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# Translating High-Temperature Microwave Chemistry to Scalable Continuous Flow Processes

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**Abstract:**

**A comparison between batch microwave and conventionally heated continuous flow scale-up protocols for three selected model reactions is presented. Using high-temperature/-pressure conditions as process intensification principles, reaction times for all three transformations were reduced to a few seconds or minutes at temperatures ranging from 180−270 °C utilizing sealed vessel microwave conditions on small scale (2 mL). Successful scale-up of two out of three reactions in a multimode batch microwave reactor on a ∼1 L scale produced product quantities of ∼0.5 kg within less than one hour of overall processing time. Moving to a continuous flow format in a high-temperature/high-pressure stainless steel microcapillary microreactor (4−16 mL reactor volume) all three transformations were scalable with significantly increased space-time yields compared to the microwave batch protocols. A critical evaluation of both scale-up principles is made.**

## Introduction

High-speed microwave-assisted synthesis continues to attract considerable attention in the scientific community with new and innovative applications being reported on an almost routine and daily basis.[1,2] In many instances, the use of sealed-vessel high-temperature microwave processing has been shown to dramatically reduce reaction times, increase product yields, and to enhance product purities compared to conventionally heated experiments.[1,2] In particular in the pharmaceutical, agrochemical, and related industries, microwave-assisted synthesis is used extensively as frontline methodology in most discovery programs.[3] As a consequence, a significant number of microwave protocols have already made their way into kilolabs and process research laboratories, where the lack of suitable large-scale microwave instrumentation often represents a serious problem.[4]

Nonetheless, in the past few years, impressive progress has been achieved in translating small-scale microwave chemistry from the milligram or gram scale (typically performed in a single-mode reactor) to a larger-scale batch format using multimode microwave instrumentation.[5,6] By either using one large vessel or several smaller vessels in parallel (multivessel rotor systems), volumes of up to several liters can be processed in a single microwave irradiation experiment using commercially available benchtop reactors. This generally provides products on a >100 g scale and may even lead to multikilogram product quantities if automated.[5,6] However, when moving to larger and larger batch reactors many of the genuine benefits of small-scale microwave chemistry are in fact lost. In particular, the rapid heating and cooling profiles obtained on a small scale in high power-density single-mode cavities can often not be duplicated on a larger scale in a multimode instrument. In addition, many of the large-scale reactors—due to safety concerns—do not have the same temperature/pressure ratings as modern single-mode instruments (300 °C/30 bar).[7] Thus, the high reaction temperatures and rapid heating rates responsible for the fast kinetics in a typical small-scale microwave experiment can generally not be mimicked on scale, leading to prolonged reaction and overall processing times.[5,6] Similar arguments can be made for the cooling period, where rapid cooling from the high temperatures attained in a microwave experiment to ambient conditions can sometimes be essential to minimize product decomposition.[8] Finally, one of the main limitations of microwave scale-up technology is the restricted penetration depth of microwave irradiation into absorbing materials, i.e. solvents or reaction mixtures. At the typical operating frequency of most microwave reactors (2.45 GHz),

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(7) Kappe, C. O.; Dallinger, D.; Murphree, S. S. *Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments, and Protocols*; Wiley-VCH: Weinheim, 2009.

(8) An exception is the Biotage Advancer multimode instrument possessing a flash cooling option, whereby the contents of the pressurized 350 mL reaction vessel are ejected into a holding tank (expansion cooling). See ref 6d for details.

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the penetration depth is in the order of a few centimeters, depending on the dielectric properties of the medium.[9]

As a consequence of the apparent limitations of large-scale batch microwave processing, recent efforts have focused on performing microwave chemistry under continuous flow conditions.[5,10,11] The typically short reaction times—in the order of a few minutes or even seconds—experienced in high-temperature microwave chemistry protocols form an ideal basis for continuous flow processing where short residence times are essential. Using either single-mode or multimode microwave instruments, successful examples of microwave-assisted continuous flow processing have been reported in the literature using a variety of different formats.[10,11] Applying a flow regime, many of the advantages of small-scale microwave heating (rapid heating and cooling) are reinstated, with limited penetration depths typically not being an issue.[10,11] However, because of the comparatively low pressure limits of commercially available microwave flow systems (~20 bar),[7] genuine high-temperature/-pressure processing is generally not possible.

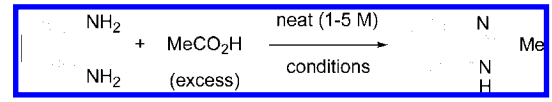
In this contribution we evaluate the scale-up efficiencies for several synthetic transformations executed at high temperature, comparing batch microwave protocols with continuous flow procedures that employ a conventionally heated high-temperature/-pressure microreactor setup (350 °C/180 bar). Because of the high surface-to-volume ratio in microreactors of this type, heat transfer to the reaction mixture is very efficient, thus mimicking the advantages of using microwave dielectric heating on a small scale.[12,13]

## Results and Discussion

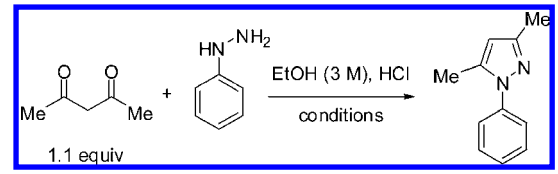
**General Considerations.** In the past few years, the chemical industry has started to explore different means of so-called "Process Intensification" technologies which demand abrupt changes in traditional processing and a search for game-changing improvements.[14] The idea to deliberately explore, for example, high-temperature/high-pressure or otherwise very unusual process conditions for process intensification of chemical reactions is a recent concept termed "Novel Process Windows".[15] Here, the general notion is to operate at conditions which considerably speed up conversion rates, while maintaining selectivity. In order to evaluate the differences between batch microwave and continuous flow processing in a high-temperature regime, three model transformations were selected (Schemes 1, 2, and 3). As a significant limitation of current continuous flow/microreactor technology suitable for organic synthesis is the more or less strict requirement for homogeneity,[12,13] only transformations were chosen that were completely homogeneous and did not lead to direct product precipitation at the end of the synthesis. In order to enable a high throughput in the flow experiments, all reactions were initially optimized for the shortest possible reaction time using different single-mode microwave reactors on a millimolar scale. In a subsequent step, these conditions were translated to a larger scale (~200 mmol) employing a multimode parallel batch microwave reactor (Synthos 3000, Anton Paar GmbH),[16] before ultimately being adapted to a continuous flow regime which by definition has the potential of production-scale capabilities.[17]

The choice for a parallel microwave batch reactor (i.e., a multivessel rotor system as compared to one large vessel) was governed by penetration depth issues. With a typical penetration

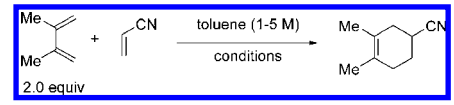
***Scheme 1.*** **2-Methylbenzimidazole formation from *o*-phenylendiamine**




***Scheme 2.*** **3,5-Dimethyl-1-phenylpyrazole formation**




***Scheme 3.*** **Diels–Alder cycloaddition of 2,3-dimethylbutadiene with acrylonitrile**





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depth for most absorbing solvents in the order of just a few centimeters,[7,9] the microwave power density inside a large batch reactor (>1 L of volume) may only be a small fraction of the density on the surface. Therefore, solvents or reagents in the center of the reaction vessel will be heated mostly by convection and not by direct "in core" microwave dielectric heating.[7] In addition, temperature gradients in large batch reactors irradiated by microwaves may be experienced, leading to undesirable overheating of parts of the reaction mixture. A recent investigation into this effect using IR thermography and a multiple fiber-optic temperature monitoring system has confirmed that even for a comparatively small cylindrical reaction vessel (i.d. 4 cm) significant temperature differences between the center and regions close to the surface of the reactor were observed when heating strongly microwave-absorbing aqueous reaction mixtures in a multimode microwave cavity.[18]

In order to further investigate these effects in the context of large-scale microwave-assisted organic synthesis we have studied the temperature distributions within a microwave-irradiated 2 L cylindrical Pyrex beaker (24 cm × 12 cm) filled with 1 L of solvent. For these experiments a 1000 W MicroSYNTH multimode microwave reactor (Milestone s.r.l.) fitted with both an external IR and internal fiber-optic temperature sensor was employed.[7,19] In addition, the temperature at four different locations within the sample was monitored by a four-channel external fiber-optic probe measurement device (Figure S1, Supporting Information).[20] As shown in Figure S2 in the Supporting Information, the time required for heating even well-absorbing standard organic solvents with a high loss tangent (tan $\delta$)[21] such as ethylene glycol (tan $\delta$ = 1.350), 1-butanol (tan $\delta$ = 0.571), or NMP (tan $\delta$ = 0.275) from ambient conditions to 100 °C using the full 1000 W magnetron power was in the range of 2−4 min. For distilled water (tan $\delta$ = 0.123) the heating ramp to 100 °C was already ∼5 min, and the low-absorbing toluene (tan $\delta$ = 0.040) could not be heated at any significant rate in this multimode reactor. Note that with employing magnetic stirring, no temperature differences between the four fiber-optic probe positions were seen for any of the solvents examined (data not shown).

With repeating the experiments described above without stirring, considerable temperature gradients of up to 60 °C were seen for solvents such as, for example, ethylene glycol (Figure S3, Supporting Information). In general, with the multimode microwave reactor setup shown in Figure S1, Supporting Information, fiber-optic probes located closer to the top surface or edge of the reactor displayed higher temperatures, whereas fibers located near to the bottom or in the center of the 1 L reactor exhibited lower temperatures. These experiments clearly demonstrate the "dilemma" of large-scale batch microwave synthesis: with strongly absorbing reaction mixtures bulk heating at reasonable rates is possible but is mostly a consequence of conventional heat transfer mechanisms from the "skin" of the reactor to the inside due to efficient agitation (not unlike in a conventionally heated reactor). In case of weakly absorbing media the penetration depth is sufficiently high, but heating is inefficient, and often the desired reaction temperatures cannot be reached.

***Table 1.*** **Temperature dependence for the condensation of *o*-phenylenediamine with acetic acid (Scheme 1)[a]**

| temperature (°C) | pressure (bar) | time[b] |
|---|---|---|
| 25 | – | 9 weeks |
| 60 | – | 3 days |
| 100 | – | 5 h |
| 130 | 2 | 1 h |
| 160 | 4 | 10 min |
| 200 | 9 | 3 min |

[a] Reaction conditions: 1 M solution of *o*-phenylenediamine in acetic acid (2 mmol in 2 mL solvent). Conversions determined by GC/MS. See Figure S5 in the Supporting Information for conversion profiles. [b] Reaction times for microwave runs (130−200 °C) refer to total irradiation times, not to hold times at the maximum temperature.

**Batch Microwave Processing.** *Case Study 1: Benzimidazole Synthesis.* As a first model reaction the generation of 2-methylbenzimidazole by condensation of *o*-phenylenediamine with acetic acid was chosen (Scheme 1). Benzimidazoles are an important class of heterocycles, and the scaffold is contained in numerous biologically active substances.[22] Although several synthetic methods for the preparation of benzimidazoles are known, the condensation of *o*-phenylenediamines with carboxylic acids is conceptually one of the most simple and therefore valuable methods.[22] A number of microwave-assisted protocols have already been reported in the literature.[23,24]

Our investigations started with a full kinetic analysis for the benzimidazole condensation process over a wide temperature range. Employing a 1 M solution of *o*-phenylendiamine in acetic acid, the required reaction times in order to achieve full conversion were determined using either conventional heating in sealed glass vials immersed in a silicon carbide microtiter plate (25−100 °C)[25] or by controlled single-mode microwave heating (130−200 °C) in a 400 W Initiator Eight 2.5 EXP platform (Biotage AB).[7] As shown in Table 1, the time required for full conversion in this condensation reaction could be reduced from 9 weeks at room temperature to a mere 3 min at 200 °C. From these kinetic data the pre-exponential factor *A*

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(21) The ability of a specific solvent to convert microwave energy into heat at a given frequency and temperature is determined by the so-called loss tangent (tan $\delta$), expressed as the quotient, tan $\delta = \varepsilon''\varepsilon'$. A reaction medium with a high tan $\delta$ at the standard operating frequency of a microwave synthesis reactor (2.45 GHz) is required for good absorption and, consequently, for efficient heating. Solvents used for microwave synthesis can be classified as high (tan $\delta > 0.5$), medium (tan $\delta$ 0.1−0.5), and low microwave absorbing (tan $\delta < 0.1$). See ref 9 for further details.
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***Table 2.*** **Scale-up efficiencies for the condensation of *o*-phenylenediamine with acetic acid (200 °C/5 min) comparing single- and multimode microwave reactors (Scheme 1)[a]**

| instrument | reaction volume (mL) | yield in g (%) | ramp/hold/cooling[b] time (min) | overall processing time (min) |
|---|---|---|---|---|
| Monowave 300 | 20 | 9.44 (95) | 1/5/6 | 12 |
| Initiator EXP 2.5 | 20 | 9.35 (94) | 2/5/5 | 12 |
| Discover LabMate | 20 | 9.13 (92) | 2/5/6 | 13 |
| Synthos 3000 (XQ 80) | 4 × 10 = 40 | 18.68 (94) | 5/5/17 | 27 |
| Synthos 3000 (HF 100) | 16 × 60 = 960 | 465.7 (98) | 15/5/30 | 50 |

[a] Reaction conditions: 5 M solution of *o*-phenylenediamine in acetic acid. For further information refer to main text and the Experimental Section. See Figure S6, Supporting Information for a graphical representation of heating profiles. [b] Time required for cooling from 200 to 50 °C by compressed air (6 bar, single-mode reactors) or a cooling fan (multimode reactor), respectively.

($3.1 \times 10^8$) and the activation energy ($E_a = 73.43$ kJ/mol) were determined using a classical Arrhenius plot (see Figure S4, Supporting Information). Employing a 850 W Monowave 300 single-mode microwave reactor (Anton Paar GmbH) with a maximum temperature/pressure operational limit of 300 °C/30 bar,[21] the reaction temperature was further increased up to 270 °C (~29 bar internal pressure). At this point the condensation is so fast, that it is difficult to appropriately evaluate the required reaction time for full conversion, as no starting material was detected after a 1 s hold time at 270 °C (ramp time from 25 to 270 °C ~90 s). Importantly, the heterocycle formation stayed remarkably clean even at 270 °C, and no byproducts could be identified by GC/MS, HPLC−UV, or $^1$H NMR analysis of the crude reaction mixture, even on extended exposure at these high temperatures (30 min). Isolated product yields were in the range of 92−99% following a simple extractive purification protocol (see Experimental Section).

In the next phase we evaluated the scale-up potential of the benzimidazole synthesis using batch microwave protocols. Since most sealed-vessel microwave instruments do not allow processing above 20 bar of pressure,[7] a reaction temperature of 200 °C (~10 bar pressure) was selected for all subsequent microwave experiments. In order to increase throughput, the concentration was raised from 1 to 5 M. Even at this rather high concentration level the reaction mixture was still homogeneous and not too viscous for microwave processing using magnetic stirring as agitation method. Fine-tuning of the reaction conditions at this higher concentration led to a slightly extended reaction time of 5 min at 200 °C in order to ensure complete conversion to product. An initial scale-up was performed employing three different single-mode microwave reactors (Monowave 300, Initiator EXP 2.5, Discover LabMate)[7] on a ~20 mL scale (8.1 g of *o*-phenylenediamine in 15 mL of solvent). In the second phase the conditions were transferred to a multimode microwave instrument (Synthos 3000)[16] using both 8- and 16-multivessel rotor systems that allow processing of up to ~1 L of reaction volume. The results in terms of production efficiency and overall processing times are shown in Table 2. In general, each reaction produced the desired benzimidazole product in very high yield and purity as expected from the small-scale experiments. For all transformations a hold time of 5 min at 200 °C was chosen. However, the actual processing times including ramp and cooling times varied significantly due to differences in heating and cooling efficiencies.

As seen from the data presented in Table 2, all three single-mode instruments allowed for a rapid heating of the reaction mixture to the target temperature of 200 °C. Since acetic acid has a reasonably high loss tangent ($\tan \delta = 0.174$),[21] microwave dielectric heating is comparatively efficient for this transformation. In particular the high powered Monowave 300 (850 W magnetron power) and the Initiator 2.5 EXP (400 W) enabled short ramp times in the order of ~1 min. For the Discover LabMate (300 W) a slightly longer heating time was experienced, probably also as a consequence of the larger vessel used in this instrument (80 mL compared to 30 mL for the Monowave and Initiator). Employing the Synthos 3000 multimode reactor (1400 W maximum magnetron power)[16] an initial scale-up experiment was conducted in the 8-vessel rotor (XQ 80), filling four of the 80 mL quartz vessels with 10 mL each of reaction mixture. Finally, a full capacity scale-up experiment was performed in the 16-vessel rotor system (HF 100) filling each of the 16 Teflon vessels close to their maximum suggested filling volume of 60 mL. This resulted in a total processing volume of ~960 mL and provided an overall combined benzimidazole product yield of 465.7 g. Not surprisingly based on our previous scale-up studies with this reactor,[16] the yields obtained from each of the individual 16 vessels were virtually identical (95−99%) and showed no deviations in terms of product purity. However, because of the comparatively large volume and low power density in a multimode microwave reactor, heating nearly 1 L of reaction mixture to 200 °C from room temperature required 15 min. Combined with the comparatively inefficient cooling system (fan cooling) the total processing time for this particular experiment was 50 min, not taking into account the time required to fill, manipulate, close, and open all 16 individual vessels.

*Case Study 2: Pyrazole Synthesis.* As a second model reaction the condensation of acetylacetone with phenylhydrazine in ethanol under acidic conditions was evaluated (Scheme 2). The formed 1-arylpyrazole represents an important pharmacophore present in several drug substances,[27] and microwave-assisted protocols for the general condensation step outlined in Scheme 2 have recently been reported.[24] After optimizing for concentration, molar ratio of starting materials, and amount of HCl additive the best conditions ultimately involved a 3 mol/L phenylhydrazine solution in ethanol, 1.1 equiv of acetylacetone,

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***Table 3.*** **Scale-up efficiencies for the condensation of acetylacetone with phenylhydrazine (180 °C/s) comparing single- and multimode microwave reactors (Scheme 2)[a]**

| instrument | reaction volume (mL) | yield in g (%) | ramp/cooling[b] time (min) | overall processing time (min) |
|---|---|---|---|---|
| Monowave 300 | 20 | 9.40 (91) | 1.5/4.5 | 6 |
| Initiator EXP 2.5 | 20 | 9.29 (90) | <1/3.2 | 4 |
| Synthos 3000 (XQ 80) | 4 × 10 = 40 | 19.34 (94) | 2.5/12.5 | 15 |
| Synthos 3000 (HF 100) | 16 × 60 = 960 | 468 (95)[c] | 13/30 | 43 |

[a] Reaction conditions: 3 M solution of phenylhydrazine in ethanol, 1.1 equiv acetylacetone, 1 mol % HCl. For further information refer to main text and the Experimental Section. See Figure S9, Supporting Information for a graphical representation of heating profiles. [b] Time required for cooling from 180 to 50 °C by compressed air (6 bar, single-mode reactors) or a cooling fan (multimode reactor), respectively. [c] Only 4 out of the 16 vessels were worked up to provide 28.8−29.6 g of product from each individual vessel. The value presented in the table is the calculated total yield from this run.

and 1 mol % HCl as an additive. Performing the condensation more concentrated or neat resulted in lower conversion and a biphasic mixture unsuitable for the planned flow synthesis approach. Full conversion was achieved after 8 h at 25 °C, after 1 h at 60 °C, or after 10 min at 100 °C (Figure S7, Supporting Information). With the aim of reducing the reaction time to a minimum, the cyclocondensation was subsequently performed within a temperature range of 100−180 °C under sealed vessel microwave conditions (Table S1, Supporting Information). Finally, a reaction temperature of 180 °C under microwave conditions[28] was chosen as this can be expected to provide the desired target pyrazole within a few seconds and the heterocycle formation retained a clean purity profile in this temperature regime as evidenced by HPLC−UV, GC/MS and $^1$H NMR monitoring. Indeed, running on an 1 mmol scale in the Initiator 2.5 EXP with a set hold time of 1 s full conversion and a 90% isolated product yield was obtained. The overall processing time including heating and cooling was ∼2 min with a maximum attained internal pressure of ∼17 bar (Figure S8, Supporting Information).

With these data in hand a batch microwave scale-up of the pyrazole synthesis was performed, again executing the reaction first in single-mode microwave reactors using larger process vials (30−80 mL), followed by a scale-up in the Synthos 3000 multimode instrument (Table 3). Since ethanol is a strongly microwave-absorbing solvent (tan $\delta$ = 0.941)[21] microwave dielectric heating was very efficient in both single-mode and multimode instruments. Because of the resulting high internal pressure of close to 18 bar at 180 °C reaction temperature, the pyrazole synthesis was not carried out in the Discover LabMate system as the 80 mL reaction vessel for the Discover should not be used at these high pressures (suggested pressure limit 15 bar).[7] Similar to the benzimidazole synthesis described above the full-scale run using the 16-vessel rotor involving almost 1 L total reaction volume can provide substantial amounts of pyrazole product (468 g) in high yield and purity. It should be stressed, however, that for both the benzimidazole and the pyrazole examples the potential advantage of a 1−5 s reaction time at these high temperatures (process intensification) cannot truly be exploited due to the slow heating and cooling cycles experienced in a large batch experiment.

*Case Study 3: Diels−Alder Cycloaddition.* Diels−Alder 4$\pi$ + 2$\pi$ cycloaddition reactions arguably belong to the most useful synthetic transformations known. These pericyclic processes are employed extensively for the production of polycyclic ring systems, and are also used widely in the field of natural product synthesis.[29] Numerous Diels−Alder processes have been studied under microwave conditions due to the long reaction times and elevated temperatures often required.[1,2] For the current studies we have chosen the cycloaddition between 2,3-dimethylbutadiene and acrylonitrile in toluene to provide the corresponding cyclohexene adduct (Scheme 3). This cycloaddition reaction has been previously studied under microwave conditions[30] but is generally difficult to carry out using dielectric heating since toluene is a poor microwave absorber (tan $\delta$ = 0.040),[21] and both starting materials do not contribute significantly to the overall loss tangent of the reaction mixture. Reaction times of 10 min at 250 °C leading to full conversion have nevertheless been achieved by employing so-called silicon carbide passive heating elements that facilitate heating the reaction mixture under microwave conditions.[30]

In order to obtain the required kinetic information, the conversion of a 2:1 mixture of butadiene to acrylonitrile in toluene (1 mol/L acrylonitrile) was evaluated at different temperatures. This exceedingly slow transformation requires several months to go to completion at room temperature, 20 days at 60 °C, and still 5 days at 100 °C (Figure S10 in the Supporting Information). In agreement with our previous results[30] it was nevertheless possible to achieve near quantitative conversion and ∼85% isolated yield of pure product under sealed vessel microwave conditions at 250 °C (17 bar) within 20 min or at 270 °C (21 bar) within 5 min. It should be emphasized that, when using the Initiator EXP 300 W model in 2006, it was not possible to heat the same reaction mixture (2 mL) to 250 °C in the absence of heating aids.[30] Only with the more recently introduced Initiator EXP 2.5 (400 W) and selecting the option "low absorbing" can heating to 250 °C be realized, even on a 20 mL scale, albeit requiring a ramp time of 7 min. Similarly, microwave heating to 270 °C was possible in the Monowave 300 (850 W) within 5 min (Figure S11, Supporting Information). The most efficient heating could be obtained, however, utilizing a custom-made reaction vessel made out of silicon carbide.[26] In this case heat transfer to the reaction mixture almost exclusively occurs via classical conduction phenomena from the strongly microwave-absorbing and highly conductive silicon carbide ceramic, which also requires only a fraction of microwave power compared to using a standard Pyrex reaction vessel (see Figure S12, Supporting Information).[26]

(28) Glasnov, T. N.; Groschner, K.; Kappe, C. O. *ChemMedChem* **2009**, *4*, 1816–1818, and refs cited therein.

(29) (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (b) Pindur, U.; Lutz, G.; Otto, G. *Chem. Rev.* **1993**, *93*, 741–761.

(30) Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2006**, *71*, 4651–4658.

On a 1 mol/L concentration level, scale-up from 2 to 20 mL volume was only possible in the Monowave 300 and Initiator EXP 2.5 single-mode reactors (Figure S13, Supporting Information). Applying the full 300 W power of the Discover microwave reactor, a maximum temperature of ~140 °C was reached after 15 min, in line with previous observations that low-absorbing solvents such as toluene are not easily heated on a larger scale using this single-mode instrument.[31] Similarly, heating of the Diels−Alder toluene reaction mixture in the Synthos 3000 (4 × 10 mL volume, XQ 80 rotor) proved more or less ineffective with a temperature ~115 °C being reached after 7 min of microwave irradiation with 1400 W magnetron power. A full scale-up in the 16 vessel rotor was therefore not attempted. This example clearly highlights the limitations of microwave batch scale-up for low absorbing reaction mixtures.

**Continuous Flow Processing.** The microreactor system used for flow synthesis in this work was a high-temperature, high-pressure microtubular flow unit that can be used for processing homogeneous reaction mixtures (X-Cube Flash, Thales Nanotechnology Inc.).[32,33] This reactor uses stainless steel coils (i.d. 1000 $\mu$m) of variable length (4, 8, and 16 mL volume) that can be directly heated across their full length by electric resistance heating to temperatures up to 350 °C. The reaction mixture is introduced to the reactor block containing the steel coils and a heat exchanger via one or more standard HPLC pumps (flow rate: 0.01−10.0 mL/min). The system pressure valve sets and stabilizes the set pressure value between a pressure range of 50−180 bar.[32]

The adaptation of all three microwave protocols discussed above (Schemes 1−3) to a flow regime in the X-Cube Flash reactor was investigated.[33] As heating in this instrument is performed by conventional heat transfer, the dielectric properties of the reaction medium become irrelevant. Before moving to a flow format we ensured that the dramatic rate enhancements seen for all three reactions (Schemes 1−3) on going from room temperature to 180−270 °C were in fact only due to a thermal effect and not to a direct involvement of the electromagnetic field, and therefore could be mimicked in a conventionally heated flow system. For this purpose all three transformations were repeated in the Monowave 300 reactor employing a reaction vessel made out of strongly microwave-absorbing silicon carbide. This technology allows separation of thermal from electromagnetic field effects.[26] As expected, the results using genuine microwave dielectric heating and heating by conduction in the silicon carbide vessel were identical.

*Case Study 1: Benzimidazole Synthesis.* Since the temperature and pressure limits of the flow reactor (350 °C/180 bar) are significantly higher than those attainable in standard microwave reactors, we have chosen a reaction temperature of 270 °C (130 bar set pressure) for the benzimidazole synthesis (Scheme 1). Based on the successful microwave experiment in the Monowave 300 at 270 °C described above and a calculation of the rate constants using the Arrhenius equation, a reaction time (= residence time) of 1 s at this temperature should suffice in order to provide full conversion for benzimidazole formation (Table 4).

***Table 4.*** **Calculated reaction temperature for different conversion levels at 1 s reaction time in the benzimidazole formation (Scheme 1, Figure S4, Supporting Information)[a]**

| conversion (%) | rate constant $k$ ($s^{-1}$) | temperature (°C) |
|---|---|---|
| 90 | 2.30 | 198.7 |
| 99 | 4.61 | 216.8 |
| 99.9 | 6.91 | 228.1 |
| 99.99 | 9.21 | 236.4 |
| 99.999 | 11.51 | 243.1 |
| 99.9999 | 13.82 | 248.6 |
| 99.99999 | 16.12 | 253.4 |

[a] Based on the following Arrhenius parameters: $A = 3.1 \times 10^8$, $E_a = 73.43$ kJ/mol.

Employing the X-Cube Flash flow system we initially attempted to process a 5 M stock solution of *o*-phenylenediamine in acetic acid through the stainless steel coil applying a single HPLC pump. Unfortunately, the viscosity of the reaction mixture proved to be too high for pumping by the standard HPLC pumps/valves integrated into the X-Cube Flash reactor. Therefore, the concentration of the reaction mixture was reduced to 1 M which allowed successful processing through the flow instrument without problems. Since the calculated reaction time at 270 °C is less than 1 s, a 4 mL reaction coil and a flow rate of 8.0 mL/min were chosen. This combination results in a residence time of 30 s in the stainless steel coil which should prove sufficient to allow complete conversion.[32] Indeed full conversion and a high isolated product yield (50.7 g, 94%) was obtained, processing ~400 mL of reaction mixture (0.40 mol *o*-phenylenediamine) through the flow system for one hour. Attempts to use higher flow rates (>10 mL/min) or to increase the concentration to 3 mol/L were unsuccessful, leading to a pumping failure and to an abortion of the experiment. Although the obtained amount of benzimidazole within 1 h is significantly smaller compared to that with the microwave batch experiment described in Table 2 (in part as a consequence of the less concentrated reaction mixture), in general the easy scalability of continuous flow processes makes this an attractive alternative compared to batch methods (see Table 5).[12,13,17]

*Case Study 2: Pyrazole Synthesis.* For the pyrazole synthesis, the same concentration as in the batch experiments could be used for flow processing without any pumping/viscosity problems (3 M), therefore allowing a direct comparison between the two methods. The optimized batch conditions (180 °C, 1 s hold time) were directly translated into a suitable flow regime. Similar to the benzimidazole case, the continuous flow process (180 °C/130 bar set pressure) was run using the 4 mL coil with a flow rate of the reaction mixture through the reactor of 8.0 mL/min. This corresponds to a residence of time of 30 s which is significantly more than required for full conversion based on the batch microwave experiments. Not surprisingly, complete conversion and high isolated yields were achieved (97%). As an alternative to processing the reaction mixture containing both components and HCl as a catalyst, a similar experiment was performed where the substrates were introduced into the flow

(31) Loones, K. T. J.; Maes, B. U.; Rombouts, G.; Hostyn, S.; Diels, G. *Tetrahedron* **2005**, *61*, 10338–10348.
(32) For a detailed description of this instrument, see: Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *Chem. Eng. Technol.* **2009**, *32*, 1702–1716.
(33) For recent examples of transforming microwave batch to high-temperature continuous flow processing using this instrument, see: (a) Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, *9*, 1321–1325. (b) Glasnov, T. N.; Findening, S.; Kappe, C. O. *Chem.—Eur. J.* **2009**, *15*, 1001–1010.

***Table 5.*** **Comparison of multimode microwave batch and continuous flow scale-up efficiencies for three model reactions (Schemes 1−3)[a]**

| | benzimidazole synthesis (Scheme *1*) | pyrazole synthesis (Scheme *2*) | Diels−Alder reaction (Scheme *3*) |
|---|---|---|---|
| Microwave Batch | | | |
| temperature (°C) | 200 | 180 | − |
| reaction time (min) | 5 | 0.017 (1 s) | − |
| processing time (min) | 50 | 43 | − |
| concentration (mol/L) | 5 | 3 | − |
| reaction volume (mL) | 960 | 960 | − |
| yield (g) | 465.7 | 468 | − |
| space-time yield (kg/m$^3$s)[b] | 0.16 | 0.19 | − |
| Continuous Flow | | | |
| temperature (°C) | 270 | 180 | 280 |
| residence time (min) | 0.5 | 0.5 | 2 |
| flow rate (mL/min) | 8 | 8 | 8 |
| concentration (mol/L) | 1 | 3 | 2.2 |
| reactor volume (mL) | 4 | 4 | 16 |
| yield/hour (g) | 50.7 | 225.8 | 80.4 |
| space-time yield (kg/m$^3$s)[c] | 3.52 | 15.7 | 1.4 |

[a] Microwave batch experiments were performed in a Synthos 3000 multimode instrument using a 16-vessel rotor system (HF 100). Flow experiments were performed in a X-Cube Flash microreactor setup. Further details are presented in Tables2 and3, and in the Experimental Section. [b] Based on a reaction volume of 960 mL for the Synthos 3000 reactor. The maximum suggested filling volume is 1 L. [c] Based on a reactor coil volume of 4 or 16 mL, respectively. The total dead volume of the instrument from inlet to receiver is 4 mL higher.

system separately via the two available HPLC pumps. In this case a 6.6 M stock solution of acetylacetone in ethanol and a 6 M ethanolic solution of phenylhydrazine containing 1 mol % HCl were introduced via two pumps into a T mixer on the X-Cube Flash platform before the reaction mixture was fed into the heated reactor coil. In this case the two HPLC pumps were operated with a flow rate of 4 mL/min each (total flow rate of 8 mL/min). These conditions led to essentially the same results as with using the premixed solution and provided a 95% yield pyrazole product.

After operating the flow reactor for one hour, a reaction volume of ∼450 mL could be processed, leading to an isolated pyrazole yield of 225.8 g (1.31 mol, 97%). This value compares well with the results obtained in the microwave batch experiments displayed in Table 3, in particular if one considers that the results in the flow experiments were derived from a single reactor coil of 4 mL volume (as compared to a ∼1 L volume in the batch run). The difference in space-time yields as indicated in Table 5 is therefore substantial, clearly favoring the continuous flow process. Again, the use of higher flow rates was not possible for technical reasons.

*Case Study 3: Diels−Alder Cycloaddition.* The Diels−Alder process shown in Scheme 3 was previously investigated in our laboratories using continuous flow processing in the X-Cube Flash reactor, albeit not with an intention to study the scale-up potential of this process under flow conditions.[33a] In contrast to the two other transformations studied herein, this cycloaddition reaction is exceedingly slow with a reaction time in the order of minutes rather than seconds even at temperatures as high as 270 °C. The previously chosen conditions for flow processing (250 °C, 0.8 mL flow rate, 4 mL coil, 2 M concentration)[33a] therefore needed to be modified in order to increase the throughout. Raising the reaction temperature to 280 °C (130 bar set pressure) and changing to a 16 mL stainless steel coil allowed a significant increase in the flow rate to 8.0 mL/min. The resulting residence time of ∼2 min in the heated coil was sufficient to lead to full conversion in this cycloaddition at 280 °C in agreement with the batch microwave results described above. Finally, the concentration was increased from 1 M to ∼2.2 M which led to a throughput of 80.4 g/h of pure isolated product (82% yield). For this Diels−Alder cycloaddition in toluene it was technically feasible to raise the concentration of starting materials to 5 M, keeping a flow rate of 8.0 mL/min, without experiencing any pumping difficulties. However, under these conditions a significant increase in the measured coil temperature to ∼50 °C above the present value of 280 °C was observed. We ascribe this phenomenon to the exothermicity of the Diels−Alder process which under high concentration leads to a significant amount of heat that is difficult to control, even in a stainless steel microreactor of this type.[32] For the ∼2.2 M run, the thermal overshoot measured on the coil was only 3−4 °C. Since for the Diels−Alder process using toluene as solvent a microwave batch scale-up is not feasible because of the low microwave absorptivity of the reaction mixture, the throughput obtained in the flow platform presents a significant improvement over existing procedures.

Table 5 presents a comparison of the microwave scale-up experiments performed in the multimode Synthos 3000 batch reactor with the flow experiments in the X-Cube Flash microreactor. While for the Diels−Alder reaction a scale-up under microwave conditions is not possible at all, it can be seen that for the other two processes the batch microwave approach—for a single batch run—provides more product quantity than the flow experiment in the same time frame of ∼1 h. However, considering the scale-up potential beyond a few 100 g of material to production scale and the fact that the current microwave batch approach has probably reached its limits with ∼1 L reactor volume, it can be easily seen that, given the significantly higher space-time yields[35] resulting from the microreactor process, the continuous flow approach will probably be the method of choice for further scale-up, applying numbering-up or similar strategies.[17]

## Concluding Remarks

In summary, we have performed a comparison of the scale-up efficiencies of three selected synthetic transformations, employing either microwave batch or conventionally heated continuous flow processing. It has been shown that microwave-assisted protocols on scale require a reasonably strongly microwave absorbing reaction medium (tan $\delta$) in order to allow efficient heating by dielectric mechanisms. In case the absorptivity of the solvent/reaction mixture is too low (as for the Diels−Alder cycloaddition shown in Scheme 3), microwave processing on scale becomes difficult if not impossible. On the other hand, if a large volume (>1 L) of a strongly microwave absorbing reaction mixture is heated by microwave irradiation, temperature gradients due to penetration depth issues will result, and therefore efficient stirring is required in order to minimize these differences in temperature. Thus, in our opinion, microwave batch scale-up experiments of this type more closely resemble the situation of a conventionally heated batch reactor, since several key benefits of small scale microwave chemistry that rely on efficient and rapid "in core" volumetric heating of

the reaction mixture are in fact lost.[34] It appears that the recent popularity of these reactors is more related to the convenience of having a benchtop autoclave system available that allows to work with superheated solvents under carefully controlled temperature/pressure conditions, rather than being connected to any scientific rationale related to the use of microwave dielectric heating. Another important aspect when considering the use of microwave technology on larger scale relates to the energy consumption of the utilized reactor system.[36] In the present work no energy comparison between microwave batch and conventionally heated flow reactors have been made, but this issue clearly also needs to be addressed in the future.[36]

Conventionally heated microreactors do not rely on dielectric heating, and therefore the dielectric properties (tan $\delta$) of the reaction mixtures are irrelevant. Importantly, because of the high surface-to-volume ratio of a typical microreactor, rapid heat transfer to and from the reaction mixture can be attained (heat exchange), therefore more closely mimicking the situation of a small scale microwave experiment. In addition, compared to a standard microwave batch reactor, higher temperatures and pressures can be attained utilizing an appropriate microreactor (see above), therefore allowing a significant further process intensification. In all three examples discussed herein, conventional processing at the reflux temperature of the solvent required estimated reaction times of ~30 min (80 °C, pyrazole synthesis in ethanol), 2 h (120 °C, benzimidazole synthesis in acetic acid), and 2−3 days (110 °C, Diels−Alder reaction in toluene). Using sealed vessel microwave heating on a small scale (2 mL) at up to 270 °C these reaction times could be reduced to a few seconds or minutes (in the case of the Diels−Alder reaction). However, in translating small-scale microwave heating to a larger-scale batch process the advantages of reaction times in the order of a few seconds or minutes were lost since the heating and cooling profiles on a ~1 L scale were vastly different compared to small-scale runs, requiring overall processing times close to 1 h. In contrast, in the stainless steel microcapillary reactor described herein, processing of up to 350 °C with a set pressure of 180 bar can be performed. In this way, the short reaction times derived from the small-scale microwave experiments could be translated to residence times in a continuous flow process. By increasing the flow rate, the residence times can be adjusted to the reaction times obtained from kinetic studies as shown for the benzimidazole synthesis. Although the continuous flow reaction system used in this study is not designed for performing at high flow rates for production-scale purposes, the space-time yields obtained with this benchtop instrument were significantly higher (up to a factor of 80) than those resulting from the batch experiments. It is therefore clear that high-temperature/-pressure flow processing has a significant potential for the manufacturing industry. At the same time it needs to be emphasized that not all chemical transformations can be executed at these extreme conditions and that the issue of heterogeneous reaction mixtures still remains a major obstacle for continuous flow processing.

## Experimental Section

**General Methods.** All chemicals were purchased from commercial sources and were used without further purification. Analytical HPLC analysis (Shimadzu LC 20 AD) was carried out on a C 18 reversed-phase analytical column (150 mm × 4.6 mm, particle size 5 $\mu$m) using mobile phases A (water/acetonitrile, 90:10 (v/v) + 0.1% TFA) and B (acetonitrile + 0.1% TFA) at a flow rate of 1 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 9 min, hold at 100% solution B for 1 min. GC/MS (FOCUS-GC/DSQ II MS, ThermoFisher) monitoring was based on electron impact ionization (70 eV) using a HP/5MS column (30 m × 0.250 mm × 0.025 $\mu$m). After 1 min at 50 °C the temperature was increased in 25 °C/min steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium and the flow rate 1.0 mL/min in constant flow mode. The identity of the peaks in the chromatograms was confirmed by computerized comparison with the NIST library.

**Microwave and Continuous Flow Equipment.** Reaction optimization on small scale was performed either in an Initiator 2.5 EXP (Biotage AB), a Monowave 300 (Anton Paar GmbH, or a Discover LabMate (CEM Corp.) in Pyrex microwave process vials using standard procedures.[7] Alternatively, optimization was performed in a silicon carbide microtiter platform in combination with a standard hot plate employing GC/HPLC vials.[25] For the batch scale-up experiments the reactions were performed in the largest available reaction vessels for the above-mentioned single-mode reactors (30−80 mL) on a 20 mL scale.[7] For the multimode microwave irradiation experiments a Synthos 3000 (Anton Paar GmbH) was used, employing 8-vessel (XQ 80) and 16-vessel rotor systems (HF 100) as previously reported.[16] For the measurement of temperature gradients in a batch microwave reactor a MicroSYNTH multimode platform (Milestone s.r.l.)[19] in conjunction with a four-channel fiber-optic temperature probe system (OpSens) was utilized.[20] Microwave chemistry using silicon carbide (SiC) reaction vials was performed using internal fiber-optic temperature control in a Monowave 300 microwave reactor as previously reported.[26] All flow chemistry described herein was performed in an X-Cube Flash stainless steel microreactor (ThalesNano Inc.) according to the general principles as previously described.[32,33]

**Temperature Gradient Measurements (MicroSYNTH).** To investigate the temperature gradients in a batch microwave heating experiment, five high-boiling solvents with different microwave absorption characteristics were heated in a 2 L cylindrical Pyrex beaker (24 cm × 12 cm) in 1 L quantity. The beaker was equipped with four fiber-optic probes to measure the temperature inside the solvent accurately and locate any temperature gradients (Figure S1, Supporting Information). The internal temperature was monitored by a multichannel signal conditioner (TempSens signal conditioner, Opsens).[20] Up to four OTG-F fiber-optic temperature sensors can be used for

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(35) For space-time yield calculations in microreactors, see: (a) Kestenbaum, H.; de Oliviera, A. L.; Schmidt, W.; Schüth, F.; Erhfeld, W.; Gebauer, K.; Löwe, H.; Richter, T.; Lebiedz, D.; Untiedt, I.; Züchner, H. *Ind. Eng. Chem. Res.* **2002**, *41*, 710–719. (b) Löb, P.; Löwe, H.; Hessel, V. *J. Fluorine Chem.* **2004**, *125*, 1677–1694. (c) Jähnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, V.; Löwe, H.; Wille, C.; Guber, A. *J. Fluorine Chem.* **2000**, *105*, 117–128. See also ref 17b for a more comprehensive discussion.
(36) For a controversial discussion on the energy efficiency of microwave batch reactors, see: (a) Komorowska, M.; Stefanidis, G. D.; Gerven, T.; Stankiewicz, A. I. *Chem. Eng. J.* **2009**, *155*, 859−866. (b) Moseley, J. D.; Woodman, E. K. *Energy Fuels* **2009**, *23*, 5438−5446.

simultaneous accurate temperature measurement (sample rate: 2.8 s when 4 probes are used simultaneously). One liter of ethylene glycol, distilled water, butanol, toluene, and *N*-methyl-2-pyrrolidone (NMP) were irradiated either with constant power (1000 W) with magnetic stirring (Figure S2, Supporting Information) or in a temperature-controlled run where the temperature was controlled by the fiber optic provided by the MicroSYNTH (Figure S3, Supporting Information).

**Synthesis of 2-Methylbenzimidazole (Scheme 1).** *Batch Microwave Conditions. (a) Single-Mode Conditions.* A 10 mL Pyrex vessel was equipped with *o*-phenylenediamine [2 mmol (216 mg)], 2 mL of AcOH (~1 mol/L), and a stir bar. Microwave heating was performed at 200 °C for 5 min hold time in a Monowave 300 reactor. After cooling, the excess of AcOH was evaporated under reduced pressure, and the generated 2-methylbenzimidazole was precipitated by adding a saturated aqueous potassium carbonate solution, followed by extraction (three times) with ethyl acetate. The combined organic phases were dried over sodium sulfate, filtered, and evaporated under reduced pressure to provide 253 mg (96%) of pure 2-methylbenzimidazole, mp 179−180 °C (lit.[23a] mp 177−180 °C). In addition, an analogous experiment was performed using a 10 mL reaction vial made out of a SiC vessel equipped with the same starting mixture and a stir bar. The SiC vessel was heated for 5 min at 200 °C, and the workup was performed as described above, leading to an identical GC/MS purity profile of the crude reaction mixture and isolated yields as in the experiment involving the Pyrex vial.

*(b) Multimode Conditions (Table 2).* The large-scale microwave irradiation experiment was carried out in a Synthos 3000 multimode batch instrument. A dedicated rotor (HF 100) was equipped with 16 100 mL PTFE-TMF vessels (60 mL maximum filling volume), containing stir bars, which were subsequently inserted into ceramic vessel jackets to resist high pressures (40 bar) and temperatures (240 °C). Each vessel was equipped with *o*-phenylenediamine [225 mmol (24.3 g)] and 45 mL of AcOH (5 mol/L) and subsequently capped with special seals and protective PEEK caps. The individual vessels were placed in the corresponding rotor, fixed by screwing down the upper rotor plate, and finally the rotor was closed with a protection hood (for details see reference 16). After heating the vessel for 5 min at 200 °C (Table 2), cooling was accomplished by a fan, and the workup for the individual vessels was performed as described above to provide a combined yield of 465.7 g (98%) of benzimidazole product.

*Continuous Flow Processing.* *o*-Phenylenediamine [0.4 mol (43.2 g)] was dissolved in 400 mL of AcOH (1 mol/L) by using an ultrasonic bath and stirring the reaction mixture for 5 min at 60 °C. A homogeneous solution was obtained in an 1 L Erlenmeyer flask. The X-cube flash instrument was equipped with a stainless steel reaction coil (4 mL volume, 30 s residence time at 8 mL/min flow rate). The reaction parameters—temperature (200 °C), 8 mL/min flow rate, and pressure (130 bar)—were selected on the flow reactor, and processing was started, whereby only pure solvent (AcOH) was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was assured. At that point the inlet tube was switched from the solvent flask to the 1 L reaction flask containing the freshly prepared reaction mixture. After processing through the flow reactor, the inlet tube was dipped back into the flask containing pure AcOH and processed for 10 min further, thus washing from the system any remaining reaction mixture. The excess of AcOH was removed under vacuum, and the product was isolated as described above (50.7 g, 94%).

**Synthesis of 3,5-Dimethyl-1-phenyl-1H-pyrazole (Scheme 2).** *Batch Microwave Conditions. (a) Single-Mode Conditions.* A 10 mL Pyrex vessel was equipped with phenylhydrazine [6 mmol (648 mg, 588 μL)], acetylacetone [6.6 mmol (660 mg, 678 μL)], conc. HCl [1 mol % (5 μL)], 730 μL of EtOH (~3 mol/L, total reaction volume ~2 mL), and a stir bar. The reaction mixture was heated at 180 °C for 1 s. After cooling to ambient conditions, solvent was evaporated under reduced pressure and the crude residue treated with saturated aqueous $K_2CO_3$ solution (~5 mL). The resulting aqueous mixture was extracted three times with ethyl acetate, the combined organic phases dried over sodium sulfate, filtered and evaporated in vacuum to provide 950 mg (92%) of pure pyrazole as a orange-colored oil (HPLC−UV purity at 215 nm >99%, $^1$H NMR purity >98%). In addition, an analogous experiment was performed using a 10 mL reaction vial made out of SiC vessel equipped with the same starting mixture and a stir bar. The SiC vessel was heated for 1 s at 180 °C, and the workup was performed as described above, leading to an identical HPLC−UV purity profile and isolated yields as in the experiment involving the Pyrex vial.

*(b) Multimode Conditions (Table 3).* For microwave batch scale-up in the Synthos 3000, 16 100 mL PTFE-TMF vessels were each equipped with phenylhydrazine [180 mmol (19.4 g, 17.7 mL)], acetylacetone [198 mmol (19.7 g, 20.3 mL)], conc. HCl [1.8 mmol (150 μL, 1 mol %)], 22 mL of EtOH (~3 mol/L), and a stir bar and subsequently capped with special seals and protective PEEK caps. The individual vessels were placed in the corresponding rotor, fixed by screwing down the upper rotor plate, and finally the rotor was closed with a protection hood (for details see reference16). After heating the vessel for 1 s at 180 °C (Table 3) cooling was accomplished by a fan, and the workup for the individual vessels was performed as described above for 4 out of 16 vessels to provide a combined yield of 117 g (94%) of pyrazole product. The calculated overall yield for the complete run was 468 g.

*Continuous Flow Processing.* A 1 L Erlenmeyer flask was equipped with phenylhydrazine [1.35 mol (145.8 g, 133.7 mL)], acetylacetone [1.485 mol (148.5 g, 151.5 mL)], conc. HCl [13.5 mmol (1.1 mL, 1 mol %)], 164 mL of EtOH (~450 mL total volume), and a stir bar. The starting mixture was stirred for ~3 min, while the X-cube flash instrument was equipped with a stainless steel reaction coil (4 mL volume, 30 s residence time at 8 mL/min flow rate). The reaction parameters—temperature (180 °C), 8 mL/min flow rate and pressure (130 bar)—were selected on the flow reactor, and processing was started, whereby only pure solvent (EtOH) was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was assured. At that point the inlet tube was switched from the solvent flask to the 1 L reaction flask containing the freshly prepared reaction mixture. After

processing through the flow reactor, the inlet tube was dipped back into the flask containing pure AcOH and processed for 10 min further, thus washing from the system any remaining reaction mixture. The excess of EtOH was removed under vacuum, and the product was isolated as described above (225.8 g, 97%).

**Synthesis of 3,4-Dimethylcyclohex-3-enecarbonitrile (Scheme 3).** *Batch Microwave Conditions.* Single-mode conditions: A 10 mL Pyrex vessel was equipped with a stir bar, acrylonitrile [2 mmol (106.4 mg, 133 $\mu$L)], 2,3-dimethylbutadiene [4 mmol (328.2 mg, 452 $\mu$L)], and 2 mL of toluene (1 mol/L). Microwave heating was performed at 270 °C for 5 min hold time in a Monowave 300 reactor. After cooling the product was obtained by evaporating toluene and excess of 2,3-dimethylbutadiene under reduced pressure to provide 221 mg (82%) of Diels−Alder product (HPLC−UV purity at 215 nm 97%, $^1$H NMR purity >95%).[30] In addition, an analogous experiment was performed using a 10 mL reaction vial made out of SiC vessel equipped with the same starting mixture and a stir bar. The SiC vessel was heated for 5 min at 270 °C, and the workup was performed as described above, leading to an identical HPLC−UV purity profile and isolated product yield as in the experiment involving the Pyrex vial.

*Continuous Flow Processing.* Acrylonitrile [0.72 mol (38.2 g, 47.7 mL)], 2,3-dimethylbutadiene [1.44 mol (118 g, 162.6 mL)], and 120 mL of toluene (330 mL total volume, ∼2.2 mol/L) were stirred for ∼3 min in a 500 mL Erlenmeyer flask. At the same time the X-cube flash instrument was equipped with a stainless steel reaction coil (16 mL volume, 2 min residence time at 8 mL/min flow rate). The reaction parameters—temperature (280 °C), 8 mL/min flow rate and pressure (130 bar)—were selected on the flow reactor, and processing was started, whereby only pure solvent (toluene) was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was assured. At that point the inlet tube was switched from the solvent flask to the 1 L reaction flask containing the freshly prepared reaction mixture. After processing through the flow reactor, the inlet tube was dipped back into the flask containing pure toluene and processed for further 10 min, thus washing from the system any remaining reaction mixture. The excess of toluene was removed under vacuum, and the product was isolated as described above (80.4 g, 82%).


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**Note Added after ASAP:** In the version published on December 4, 2009, there was a production error in Scheme 3. That error has been corrected in the version published December 16, 2009.

## Supporting Information Available

Kinetic studies of the performed reactions, temperature/power profiles, and images of equipment used in this study. This material is available free of charge via the Internet at http://pubs.acs.org.


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