Organic Process Research & Development

Article

pubs.acs.org/OPRD

A Continuous-Flow Microwave Reactor for Conducting High-Temperature and High-Pressure Chemical Reactions

Jennifer M. Sauks,[†,‡] Debasis Mallik,[‡] Yuri Lawryshyn,[†] Timothy Bender,[†] and Michael Organ*[,†,‡]

[†]Department of Chemical Engineering and Applied Chemistry, University of Toronto, 200 College Street, Toronto, Ontario, Canada M5S 3E5

[‡]Department of Chemistry, York University, 4700 Keele Street, Toronto, Ontario, Canada M3J 1P3

Supporting Information

ABSTRACT: A continuous-flow microwave reactor with a unique pressure control device is described. The reactor has been designed to withstand extremely high pressure without the involvement of a conventional backpressure-creating device that commonly results in carryover and cross-contamination problems. The reactor efficiency has been evaluated by product conversions using two model reactions, namely, the Claisen rearrangement and the synthesis of benzimidazole.

INTRODUCTION

Microwave reactors were first used for organic synthesis in the late 1980s as an alternative to hot plates and oil baths.[1] It was soon discovered that for some chemistry, microwave irradiation offered significant improvements over conventional heating methods, including shorter reaction times,[2] cleaner reaction profiles,[3] increased yields, and improved selectivity.[4,5] Despite these advantages, lab-scale microwave-mediated reactions are not transferred readily to larger scales because the irradiation is distributed less uniformly in the irradiation zones of larger microwaves. Typical preproduction runs in litre-scale microwaves frequently suffer from lack of reproducibility during process validation.[6,7] Furthermore, research has shown that the penetration depth of microwave irradiation into strong microwave-absorbing solvents (e.g., DMI or DMA) at 2.45 GHz is only a few centimetres and that, depending on the nature of the reactants, a significant portion of this microwave radiation is reflected back.[8] For these reasons, microwave-based technology has been restricted to devices of only a few litres in capacity, and the most commonly used devices in the field (e.g., Biotage, CEM) can only handle up to a few millilitres.

There are also major safety concerns surrounding the use of large pressurized batch reactors. Microwave energy is absorbed directly by the reaction mixture (i.e., solvent and/or reactants), which can lead to superheating that can cause rapid exotherms and explosions.[9] We envisioned that the distribution of microwave energy can be kept uniform and the operation can also be performed safely if we restrict the reaction space to a small volume (e.g., a capillary or a narrow tube) and continuously flow reactants through this space to produce bulk products. This strategy of "scaling out" a chemical transformation, in contrast to the traditional progressive "scaling up" of batch reactions, is one of the reasons why continuous-flow synthesis is gaining in popularity.

Continuous-flow organic syntheses using conventional energy sources (e.g., photo-, sonic, and heat exchangers) have already taken the leap from academic research laboratories to the commercial world, as evidenced by Eli Lilly, for example, who have integrated such technologies into their process optimization plants with the intent of completely eliminating large-scale batch reactors.[10] One of the biggest advantages of continuous-flow synthesis resides in its ability to make product *on demand*, thereby drastically reducing the cost during lead optimization. When larger, kilogram-scale samples of lead compounds are required for toxicological and early-phase clinical studies, extensive process development is usually required to accommodate scale-up using traditional batch reactors. By "scaling out" using continuous-flow reactors, process development would be mitigated to a large extent. However, continuous processes based on challenging reactions that require significant heating and/or prolonged reaction times are far less commonly encountered in the literature. The efficiency of heat exchangers becomes critical when the demand for heat activation is high and the residence time in the flow reactor is short. Although small flow channels improve heat and mass transfer because of the high surface area-to-volume ratio, our early research showed that when a reaction is performed in a capillary tube, convectional heating is insufficient for reactions requiring a large amount of heat (e.g., the Claisen rearrangement). We envisioned that if continuous flow were coupled with microwave irradiation, the resultant hybrid reactor would possess the benefits of both technologies. Consequently, in 2005 we developed *microwave-assisted continuous flow for organic synthesis* (MACOS),[11] a capillary reactor technology that was found to be highly effective for a variety of reactions including cross-coupling,[11] ring-closing metathesis,[11] nucleophilic aromatic substitution,[11] Wittig,[11] aza-Michael addition,[12,13] and Heck reactions.[14] Moreover, our metal-coated capillaries were found to perform excellently in various transition-metal-catalyzed reactions involving palladium,[15] gold,[16,17] and copper.[18] Using our first-generation reactor, we also successfully demonstrated the ability to scale out a variety of organic reactions, including those with high-energy

Special Issue: Continuous Processes 14

Received: February 1, 2013

dx.doi.org/10.1021/op400026g | *Org. Process Res. Dev.* XXXX, XXX, XXX–XXX

compounds (e.g., preparation of azides by the Aube−Schmidt reaction),[19] synthesis of sultams,[20] and pericyclic reactions.[21]

Although the preliminary results from our first-generation reactor were very encouraging, the reactor lacked a system to create backpressure, and therefore, reactions could not be heated to high temperatures without undergoing phase changes. Many organic transformations must be heated, some significantly, in order for any product to form. For example, many cross-coupling reactions are heated for prolonged periods at or beyond 100 °C, while pericyclic reactions require temperatures in excess of 180 °C. The bomb design of commercial batch microwaves allows them to withstand moderately high pressures (~20−30 bar), and this is key to their ability to reach higher temperatures, often well above the boiling point of the reaction solvent. While the design of bombs to suit batch applications has been relatively easy, the ability to create high pressure within a constantly flowing system has remained elusive. For the most part, continuous-flow microwave reactors are limited to operating pressures of approximately 20 bar (290 psi),[22] with a few reaching 34 bar (500 psi) (Figure 1).[22q] These limitations stem from the materials used

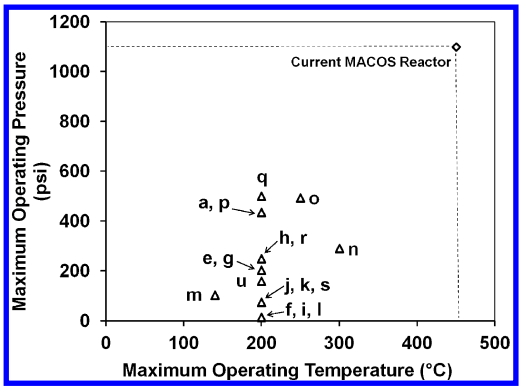

Figure 1. Pressure−temperature profile of reactors reported in the literature.

to construct the reactor and/or connectors, but even more confounding has been the use of low-backpressure-generating devices. Backpressure regulators generate and hold system pressure via direct contact of a spring-loaded plate against the flowing solution,[23] which can lead to serious clogging issues.[24] In an HPLC instrument, these regulators do not have steady-state problems because the analyte concentration is too low to cause plugging or carryover. However, in flow reactors, conventional backpressure regulators are not practical because fouling can occur even at moderate reactant concentrations, causing the reactors to suffer from carryover. The shearing forces that are created when viscous matter is forced through a constriction can induce precipitation. In turn, this compromises the backpressure regulator's ability to seat properly, leading to an inability to maintain the system pressure, which means that the run must be terminated. Further, these precipitates continue to bleed into later runs, thus contaminating them and leading to erroneous analyses. This paper describes our newest iteration of the MACOS design, a continuous-flow capillary microwave reactor design that is capable of performing liquid-phase organic reactions using both polar and nonpolar mixtures under high-temperature and high-pressure conditions *without contacting and/or constricting the flowing stream of reagents, reactants, and solvents.*

RESULTS AND DISCUSSION

Two high-pressure syringe pumps (P-1 and P-2) (Harvard Apparatus, OEM 2022) equipped with 2.5 mL stainless steel high-pressure syringes (Harvard Apparatus) are used to pump reactants from reservoirs R-1 and R-2 into the reactor (Figure 2). Two reciprocating pumps work together to continuously

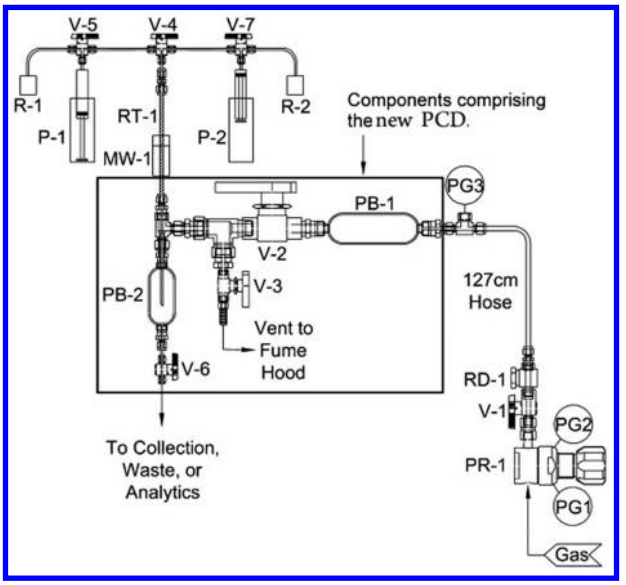

Figure 2. Detailed schematic of the new PCD.

infuse each reactant into the reactor indefinitely. The reactants are pumped into a reactor tube (RT-1), which can consist of microwave-transparent (e.g., quartz) or microwave-conducting (e.g., SiC) materials.[25−27] Reducing ferrules connect RT-1 to the rest of the system, and stainless steel tubing connects all parts of the system. RT-1 is placed vertically through the end of the waveguide of a modified Biotage Initiator Synthesizer (MW-1), through which a window was machined into the outward-facing wall of the waveguide to allow an external high-definition infrared (IR) camera to monitor the reactor tube surface temperature.[28] The bottom or outlet of the reactor tube is attached to the backpressure-creating device (BPD) using a stainless steel outage tube (OT-1) welded to the interior of the flow channel. This unique piece guides the flow of the products from the reactor to the bottom of the pressure chamber (PB-2).[29] The remaining components of the pressure control device (PCD) include a nitrogen gas cylinder (which also provides an inert atmosphere for air/moisture-sensitive reactions), a pressure regulator (PR-1), a pressure ballast (PB-1), a pressure relief valve (V-3), and the sample cylinder (PB-2).

The purpose of the PCD is to introduce and regulate the reactor pressure and ensure that no pressure fluctuations occur during a reaction. The entire flow reactor has been tested up to (at least) 73 bar (1100 psi) with no leaks or system failure. The reactor has been built in such a way that the operating volume of the pressure ballast (PB-1) is (at least) 10 000 times greater than the total volume of the rest of the system, and therefore, the reactor operates as if in its own open environment. The PCD uses gas to supply pressure, not a mechanical part located in the fluid stream (such as conventional backpressure regulators). This is ideal for performing reactions that may have damaging effects on traditional regulators. Of equal importance, the lack of physical constriction of the flow stream

dx.doi.org/10.1021/op400026g | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

eliminates reactor plugging due to clogging, which is invariably encountered when conventional backpressure regulators are used. The nitrogen gas cylinder initially charges PB-1 to the desired operating pressure prior to a reaction. This pressure is usually determined by the lowest-boiling substance in the reaction mixture and is selected to be greater than the vapor pressure of this substance at the desired operating temperature. This ensures that the mixture remains in the liquid phase throughout the duration of the reaction. Once the pressure ballast (PB-1) is filled, the nitrogen gas cylinder is isolated from the reactor using a shut-off valve (V-1). Through valve V-6, pressure chamber PB-2 is emptied repeatedly with no loss of pressure, allowing a limitless amount of product to be produced, analyzed in-line in real time, and collected.[30]

Temperature, Power, and Flow Rate Characteristics of the Reactor. The reactor was initially tested to determine the temperature versus power relationship using air in the SiC tube reactor. Because SiC heats up in the presence of microwave irradiation and effectively shields the interior of the tube from the irradiation, it was hypothesized that for any given solution flowing through the tube, the average external tube surface temperature at a given power rating would be constant. In light of the high heat transfer coefficient of SiC, the inner wall temperature of the tube should almost instantaneously become the same as the outside wall temperature.[31] Because of the high surface area-to-volume ratio associated with this mesoscale reactor, the solvent should rapidly heat up to this same temperature, importantly, irrespective of which solvent it is, and the unique and effective backpressure-creating system should hold it in the liquid state. This hypothesis was tested and found to be true. The average tube surface temperature was monitored over a range of power settings (30–70 W) for three substances flowing through the SiC reactor tube (RT-1): air, toluene, and acetic acid (Figure 3). With a temperature

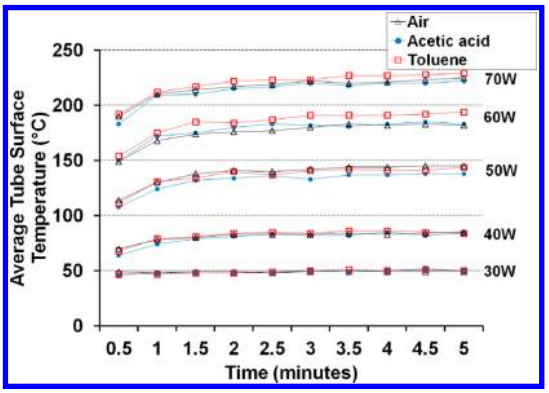

Figure 3. Determination of the steady-state time for the average tube surface temperature for various fluids at a flow rate of 100 μL/min.

variance of about ±4 °C for each measurement, which is within the normal fluctuation range of the camera, the steady-state temperature was observed to be the same for any substance flowing through the reactor at a given power setting. It should be noted that in conventional microwave reactors, it would be impossible to heat solvents with low loss tangent values (e.g., toluene) to this degree (e.g., 250 °C), as they are essentially microwave-invisible. This is one of the benefits of using the SiC reactor tube. Averaging the steady-state temperature values from these experiments, a general temperature versus power trend was determined (Figure 4). Additionally, the effect of the

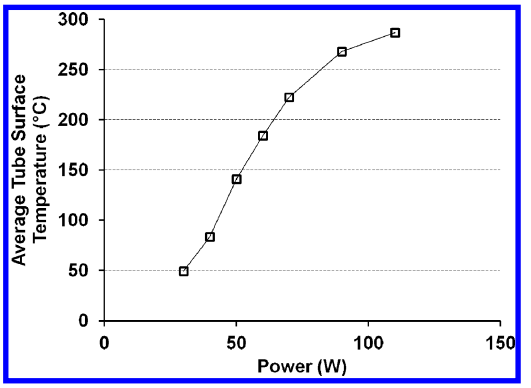

Figure 4. Relationship between microwave power and average tube surface temperature.

flow rate on the heating of the SiC reactor was also tested over a range of flow rates from 50 to 300 μL/min, which correspond to residence times of 2 min to 30 s, respectively. It was observed in tests completed with toluene that there was a minimal effect of the flow rate on the average tube surface temperature (Figure 5). To demonstrate the heating and

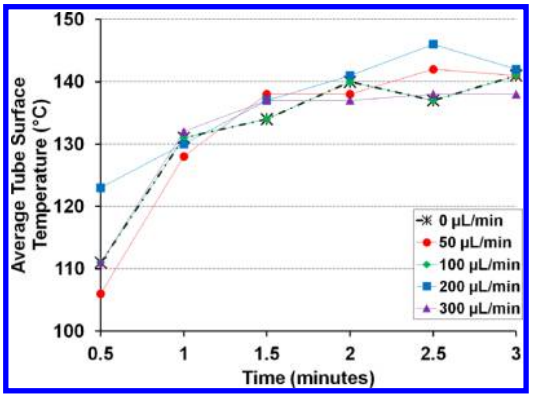

Figure 5. Graphical representation of the effect of the flow rate on the steady state of the average tube surface temperature using toluene.

pressure capabilities of the reactor, water was heated in the reactor to just below its supercritical point (373 °C) for an extended period of time with no problems.

Reactor Validation. The synthesis of 2-methylbenzimidazole (Figure 6) and the Claisen rearrangement of allyl phenyl ether (Figure 7) were chosen to verify the new MACOS reactor design, as there is wide documentation of these high-energy transformations under microwave irradiation in the literature. The Claisen rearrangement, which takes many hours at ~200 °C in an oil bath, failed to proceed at all in a batch microwave with the microwave-invisible solvent toluene.[25] This reaction did proceed to full conversion under microwave irradiation using a silicon carbide passive heating element at 250 °C [13 bar (189 psi) pressure] for 105 min in toluene. Similarly, when the reaction was doped with *N*-butyl-*N*′-methylimidazolium hexafluorophosphate (bmimPF_6) and microwaved in toluene (250 °C), the reaction was complete in 105 min. With these two methods, the heating element had to be removed prior to workup and analysis.[25] More recently, it was reported that a high-temperature/high-pressure conventionally heated microreactor (X-Cube Flash) achieved a high yield and purity (<5% byproducts) using toluene as the solvent at 240 °C [100 bar (1450 psi) pressure].[32,33] With our flow microwave reactor

dx.doi.org/10.1021/op400026g | Org. Process Res. Dev. XXXX, XXX, XXX–XXX

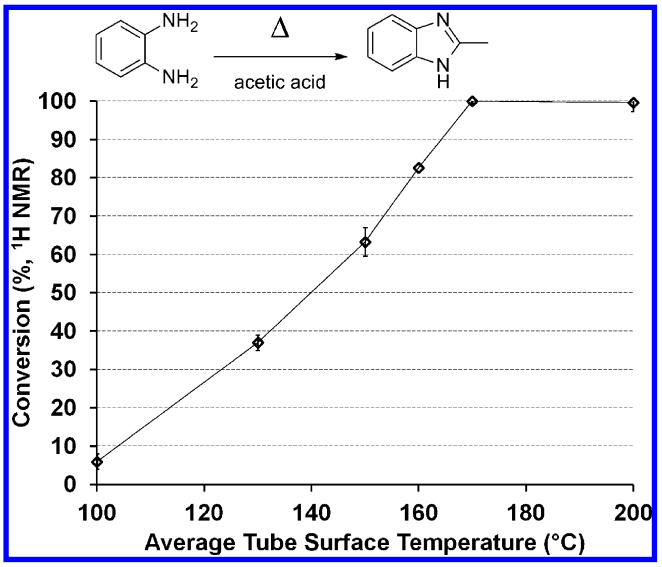

Figure 6. Experimental correlation between average tube surface temperature (measured by the external FLIR camera) and the percent product conversion from benzimidazole synthesis.

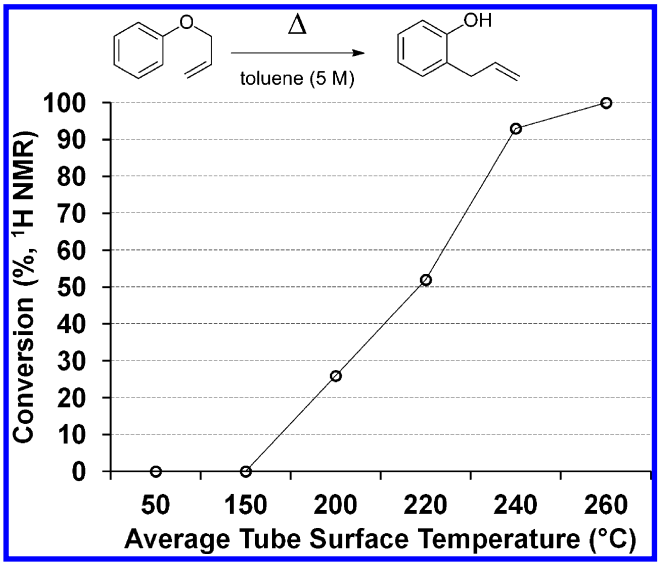

Figure 7. Experimental correlation between average tube surface temperature (measured by the external FLIR camera) and the percent product conversion from the Claisen rearrangement reaction.

setup (260 °C under 580 psi of pressure), quantitative conversion was achieved with a 5 M solution at a flow rate of 25 μL/min, which corresponds to a 4 min residence time (Figure 5). Although the current reactor is equipped to run at a relatively low flow rate (e.g., 25 μL/min in the above example), with the unique design of the PCD, we successfully demonstrated the ability of our reactor to handle a very concentrated solution of reagents (e.g., 5 M in the above example) without any clogging or carryover problems. Our ability to conduct reactions at this level of concentration allows us to enhance greener output.

Kappe's group reported a benzimidazole synthesis using a conventionally heated microreactor (X-Cube Flash) that could process a 1 M solution of *o*-phenylenediamine in acetic acid at 270 °C [130 bar (1885 psi) pressure] with a 30 s residence time to achieve a 94% isolated yield of benzimidazole.[34] Attempts to increase the flow rate or reactant concentration led to pumping failure.[30] With our flow microwave setup, full conversion of *o*-phenylenediamine to benzimidazole was achieved at 170 °C with a residence time of 30 s. This result was found to be on par with the lowest residence time reported to date for this type of cyclization reaction.[35] When the temperature was raised to 313 °C and the backpressure was adjusted accordingly to 720 psi, we were able to flow our reactor at 1 mL/min, which is the highest rate possible with the OEM 2022 pump modules, and complete conversion was still maintained. *This corresponds to a residence time of less than 6 s to achieve 99+% conversion.* This will have a dramatic impact on sustainable manufacturing (i.e., continuous scale-out chemical production) with this reactor setup.

SUMMARY AND CONCLUSIONS

The novel high-pressure/high-temperature microwave flow reactor disclosed in this article operates in unique reaction space that is far removed from the capability of any other similar system reported thus far. Key to this distinctive capability is our pressure control device (PCD), which offers an effective method to pressurize a continuous-flow reactor using gas, thereby eliminating any of the potential mechanical failures or clogging issues that all conventional and currently available backpressure regulators face. The system has been shown to operate continuously at 1100 psi (at least), achieving temperatures that can be several hundred degrees above the boiling points of the solvents and reagents employed. The use of a silicon carbide reactor tube allows for a unique environment in which to perform chemistry using microwave irradiation, meaning that any solvent, including microwave-transparent solvents (e.g., toluene), can be employed effectively. Two reactions with high transition-state barriers, the Claisen rearrangement and the benzimidazole synthesis, were used to validate this new reactor. In the case of the latter, the reaction could be heated to the supercritical point of acetic acid, allowing the reaction to reach completion in mere seconds under continuous-flow conditions.

ASSOCIATED CONTENT

Supporting Information

Photographs and schematics of the equipment described, standard operating procedures, and synthetic procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Address: Department of Chemistry, York University, 4700 Keele St., Toronto, ON, Canada M3J 1P3. E-mail: organ@yorku.ca.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the NSERC CREATE Program, the NSERC CRD Program, the Ontario Centres for Excellence (OCE), the Center in Chemical Methodologies, and the NIH CMLD Program, NIH P50 GM069663, and NIH P41-GM076302. The authors recognize Dr. Marcus Kim of Agilent Technologies Inc. for his useful suggestions.

■ ABBREVIATIONS

DMI, 1,3-dimethyl-2-imidazolidinone; DMA, dimethylacetamide; MACOS, microwave-assisted continuous flow for organic synthesis.

■ REFERENCES

(1) Kappe, C. O. *Angew. Chem.* **2004**, *116*, 6408; *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
(2) *Microwaves in Organic Synthesis*, 1st ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2002.
(3) Hoodgenboom, R.; Paulas, R. M.; Pilotti, Å; Schubert, U. S. *Macromol. Rapid Commun.* **2006**, *27*, 1556.
(4) Loupy, A.; Maurel, F.; Sabatie-Gogova, A. *Tetrahedron* **2004**, *60*, 1683.
(5) Hoz, D. A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164.
(6) Singh, B. K.; Kaval, N.; Tomar, S.; Van der Eycken, E.; Parmar, V. S. *Org. Process Res. Dev.* **2008**, *12*, 468.
(7) Wiles, C.; Watts, P. *Beilstein J. Org. Chem.* **2011**, *7*, 1160.
(8) De La Hoz, A.; Alcázar, J.; Carillo, J.; Herrero, M. A.; Muñoz, J. D. M.; Prieto, P.; De Cózar, A.; Diaz-Ortiz, A. Reproducibility and Scalability of Microwave-Assisted Reactions. In *Microwave Heating*; Chandra, U., Ed.; InTech: Rijeka, Croatia, 2011; pp 137−162; available at www.intechopen.com.
(9) KaMa, H.; Bo, L. *Sci. China, Ser. E: Technol. Sci.* **2009**, *2*, 491.
(10) Johnson, M. D.; May, S. A.; Calvin, J. R.; Remacle, J.; Stout, J. R.; Diseroad, W. D.; Zaborenko, N.; Haeberle, B. D.; Sun, W.-M.; Miller, M. T.; Brennan, J. *Org. Process Res. Dev.* **2012**, *16*, 1017.
(11) Comer, E.; Organ, M. G. *J. Am. Chem. Soc.* **2005**, *127*, 8160.
(12) Zang, Q.; Javed, S.; Hill, D.; Ullah, F.; Bi, D.; Porubsky, P.; Neuenswander, B.; Lushington, G. H.; Santini, C.; Organ, M. G.; Hanson, P. R. *ACS Comb. Sci.* **2012**, *14*, 456.
(13) Zang, Q.; Javed, S.; Porubsky, P.; Ullah, F.; Neuenswander, B.; Lushington, G. H.; Basha, F. Z.; Organ, M. G.; Hanson, P. R. *ACS Comb. Sci.* **2012**, *14*, 211.
(14) Achanta, S.; Liautard, V.; Paugh, R.; Organ, M. G. *Chem.—Eur. J.* **2010**, *16*, 12797.
(15) Shore, G.; Morin, S.; Mallik, D.; Organ, M. G. *Chem.—Eur. J.* **2008**, *14*, 1351.
(16) Shore, G.; Organ, M. G. *Gold Bull.* **2010**, *43*, 105.
(17) Organ, M. G.; Shore, G.; Tsimerman, M. *Beilstein J. Org. Chem.* **2009**, *5*, No. 35.
(18) Shore, G.; Yoo, W. J.; Li, C. J.; Organ, M. G. *Chem.—Eur. J.* **2010**, *16*, 126.
(19) Painter, T. O.; Thornton, P. D.; Orestano, M.; Santini, C.; Organ, M. G.; Aubé, J. *Chem.—Eur. J.* **2011**, *17*, 9595.
(20) Ullah, F.; Zang, Q.; Javed, S.; Porubsky, P.; Neuenswander, B.; Lushington, G. H.; Bash, F. Z.; Hanson, P. R.; Organ, M. G. *Synthesis* **2012**, *44*, 2547.
(21) Shore, G.; Organ, M. G. *Chem. Commun.* **2008**, 838−840.
(22) (a) Bondioli, F.; Corradi, A. B.; Ferrari, A. M.; Leonelli, C. *J. Am. Ceram. Soc.* **2008**, *91*, 3746. (b) Corradi, A. B.; Bondioli, F.; Ferrari, A. M.; Focher, B.; Leonelli, C. *Powder Technol.* **2006**, *167*, 45. (c) Braun, I.; Schulz-Ekloff, G.; Wöhrle, D.; Lautenschläger, W. *Microporous Mesoporous Mater.* **1998**, *23*, 79. (d) Dressen, M. H. C. L.; van de Kruijs, B. H. P.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. *Org. Process Res. Dev.* **2010**, *14*, 351. (e) Cablewski, T.; Faux, A. F.; Strauss, C. R. *J. Org. Chem.* **1994**, *59*, 3408. (f) Chemat, F.; Poux, M.; Martino, J.; Berlan, J. *Chem. Eng. Technol.* **1996**, *19*, 420. (g) Benali, O.; Deal, M.; Farrant, E.; Tapolczay, D.; Wheeler, R. *Org. Process Res. Dev.* **2008**, *12*, 1007. (h) Glasnov, T. N.; Vugts, D. J.; Koningstein, M. M.; Desai, B.; Fabian, W. M. F.; Orru, R. V. A.; Kappe, C. O. *QSAR Comb. Sci.* **2006**, *25*, 509. (i) Groisman, Y.; Gedanken, A. *J. Phys. Chem. C* **2008**, *112*, 8802. (j) He, P.; Haswell, S. J.; Fletcher, P. D. I. *Appl. Catal., A* **2004**, *274*, 111. (k) He, P.; Haswell, S. J.; Fletcher, P. D. I. *Sens. Actuators, B* **2005**, *105*, 516. (l) Marquie, J.; Salmoria, G.; Poux, M.; Laporterie, A.; Dubac, J.; Roques, N. *Ind. Eng. Chem. Res.* **2001**, *40*, 4485. (m) Pipus, G.; Plazl, I.; Koloini, T. *Chem. Eng. J.* **2000**, *76*, 239.
(n) See Voyager at www.cem.com. (o) See MARS instruments at www.cem.com. (p) See Flowsynth at http://www.milestonesrl.com/analytical/. (q) Wilson, N.; Sarko, C.; Roth, G. *Org. Process Res. Dev.* **2004**, *8*, 535. (r) Paulus, R. M.; Erdmenger, T.; Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Macromol. Rapid Commun.* **2007**, *28*, 484. (s) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Chem.—Eur. J.* **2006**, *12*, 4407. (t) Murphy, E. R.; Martinelli, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 1734.
(23) Kawanami, H.; Matsushima, K.; Sato, M.; Ikushima, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5129.
(24) Noël, T.; Naber, J. R.; Hartman, R. L.; McMullen, J. P.; Jensen, K.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 288.
(25) Kremsner, J.; Kappe, C. O. *J. Org. Chem.* **2006**, *71*, 4651.
(26) Obermayer, D.; Gutmann, B.; Kappe, C. O. *Angew. Chem.* **2009**, *121*, 8471; *Angew. Chem., Int. Ed.* **2009**, *48*, 8321.
(27) Damm, M.; Kappe, C. O. *Mol. Diversity* **2009**, *13*, 529.
(28) See Figures S1 and S2 in the Supporting Information for photographs of the modified Biotage microwave reactor.
(29) See Figure S3 in the Supporting Information for a blow-up of the PCD.
(30) While not the focus of this manuscript, the reactor is set up with in-line continuous quality control analysis by GC/MS. A schematic (Figure S4) and photograph (Figure S5) of the whole reactor set up, including GC/MS analysis, have been included in the Supporting Information. Sample can be withdrawn constantly from the high-pressure reactor for in-line analysis using the unique design with no change in the pressure of the system.
(31) The thermal conductivity of SiC is substantially greater than that of glass at 300 K. (For representative thermal conductivities of various forms of SiC, see: Thuault, A.; Savary, E.; Bazin, J.; Marinel, S. *J. Mater. Process. Technol.* **2013**, *214*, 470. Harris, G. L. Thermal Conductivity of SiC. In *Properties of Silicon Carbide*; Harris, G. L., Ed.; EMIS Datareviews Series, Vol. *13*; IET: London, 1995; pp 5−6.) Consequently, heat transfer was assumed to be complete and instantaneous. This hypothesis was later supported experimentally. A target temperature of 100 °C (i.e., 373 K) was recorded for deionised water when an external IR camera (calibrated) was mounted at the exit port of a 25 cm long reactor cell even at a high flow rate (300 μL/min).
(32) Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *Chem. Eng. Technol.* **2009**, *32*, 1702.
(33) Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321.
(34) Damm, M.; Glasnov, T.; Kappe, C. O. *Org. Process Res. Dev.* **2010**, *14*, 215.
(35) Morschhauser, R.; Krull, M.; Keyser, C.; Boberski, C.; Bierbaum, R.; Puschner, P. A.; Glasnov, T. N.; Kappe, C. O. *Green Process. Synth.* **2012**, *1*, 281.