be concentrated axially inside the coil. The coil is automatically tuned to maximize the heating in the reactor tube by changing the frequency. Reactors of different sizes can be used by changing the length and diameter of the coil in the applicator, allowing the optimisation of reaction conditions such as residence time and flow capacity.

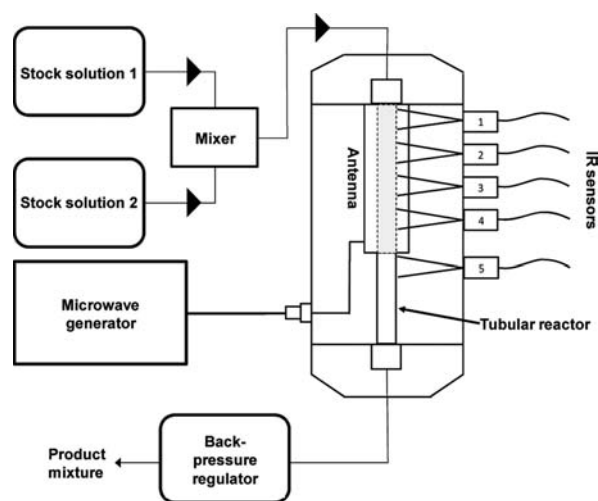


Figure 1. Schematic overview of the CF-MAOS setup. The five IR sensors are positioned 31.5, 52.0, 75.0, 97.0, and 119.0 mm, respectively, from the top of the applicator cavity.

The helical type antenna is a device with dimensions for length (measured in whole and fractional wavelengths), helical pitch, and diameter. The physical shape of the antenna determines the homogeneity of the microwave field. In the current design the antenna and applicator are optimized for irradiation of a 90 mm section of the reactor. The housing creates a ground connection for the coaxial microwave connector, is made in nonmagnetic material and has dimensions and design to contain the microwaves, shield the outside and make an environment that will allow the microwave antenna to create a homogeneous microwave field around the reactor.⁴¹

The applicator is equipped with five Optris CT IR sensors with LT22 sensing heads (Optris GmbH, Berlin, Germany). The head measures the temperature of a spot that is 7 mm in diameter at a distance of 0–100 mm. The sensors are made of stainless steel and have a function that compensates for indirect heating of the casing. As the IR sensors measure the temperature of the reactor surface, the observed temperature must be calibrated with a probe to give the temperature of the reaction mixture.⁴² Of the five IR sensors, four are positioned along the length of the helical antenna, and the fifth, close to the outlet of the reactor (Figure 1).

The Reactor. The reactor consists of a straight tube, made of microwave-transparent borosilicate glass (Figure 2). The

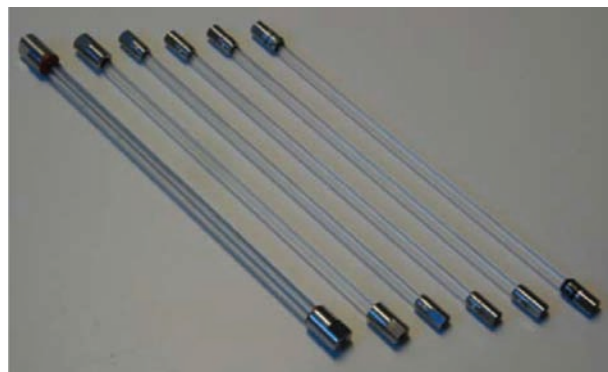


Figure 2. Photograph of different reactors.

reactors can be made of other microwave-transparent materials such as quartz or transparent ceramic, or microwave-absorbing materials, e.g. SiC or absorbing ceramics. The reactors are consumables and can be easily removed for washing or replacement when necessary. In the current design, the reactors have an inner reaction lumen of Φ 3 mm and an outer maximum Φ 9 mm. The reactors have steel connectors with a Valco fitting for easy assembly.⁴³ The steel connectors were especially designed for this instrument and are attached with a high-temperature ceramic adhesive.

The total length of the tubular reactor is 200 mm, although only 90 mm of the length is within the microwave antenna. The reaction mixture is exposed to the microwaves as it flows through the reactor.

The electric component of the electromagnetic field radiates in the transverse direction (perpendicular to the flow) along the heating zone. The field also propagates towards the outlet of the reactor. The length of the reactor heated is therefore somewhat longer than 90 mm (up to 150 mm, depending on the dielectric properties of the reaction mixture). The residence time calculations presented here are based on a heated zone of 100 mm with a corresponding volume of 0.7 mL.

The Software. Software controls the power and frequency settings of the hardware, monitors the various sensors in the system, and automatically adjusts the parameters. In this system it is possible to preset the reaction temperature (controlled by sensor number 2) or to choose a level of microwave power. The software was developed in National Instruments' Labview environment. The software is under continuous development and is not discussed further in this article.

Ancillary Equipment. Apart from the components described above, the system includes a pump, tubing, a backpressure regulator, and a product collection vessel (see Figure 1). In addition, it is possible to add multiple pump channels, multipoint injection valves, static or dynamic mixers, an autosampler, a fraction collector, and online or at-line analysis systems. As standard fittings are used, it is possible to attach all standard CF chemistry equipment, which allows high flexibility in constructing a system for specific custom applications. A photograph of the complete system used is shown in Figure 3.

Initial experiments were carried out in which solvents commonly used in MAOS were heated to study the robustness, the heating profile in the reactor, and the heating ramp-up times in the system. To measure the heating profiles, the solvents were heated to 20 °C below their boiling point at atmospheric pressure (denoted bp), then to their bp, and then to 20 °C above their bp, using a flow rate of 701 μ L/min, which corresponds to a residence time of 1 min.⁴⁴

All solvents exhibited stable temperature profiles, which could be easily kept within the preset temperature interval, ± 2 °C, using either manual or automatic tuning. The temperatures were monitored by sensor 2 since it showed the fastest response. The results are shown in Figure 4.

With the five IR sensors described above, temperature variations over the reactor inside the applicator could be measured, as exemplified in Figure 5 where EtOH was heated to 98 °C with a 1 min residence time.⁴⁵

The ramp-up times from room temperature to the boiling points for the eight different solvents were measured. As expected, the rate of increase in temperatures was generally in line with the $\tan \delta$ value of the solvents, although the heating rate for acetonitrile was higher than expected (Figure 6).

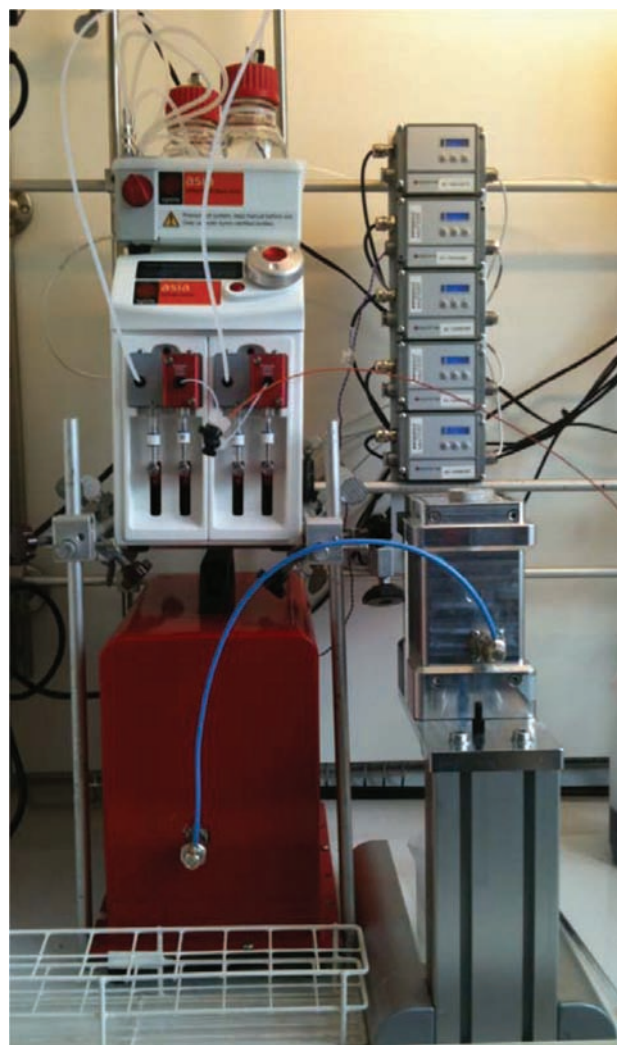


Figure 3. Photograph of the WaveCraft prototype CF-MAOS instrument showing the microwave generator (in red housing, bottom left), the five IR-sensor displays (mounted vertically in the center), the applicator (center right, connected to the generator by a blue coaxial microwave cable), and the syringe pump with pressurized storage compartment (upper left).

The instrument's relatively low energy input (max 150 W) compared to that of most batch applicators (300–1400 W)^{14,46} still gives sufficient power to reach the target temperature quickly. One benefit of the variable-frequency functionality of this instrument (2.4–2.5 GHz) is the possibility of tuning the frequency while heating, in order to compensate for the reduction in $\tan \delta$ at higher temperatures. In this way, the most energy-efficient frequencies can be used during steady-state heating.

To further study the heating pattern and to verify the values given by the five IR sensors, one of the walls of the applicator was removed, and temperature recordings were made with an FLIR IR camera using both a DMF-based Heck reaction mixture and model solvents.

The image from the IR camera is shown in Figure 7, where it can be clearly seen that the helical antenna heats the reaction mixture inside the reactor while its own temperature remains lower. The temperature profile is fairly uniform throughout the heating zone, with a slight tendency towards a higher temperature between the fourth and fifth turn from the top.

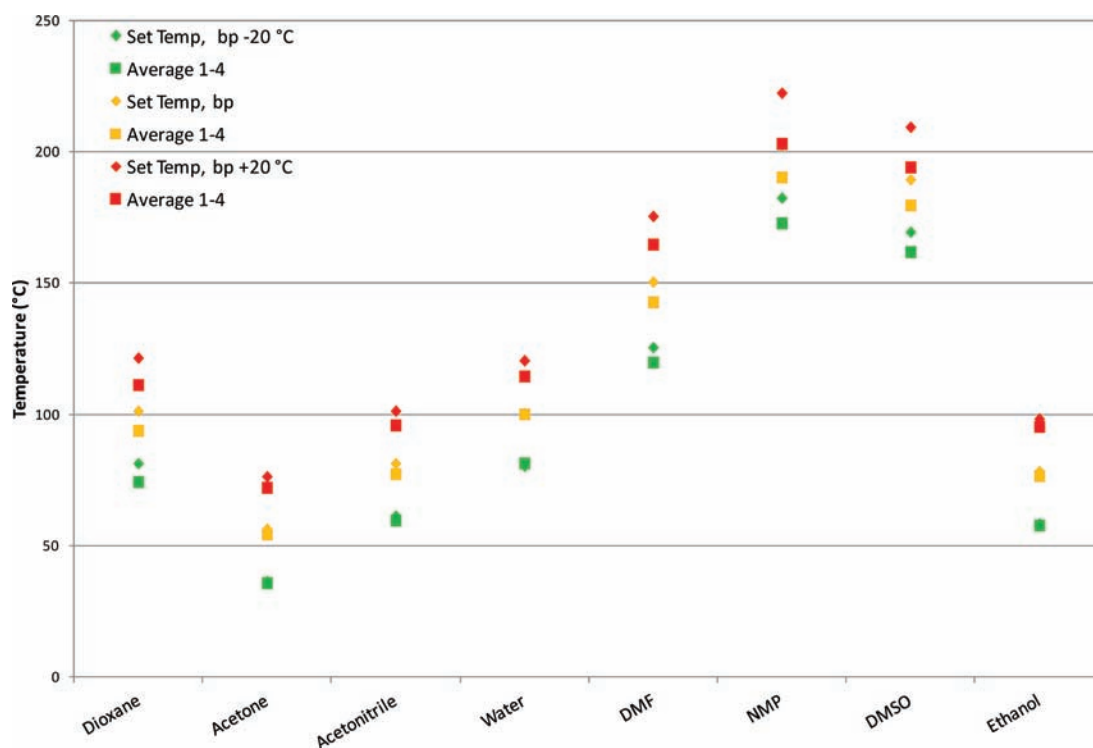


Figure 4. Data illustrating the temperature stability of the system using eight common solvents. Average 1–4 denotes the average temperature given by sensors 1–4, which are located within the heated zone as described above. For temperature profiles and detailed data, see Supporting Information, Table S-1.

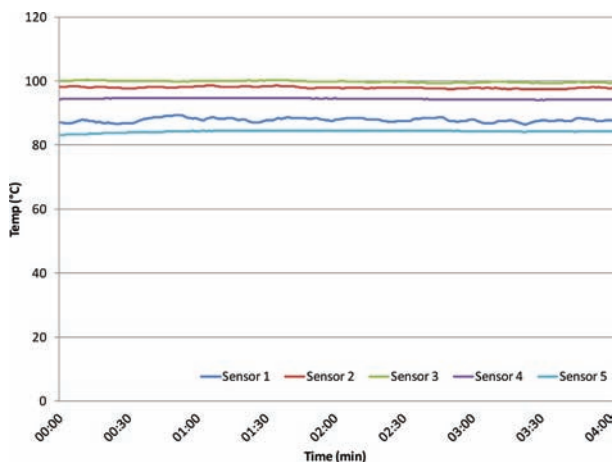


Figure 5. Temperature profiles when heating EtOH to 98 °C. Time zero is the time at which one void volume (from the pump to the collection vial) has passed through the system after the preset flow and temperature values had been reached. (Additional temperature profiles are included in section 3 of the Supporting Information.)

The temperature profile is clearly influenced by the cooler reaction mixture (room tempered) entering from the top. The temperature starts to fall after the reaction mixture leaves the region of the electromagnetic field.

EVALUATION OF MODEL REACTIONS

To test the general performance of the WaveCraft nonresonant CF-MAOS prototype, and specifically to investigate its potential for rapid screening of reaction temperatures, residence times, chemical throughput, and robustness, a range of reactions employing different solvents (strongly and weakly

microwave absorbing), metal catalysts, temperatures, and flow regimes were evaluated in proof-of-principle studies.

Temperatures between 140 and 270 °C and residence times between 20 s and 15 min were used. All reactions were run with 17 bar backpressure to allow superheating of the reaction mixtures. Before samples were collected, one void volume was discarded after the new settings had been reached to ensure that the samples collected had been exposed to homogeneous conditions. High-yielding conditions for each reaction were applied during prolonged CF processing to collect material for the determination of isolated yield and throughput. The throughput per hour is extrapolated from collection periods of 5–42 min, depending on the reaction.

Pd(II)-Catalyzed Oxidative Heck Vinylation of an Aryl Boronic Acid. Transition-metal-catalyzed reactions are becoming increasingly important in both organic and medicinal chemistry; a fact which was highlighted by the 2010 Nobel Prize in Chemistry for the discovery of palladium-catalyzed cross-coupling. The possibility of synthesizing styrenes via palladium(II)-catalyzed oxidative Heck vinylation of aryl boronic acids with vinyl acetate was first presented by Lindh et al.⁴⁷ in 2009 and a year later was adapted by Odell et al. in a useful protocol for flow synthesis using conventional heating.²⁰ Lindh et al. identified high-yielding microwave batch conditions upon heating the reaction mixture to 140 °C for 30 min,⁴⁷ while Odell et al. further optimized the reaction with regard to flow conditions, employing 150 °C and 2 min residence time in a 2-mL reactor.²⁰ We used these well-optimized conditions to adapt this reaction to our novel CF-MAOS system.

The temperature and residence time were varied between 120 and 160 °C and between 30 and 120 s, respectively, and the different conditions were evaluated by determining the ratio between the product and 4-methoxybenzonitrile as the internal

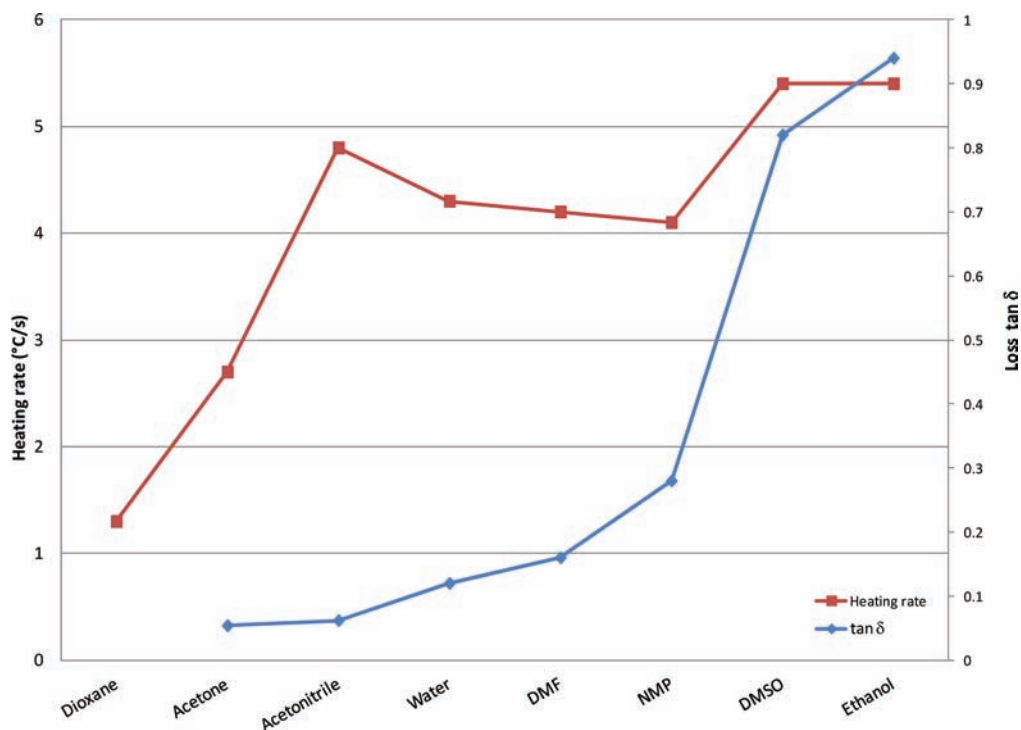


Figure 6. Heating rates for model solvents using the nonresonant CF-MAOS system. For acetone, DMF, NMP, and water, heating was software controlled. For acetonitrile, dioxane, DMSO, and ethanol, the heating was manually controlled. The heating rate was measured using a Φ 3 mm reactor and 1 min residence time, while heating each solvent from 25 °C to the bp of the solvent. No $\tan \delta$ data were available for dioxane. It should be noted that these data were obtained with the use of the prototype antenna, and may change with the further development of the instrument. For detailed data see Table S-2 in the Supporting Information.

standard (Table 1). It was quickly found possible to reduce the temperature to 140 °C and to shorten the residence time to 75 s, although the concentration of phenylboronic acid was reduced to 0.25 M compared to the 0.5 M used by Odell et al.

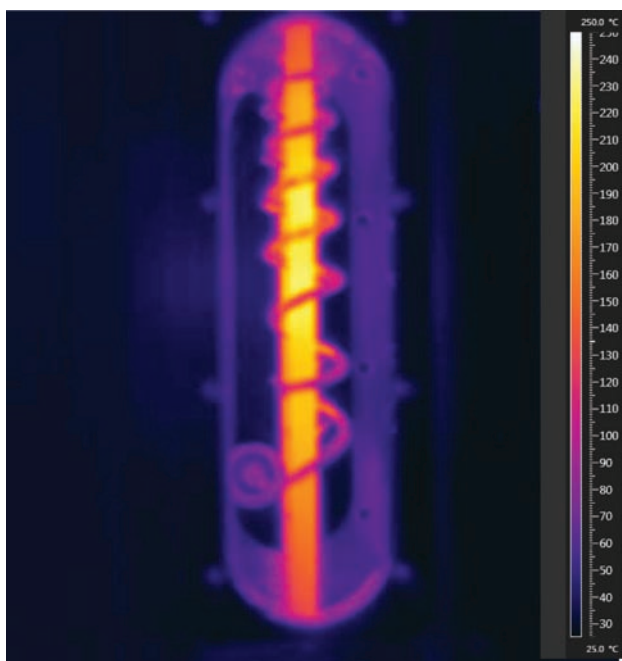


Figure 7. IR camera image of the reactor and the helical antenna during the irradiation of an oxidative Heck reaction mixture in DMF using a set temperature of 200 °C.

Table 1. Pd (II)-catalyzed oxidative Heck vinylation of phenylboronic acid: optimization parameters and results

run	RT ^a (s)	set temp. (°C)	flow/pump (μ L/min)	P/IS ^b
1	120	120	177	1.11
2	120	140	177	1.09
3	120	160	177	1.22
4	75	120	283	1.25
5	75	140	283	1.42
6	75	160	283	1.11
7	30	120	707	0.98
8	30	140	707	1.19
9	30	160	707	1.28
10 ^c	75	140	283	-

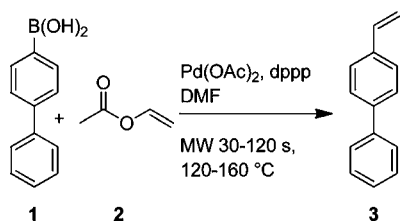
^aResidence time. ^bP/IS = Product/Internal Standard ratio. ^cRun for isolated yield, giving 66%.

to avoid precipitation and clogging. The 4-vinyl-1,1'-biphenyl product was isolated in a yield of 66% with a calculated throughput of 2.83 mmol/h (0.51 g/h), Scheme 1.

When performing oxidative Heck vinylation for the first time in the CF-MAOS system it was possible to reduce the temperature by 10 °C and shorten the residence time down to 75 s, without any substantial reduction in the yield (66% vs 68% isolated yield for the new CF-MAOS system and the conventional system, respectively).

Suzuki–Miyaura Cross-Coupling. Since Suzuki and Miyaura first presented the palladium(0)-catalyzed cross-coupling between an organoboro compound and an organic halide (or pseudohalide),^{48,49} it has become one of the most commonly used methods for C–C bond formation. The benefits of combining this reaction with microwaves are today

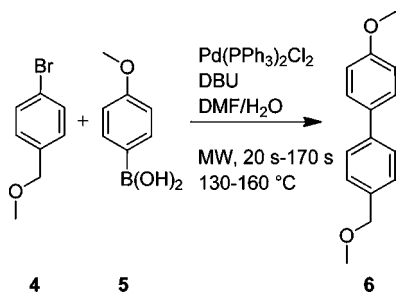
Scheme 1. Pd(II)-catalyzed oxidative Heck vinylation of phenylboronic acid carried out in the nonresonant CF-MAOS system



also well established.^{50,51} Microwave-assisted Suzuki–Miyaura coupling is commonly used by medicinal chemists and has been used, among other things, to functionalize HIV-1 protease inhibitors.^{52–54} At a time when robust, chemoselective transformations are in high demand, the importance of this synthesis route makes it a good candidate for evaluation of the CF-MAOS system. Although there are numerous reports on microwave-assisted batch-type Suzuki–Miyaura couplings, and many examples of CF reactions employing classical heating, the number of published papers on MW-assisted Suzuki–Miyaura CF reactions is limited.^{34,36,39}

Two homogeneous stock solutions were prepared for evaluation of the CF-MAOS system (see Scheme 2). The

Scheme 2. Suzuki–Miyaura cross-coupling carried out in the nonresonant CF-MAOS system



first stock solution was prepared by dissolving the precatalyst $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.150 mmol, 0.05 equiv) in DMF (0.005 M). The second stock solution, 0.1 M with respect to the 4-bromobenzyl methyl ether, was prepared by adding 4-bromobenzyl methyl ether (1.0 equiv), 4-methoxyphenylboronic acid (3.0 equiv), and DBU (3.0 equiv)⁵⁵ to DMF/water (95:5).

The two stock solutions were pumped into the reactor at the same flow rate, the reaction conditions were optimized by varying the temperature from 130 to 160 °C, and the residence time varied from 10 to 150 s, according to Table 2. In total, 10 different sets of experimental conditions were evaluated, followed by the collection of 12.7 mL (9 min collection time) of material using the best conditions.

All reactions were performed within 3 h of working time. Running the reaction under the selected protocol (150 °C with 30-s residence time) gave 4-methoxy-4'-(methoxymethyl)-1,1'-biphenyl in an isolated yield of 71% (Table 2, run 11) and the calculated throughput of 3.0 mmol/h (0.69 g/h).

Using the CF-MAOS under optimized conditions, the residence time was reduced to only 30 s, which is a considerable reduction compared to the 8 and 4 min reported previously by

Table 2. Suzuki–Miyaura cross-coupling. optimization parameters and results

run	RT ^a (min)	set temp. (°C)	flow/pump (μL/min)	conversion (%)
1	2.50	140	141	80
2	2.50	150	141	full
3	1.00	160	353	full
4	0.50	150	707	full
5	1.50	150	236	full
6	2.75	150	129	full
7	1.75	150	202	full
8	0.17	150	2121	81
9	0.17	140	2121	47
10	0.17	130	2121	21
11 ^b	0.50	150	707	full

^aRT = Residence Time. ^bRun for isolated yield, giving 71%.

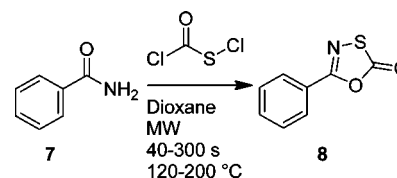
the groups of Wilson³⁴ and Comer³⁹ with lab-scale CF systems using modified, standard, single-mode microwave applicators.

Oxathiazolone Synthesis. 1,3,4-Oxathiazol-2-ones are a class of heterocycles mostly investigated as intermediates in the synthesis of various five-membered heterocycles which contain a C=N–S fragment (isothiazolines, thiadiazoles).^{56–59} Oxathiazolone derivatives have also been successfully employed as fungicides.^{60,61}

Nathan et al. recently discovered a series of selective *M. tuberculosis* (Mtb) proteasome inhibitors comprising the oxathiazolone ring.⁶² The synthesis of 5-substituted 1,3,4-oxathiazol-2-ones from the parent amide and chlorocarbonylsulfonyl chloride has been reported using thermal heating (mostly in refluxing toluene) or using MW irradiation (in 1,4-dioxane for 15 min at 100 °C).⁶²

To test the possibility of using our CF-MAOS system in drug discovery, the oxathiazolone synthesis of 5-phenyl-1,3,4-oxathiazol-2-one, a potent and selective inhibitor of Mtb proteasome,^{62,63} was evaluated in the CF-MAOS system (Scheme 3).

Scheme 3. Oxathiazolone synthesis carried out in the nonresonant CF-MAOS system



Benzamide was diluted in 1,4-dioxane to give a 0.25 M solution and connected to one of the two pump channels. A 0.75 M solution of chlorocarbonylsulfonyl chloride, in the same solvent, was connected to the other pump channel, and the two solutions were pumped into the Φ 3 mm reactor at the same flow rate. The reaction conditions were optimized by varying the temperature from 120 to 220 °C and the residence time from 40 s to 5 min, according to Table 3.

Running the reaction under the optimized conditions of 200 °C and 1 min residence time gave 5-phenyl-1,3,4-oxathiazol-2-ones in an isolated yield of 62% (Table 3, run 12) and a calculated throughput of 3.3 mmol/h (0.58 g/h).

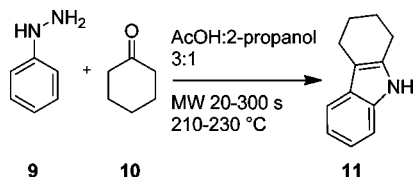
Fischer Indole Synthesis. Fischer indole synthesis⁶⁴ provides a convenient way of synthesizing indole-containing

Table 3. Oxathiazolone synthesis: optimization parameters and results

run	RT ^a (min)	set temp. (°C)	flow/pump (μL/min)	conversion (%)
1	5.00	120	71	96
2	2.50	130	141	95
3	1.25	130	283	91
4	1.25	140	283	91
5	1.25	150	283	92
6	1.25	160	283	94
7	0.67	160	530	88
8	0.67	170	530	90
9	1.25	180	283	96
10	1.25	220	283	98
11	1.25	200	283	99
12 ^b	1.00	200	353	full

^aRT = Residence Time. ^bRun for isolated yield, 62%.

molecules which, among many other applications, are common structures in several biologically active compounds.⁶⁵ A MW-assisted batch protocol was recently published,⁶⁶ as well as a protocol for indole synthesis using a CF microreactor.⁶⁷ In 2005 Bagley et al. presented a method for indole synthesis in a CF-MAOS system,³⁷ and a scale-out with good results has also recently been reported (see Scheme 4).⁶⁸

Scheme 4. Fischer indole synthesis carried out in the CF-MAOS system

In the first attempt to use the CF-MAOS setup pure acetic acid was employed as the solvent (Table 4, run 1) which

Table 4. Fischer indole synthesis: optimization and scale-out parameters and results

run	RT ^a (min)	set temp. (°C)	flow/pump (μL/min)	conversion (%)
1	5.00	220	142	97.4
2	2.50	210	284	99.7
3	2.50	220	284	99.6
4	1.25	220	568	99.4
5	1.00	230	706	98.3
6	0.63	230	1136	97.7
7	0.33	230	2120	98.0
8 ^b	0.33	230	2120	98.9

^aRT = Residence Time. ^bRun for isolated yield, 90%.

resulted in precipitation and clogging of the tubing. By changing the solvent system to a 3:1 mixture of acetic acid and 2-propanol⁶⁸ the precipitation could be avoided (Table 4, runs 2–8). Two stock solutions, one with phenylhydrazine (1 M, 30 mmol) and one with cyclohexanone (1.1 M, 33 mmol), were prepared using the 3:1 acetic acid/2-propanol solvent mixture. Although 210 °C and 2.5 min residence time gave the best conversion (Table 4, run 2) the somewhat lower conversion observed in run 7 was well compensated for by

the reduction in residence time. Thus, the conditions from run 7 were used for the first scale-out (Table 4, run 8).

Using the standard 200 mm × Ø 3 mm (1.4 mL) reactor, 230 °C and a 20 s residence time the indole was isolated in 90% yield with an impressive calculated throughput of 9.8 g/h (57.2 mmol/h).

Claisen Rearrangement. The first Claisen rearrangement using MAOS was reported 25 years ago, in 1986, by the microwave pioneers Giguere and Majetich.² When using conventional heating, high temperature and relatively long reaction times are needed, which makes the rearrangement well suited for applying MAOS.^{69–71} Procedures for Claisen rearrangements in continuous-flow systems have also been reported by other groups.^{18,68}

4-Allyloxyanisole was chosen as a model substrate since para substitution with electron-donating groups is beneficial for the reaction rate,⁷² and NMP was chosen as the solvent since polar solvents with high boiling points are beneficial for Claisen rearrangement.⁷³ 4-Allyloxyanisole was prepared according to a previously described procedure.⁷⁴ The 4-allyloxyanisole was then diluted in NMP to give a 2.03 M solution, and the CF-MAOS process was run. The reaction conditions were optimized by varying the temperature from 225–270 °C and the residence time from 1–5 min, according to Table 5. In

Table 5. Claisen rearrangement: optimisation of reaction conditions and results

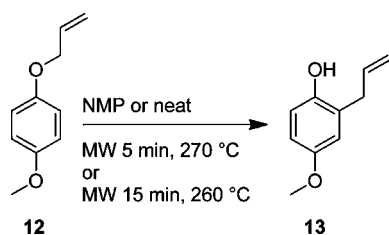
run	RT ^a (min)	set temp. (°C)	flow/pump (μL/min)	conversion (%)
1	5.0	225	141	96
2	3.0	225	236	95
3	1.0	240	707	91
4	3.0	240	236	91
5	5.0	240	141	92
6	5.0	250	141	94
7	3.0	250	236	88
8	3.0	260	236	90
9	1.0	260	707	96
10	5.0	260	141	98
11	5.0	270	141	99
12 ^b	5.0	270	141	Full
13	5.0	250	141	53
14	5.0	230	141	36
15	5.0	270	141	75
16	10.0	250	71	77
17	10.0	230	71	56
18	15.0	250	71	85
19	15.0	270	47	95
20 ^c	15.0	260	47	96

^aRT = Residence Time. ^bRun for isolated yield, giving 79%. ^cRun for isolated yield, giving 85%.

total, 11 different conditions were evaluated. Running the reaction under the optimized conditions of 270 °C and 5 min of residence time (Table 5, run 12) gave 2-allyl-4-methoxyphenol in 79% isolated yield and a calculated throughput of 13.6 mmol/h (2.23 g/h), Scheme 5 and Table 5, run 12).

In a previous study using batch conditions and indirect microwave heating using Si/C as the heat transfer material a substantially longer reaction time was required (105 min) than in our CF-MAOS setup, but the use of a less polar solvent in this earlier study should also be taken into consideration.⁷⁵

Scheme 5. Claisen rearrangement carried out in the nonresonant CF-MAOS system



More similar conditions (249 °C, 4 min residence time) were found to be suitable in a CF system with conductive heating reported by Razzaq.⁶⁸

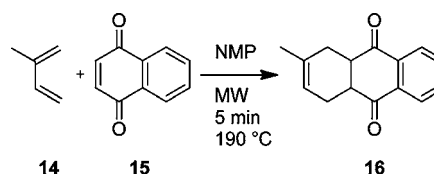
The good results obtained in the case of CF-MAOS Claisen rearrangement of 4-allyl anisole in NMP encouraged us to investigate the same model substrate but under neat conditions. The reaction parameters were reoptimized as in Table 5. In this application we also measured a mass balance for the system using one pump (99.5%). The neat 4-allyl anisole was pumped at 47 $\mu\text{L}/\text{min}$ and collected for 42 min, which corresponds to 1.974 mL.

Compared to the optimal conditions using NMP, a longer residence time of 15 min was required, due to the absence of a polar solvent suitable for MW heating, and a slightly lower temperature (260 °C) (Table 5, run 20) to achieve the corresponding 2-allyl-4-methoxyphenol in 85% isolated yield and a calculated throughput of 15.0 mmol/h (2.46 g/h).

Diels–Alder Reaction. There are many reports of the Diels–Alder reaction using MAOS with different dienes and dienophiles. Long reaction times (15–60 min) and high temperatures (160–180 °C) are common.^{76–78} A CF protocol with only 2 min residence time has been reported, but with a high set temperature (280 °C) and an even higher recorded reaction temperature (~ 330 °C).²²

The use of 1,4-naphthoquinone in Diels–Alder reactions was reported to give good results already in 1942.⁷⁹ In our first optimization experiments, temperatures between 125 and 190 °C and residence times between 1 and 5 min were investigated. The best conversion was observed at 190 °C with 5 min residence time, although the reaction was not complete (73% conversion). The temperature could not be increased further with the 17 bar backpressure regulator using acetonitrile as solvent without encountering problems due to boiling.

New high-boiling solvents were investigated, including acetic acid, DMF, and DMSO, all reported to be good solvents for the Diels–Alder reaction by Coda et al.⁸⁰ NMP was also included as a solvent with a slightly lower acceptor number (slightly less prone to act as a Lewis acid).^{81,82} The reactions were first run under microwave batch conditions in a single mode applicator at 150 and 190 °C for 5 min. DMF was initially the solvent of choice, but when heating the reaction mixture above 200 °C, byproducts were formed in increasing amounts, probably due to thermal decomposition of DMF.⁸³ NMP then became the solvent of choice, as the byproduct profile was better. However, full conversion was not achieved. The selected reaction conditions gave >95% conversion and 52% isolated yield after extensive preparative purification with HPLC (Scheme 6). Throughput for the CF-MAOS system was 4.72 mmol/h (1.07 g/h)

Scheme 6. Diels–Alder reaction carried out in the nonresonant CF-MAOS system^a

^aReaction conditions: NMP, 5 min residence time, 190 °C giving 52% isolated yield, and calculated throughput of 4.72 mmol/h, (1.07 g/h).

CONCLUSIONS

We have evaluated and presented applications for a novel nonresonance microwave applicator as the heating source in a continuous-flow synthesis system. The applicator was designed for CF chemistry, to provide uniform heat over at least a 100-mm section of a tubular borosilicate reactor, confirmed by measurements using temperature sensors and an IR camera. Due to the possibility of varying the MW frequency between 2.4 and 2.5 GHz, efficient heating could easily be achieved up to 270 °C, together with automatic tuning to match the temperature-dependent $\tan \delta$ value of the reaction mixture. Due to the excellent heating capacity, small-scale microwave batch experiments were easily adapted to nonresonance MW-assisted continuous-flow processing.

We have investigated the heating performance with a range of common solvents and demonstrated the usefulness of the system in metal-catalyzed cross-coupling, as well as in Claisen rearrangement and Diels–Alder addition, and for the synthesis of heterocycles. A scale-out with a Φ 3 mm tubular reactor proved the efficiency of CF Fischer indole synthesis with a throughput of 57 mmol/h. In our opinion, the fast heating, small reactor volume, and rapid change in reaction temperature in real time are unique features of this instrument. In conclusion, we believe the nonresonant CF-MAOS system presented here to be an unprecedented laboratory tool for safe and fast optimization of reaction conditions and scale-out synthesis.

EXPERIMENTAL SECTION

General Information. Microwave-assisted continuous flow reactions were performed on a WaveCraft nonresonant applicator prototype. The continuous flow was provided via a Syrris Asia syringe pump equipped with a Syrris ASIA pressurized input store, 1/0.5 mL or 5.0/2.5 mL syringes and an Upchurch Scientific 17 bar backpressure regulator. Analytical thin layer chromatography was performed using Merck aluminum sheets precoated with silica gel 60 F₂₅₄. Column chromatography was performed on Merck silica gel 60 (40–63 μm). Reaction temperatures were determined using the built-in online IR sensor. ¹H and ¹³C NMR spectra were recorded at 25 °C and at 399.9 and 100.6 MHz, respectively. Chemical shifts for ¹H and ¹³C were referenced to CHCl₃ and CDCl₃ for those samples with neat CDCl₃ as solvent, respectively. For those samples with CD₃OD as solvent, chemical shifts were referenced to CD₂HOD (¹H) or CD₃OD (¹³C). IR images were produced using a FLIR Thermo Vision A40M. All starting materials and reagents were commercially available and used as received.

4-Vinyl-1,1'-biphenyl (3). Two stock solutions were prepared. A reagent solution of 4-biphenylboronic acid (1) (2.50 mmol) and vinyl acetate (2) (25.0 mmol) diluted to 10

mL in DMF and a catalytic solution of Pd(OAc)₂ (0.050 mmol) and 1,3-bis(diphenylphosphino)propane (0.110 mmol) diluted to 10 mL in DMF. The two solutions were connected to each pump channel and pumped through the CF-MAOS system with residence times and temperatures between 30–120 s and 120–160 °C, respectively, for optimization purposes. A reaction mixture of 3 mL was collected over 5.3 min with a residence time of 75 s at 140 °C (283 $\mu\text{L pump}^{-1} \text{ min}^{-1}$) to determine the isolated yield for the optimized reaction conditions. The reaction mixture was transferred to a separation funnel followed by addition of 10 mL of 0.1 M NaOH (aq) and was extracted with DCM (3 \times 12 mL). The organic portions were dried over MgSO₄ and concentrated under reduced pressure (240 mbar, 25 °C). The concentrate was purified using silica flash chromatography (100% isohexane) to give 44.3 mg (0.25 mmol) **3** as white crystals in 66% isolated yield with an estimated throughput of 2.83 mmol/h (0.51 g/h). ¹H NMR (400 MHz, CDCl₃) δ 7.65–7.58 (m, 4H), 7.57.44 (m, 4H), 7.39–7.35 (m, 1H), 6.79 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.82 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.30 (dd, *J* = 10.9, 1.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 140.9, 140.7, 136.7, 136.6, 128.9, 127.4, 127.3, 127.1, 126.8, 114.0. GC–MS *m/z*: 180 (*M*⁺).

4-Methoxy-4'-(methoxymethyl)-1,1'-biphenyl (6). The 4-methoxy-4'-(methoxymethyl)-1,1'-biphenyl (**6**) was synthesized using 4-bromobenzyl methyl ether (**4**) (2.999 mmol, 0.427 mL), 4-methoxyphenylboronic acid (**5**) (9.058 mmol, 1.376 g), and DBU (9.000 mmol, 1.346 mL) dissolved and diluted to 30 mL using 1.64 mL water and DMF. The bis(triphenylphosphine)palladium(II) chloride (0.150 mmol, 0.105 g) was dissolved and diluted to 30 mL with DMF. The two solutions were connected to each pump channel and for optimization pumped through the CF-MAOS system with 10 s to 2.75 min RTU and 140–160 °C temperature. A sample for isolated yield was collected for 9 min using 0.5 min RTU (707 $\mu\text{L/pump/min}$) at 150 °C. The collected material was filtered through Celite, extracted with brine/ethyl acetate \times 3, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by silica flash chromatography using 10–20% ethyl acetate in isohexane as eluent to give 0.451 mmol (0.103 g) as a solid in 71% isolated yield and an estimated throughput of 3 mmol/h (0.687 g/h). ¹H NMR (CDCl₃, 400 MHz) δ 7.61–7.55 (m, 4H), 7.45–7.40 (m, 2H), 7.04–6.99 (m, 2H), 4.53 (s, 2H), 3.87 (s, 3H), 3.45 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 159.1, 140.1, 136.5, 133.3, 128.1, 128.0, 126.6, 114.1, 74.4, 58.0, 55.2. GC–MS *m/z*: 228 (*M*⁺). Mp: 78–82°.

5-Phenyl-1,3,4-oxathiazol-2-one (8). Pump channel 1: benzamide (**7**) (7.5 mmol, 0.908 g) was dissolved and diluted up to 30 mL with 1,4-dioxane. Pump channel 2: chlorocarbonylsulfonyl chloride (3.0 equiv, 22.5 mmol, 1.90 mL) was dissolved and diluted up to 30 mL with 1,4-dioxane. The two solutions were pumped with the same flow rate through the CF-MAOS system with 0.67–5 min RTU and 120–220 °C for the optimization runs. For the isolated yield collection, the above solutions were pumped with the same flow rate for 16 min using 1 min in RTU (353 $\mu\text{L/min/pump}$) at 200 °C. The collected material (theoretical 1.41 mmol, 0.253 g of final compound) was evaporated to give 0.278 g of crude 5-phenyl-1,3,4-oxathiazol-2-one (**6**) as an off-white solid. The crude product was purified by silica flash chromatography using 10% ethyl acetate in isohexane as eluent to give 0.87 mmol (0.156 g) in 62% isolated yield as a white solid and an estimated

throughput of 3.26 mmol/h (0.59 g/h). ¹H NMR (CDCl₃, 400 MHz) δ 7.93–7.89 (m, 2H), 7.53–7.47 (m, 1H), 7.46–7.39 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ 173.8, 157.4, 132.6, 129.0, 127.4, 125.8. GC–MS *m/z*: 179 (*M*⁺). Mp: 69–71 °C (lit. 69–71 °C).

2,3,4,9-Tetrahydro-1H-carbazole (11). Two stock solutions were prepared: a hydrazine solution of phenylhydrazine (**9**) (30 mmol) diluted to 30 mL in acetic acid/2-propanol (3:1) and a ketone solution of cyclohexanone (**10**) (33 mmol) diluted to 30 mL in acetic acid/2-propanol (3:1). The two solutions were connected to each pump channel and pumped through the CF-MAOS system with residence times and temperatures between 20–300 s and 210–230 °C, respectively, for optimization purposes. A reaction mixture of 30 mL was collected over 14 min with a residence time of 20 s at 230 °C (10 mL $\text{pump}^{-1} \text{ min}^{-1}$) to determine the isolated yield for the optimized reaction conditions. The reaction mixture was cooled down to room temperature and poured into 100 mL of ice-water under magnetic stirring which produced a pale-yellow/creamy precipitate. Stirring continued until all of the ice had melted, after which the suspension was filtrated and the precipitate washed with cold water. The washed precipitate was dried under reduced pressure overnight to give 13.4 mmol (2.3 g) of 2,3,4,9-tetrahydro-1H-carbazole as a pale, cream-colored solid in 90% isolated yield with an estimated throughput of 57.2 mmol/h (9.8 g/h). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (br. s., 1H), 7.48 (dt, *J* = 7.5, 0.8 Hz, 1H), 7.28 (dq, *J* = 7.6, 0.7 Hz, 1H), 7.16–7.06 (m, 2H), 2.77–2.70 (m, 4H), 1.99–1.85 (m, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 135.8, 134.2, 127.9, 121.1, 119.2, 117.9, 110.4, 110.3, 23.4, 23.4, 23.4, 21.0; LC–MS *m/z*: 172 [*M* + *H*]⁺. Mp: 115–117 °C (lit. 115–116 °C).

1-(Allyloxy)-4-methoxybenzene (12). The starting material to the Claisen rearrangement was synthesized by refluxing 4-methoxyphenol (200.0 mmol, 24.83 g), allyl bromide (300.5 mmol, 26.0 mL), and K₂CO₃ (220.1 mmol, 30.42 g) in 250 mL of acetone at 75 °C for 5 h.⁷⁴ The reaction was allowed to come to room temperature, and the remaining K₂CO₃ was filtered off and washed with acetone. The remaining residue was concentrated under reduced pressure and purified on Si flash column using 20% ethyl acetate in isohexane. The fractions containing product were combined and concentrated to give 186.1 mmol (30.56 g) of 1-(allyloxy)-4-methoxybenzene in 93% isolated yield as a yellowish oil. ¹H NMR (CDCl₃, 400 MHz) δ 6.92–6.82 (m, 4H), 6.07 (d quin, *J* = 17.28, 5.27 Hz, 1H), 5.42 (dq, *J* = 17.28, 1.61 Hz, 1H), 5.29 (dq, *J* = 10.49, 1.37 Hz, 4H), 4.50 (dt, *J* = 5.32, 1.54 Hz, 1H), 3.78 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 153.9, 152.7, 133.6, 117.4, 115.7, 114.6, 69.5, 55.6. LC–MS *m/z*: 165 (*M* + *H*⁺).

2-Allyl-4-methoxyphenol (13). Optimization of reaction conditions was performed using NMP as solvent and 225–240, 250–260, and 270 °C with 1, 3, or 5 min RTU. The best conversion was seen with 270 °C and 5 min RTU. Compound **13** was synthesized using **12** (60.86 mmol, 9.994 g) in NMP to a volume of 30 mL, giving a concentration of 2.03 M. The solution was connected to the pump channel and for isolated yield pumped through the CF-MAOS system with 5 min RTU at 270 °C using a 3-mm reactor. Sample for isolated yield was collected for 10 min. The crude product was purified by silica flash chromatography using 20% ethyl acetate in isohexane as eluent to give 2.267 mmol (0.372 g) of **13** as yellowish oil in 79% isolated yield and an estimated throughput of 13.6 mmol/h (2.23 g/h). ¹H NMR (CDCl₃, 400 MHz) δ 6.76 (td, *J* = 9.3, 1.6 Hz, 1H), 6.70 (s, 1H), 6.69 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.08–

5.96 (m, 1H), 5.20–5.17 (m, 1H), 5.16–5.14 (m, 3H), 3.78–3.76 (m, 3H), 3.39 (td, $J = 6.3, 1.6$ Hz, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 153.7, 147.9, 136.1, 126.5, 116.5, 116.5, 115.9, 112.6, 55.7, 35.3. LC–MS m/z : 165 ($\text{M} + \text{H}^+$).

Optimization of reaction conditions was performed with the neat, pale-yellow oil, 4-methoxy anisole, and 230–250, 260, and 270 °C with 5, 10, or 15 min in RTU. The best conversion was seen with 260 °C and 15 min in RTU. The 2-allyl-4-methoxyphenol was synthesized pumping 1-(allyloxy)-4-methoxybenzene neat (pale-yellow oil, 1.974 mL, 2.03 g, 12.36 mmol, $\rho = 1.0284$ g/mL) through the CF-MAOS system with 15 min RTU at 260 °C using a 3-mm reactor and collecting for 42 min. The crude product (brown oil, 2.02 g, mass balance = 99.5% recovered) was purified by silica flash chromatography using 5–10% ethyl acetate in pentane as eluent to give 10.50 mmol (1.725 g) in 85% isolated yield of 2-allyl-4-methoxyphenol and an estimated throughput of 15.0 mmol/h (2.46 g/h).

2-Methyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione (16). The 2-methyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione (16) was synthesized using isoprene (14) (29.99 mmol, 2.043 g) and 2,3-dihydronaphthalene-1,4-dione (15) (15.07 mmol, 2.384 g) in NMP to a total volume of 14 mL, giving a concentration of 15 of 1.07 M. The solution was connected to the pump channel and 1 bar N_2 was applied on the reservoir flask. For isolated yield the reaction mixture was pumped through the CF-MAOS system with 5 min residence time at 190 °C using a 3-mm reactor. Sample for isolated yield was collected for 20 min. The collected reaction mixture was filtered through a Si plug with 10–20% ethyl acetate in isohexane and concentrated under reduced pressure. The concentrate was dissolved in MeCN and purified on RP-HPLC using 55–90% MeCN in water with a gradient time of 7 min. Product-containing fractions were combined and concentrated under reduced pressure to give 1.574 mmol (0.356 g) in 52% isolated yield and a throughput of 4.722 mmol/h (1.07 g/h). ^1H NMR (CDCl_3 , 400 MHz) δ 8.08–8.03 (m, 2H), 7.78–7.72 (m, 2H), 5.43 (s, 1H), 3.45–3.39 (m, 1H), 3.37–3.31 (m, 1H), 2.56–2.42 (m, 2H), 2.28–2.10 (m, 2H), 1.70 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 198.4, 198.1, 134.2, 134.1, 134.0, 131.8, 126.9, 126.8, 118.5, 47.1, 46.5, 29.0, 24.9, 23.4. GC–MS m/z : 226 (M^+).

■ ASSOCIATED CONTENT

Supporting Information

Temperature profiles for solvents and reaction mixtures. LC- or GC chromatograms, and ^1H and ^{13}C NMR spectra for compounds 3, 6, 8, 11–13, and 16. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (40) WaveCraft, I Uppsala AB, Bergsbrunnagatan 11, SE 753 23 Uppsala, Sweden. <http://www.wavecraft.se/Pages/default.aspx>.
- (41) Patent application is filed and published. If granted the patent protects this design.
- (42) Many factors will potentially influence the observed IR-surface temperature illustrating the challenge to accurately measure the temperature of the reactor content correctly: (a) The sensor will not detect infrared radiation that radiates outside the \approx 7-mm measuring area. (b) The applicator inside is reflective metal which means that some heat will be reflected from the surroundings. (c) With low-microwave-absorbing reaction mixtures the amount of reflected microwaves will be high which leads to heating of the antenna. The IR sensors are therefore positioned in the housing to minimize this effect. (d) Depending on the thermal conductivity of the reactor material, there may be a time lag between when a temperature is reached in the reaction mixture and when it is measured by the sensor. (e) The heat capacity of the reaction mixture will vary which might lead to somewhat different heating patterns along the reactor. (f) Finally, the observed temperature will vary, depending on the heat dissipation from the reactor as a function of flow rate and reagent ambient temperature.
- (43) VICI, Valco Instruments Co., Inc. <http://www.vici.com/index.php>.
- (44) During all microwave heating experiments and chemical reactions, safety measurements to detect MW irradiation outside the applicator were performed. No irradiation was detected on any occasion. Neither was any MW irradiation measured outside the applicator cavity even when the applicator was open for the IR camera study.
- (45) In a later experiment the variation in temperature over the reactor was seen to be primarily dependent on the flow rate. A high flow rate with 10–30 s in RTU gives the highest temperature at sensor 3 instead of sensor 2.
- (46) Examples of power input from some of the available microwave instruments on the market: Biotage Initiator 400 W, CEM DiscoverSP 300 W, Anton Paar Monowave 850 W, Milestone Start (multimode) 1200 W, Synthos 3000 (multimode) 1400 W. All information accessed from the company homepages, respectively, 2011-08-31.
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