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Scalability of Microwave-Assisted Organic Synthesis. From Single-Mode to Multimode Parallel Batch Reactors

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Abstract:

The direct scalability of microwave-assisted organic synthesis (MAOS) in a prototype laboratory-scale multimode microwave batch reactor is investigated. Several different organic reactions have been scaled-up typically from 1 mmol to 100 mmol scale. The transformations include multicomponent chemistries (Biginelli dihydropyrimidine and Kindler thioamide synthesis), transition metal-catalyzed carbon−carbon cross-coupling protocols (Heck and Negishi reactions), solid-phase organic synthesis, and Diels−Alder cycloaddition reactions using gaseous reagents in prepressurized reaction vessels. A range of different solvents (high and low microwave absorbing), Pd catalysts (homogeneous and heterogeneous), and varying reaction times and temperatures have been explored in these investigations. In all cases, it was possible to achieve similar isolated product yields on going from a small scale (ca. 5 mL processing volume) to a larger scale (max 500 mL volume) without changing the previously optimized reaction conditions (direct scalability). The prototype, benchtop multimode microwave reactor used in the present study allows parallel processing in either quartz or PTFE-TFM vessels with maximum operating limits of 300 °C and 80 bar of pressure. The system features magnetic stirring in all vessels, complete on-line monitoring of temperature, pressure and microwave power, and the ability to maintain inert or reactive gas atmosphere.

Introduction

High-speed microwave synthesis has attracted a considerable amount of attention in recent years.[1] Since the first reports on the use of microwave heating to accelerate organic chemical transformations by the groups of Gedye and Giguerre/Majetich in 1986,[2,3] more than 2000 articles have been published in the area of microwave-assisted organic synthesis (MAOS).[4] The initial slow uptake of the technology has been attributed to its lack of controllability and reproducibility, coupled to a general lack of understanding of the basics of microwave dielectric heating. However, since the late 1990s, the number of publications related to MAOS has increased dramatically to a point where it might be assumed that, in a few years, most chemists will probably use microwave energy to heat and drive chemical reactions. In fact, it appears that rapid microwave protocols can be developed for most chemical transformations requiring heat. A large number of review articles and several books provide extensive coverage of the subject.[4−6] Apart from traditional organic synthesis, more recent applications of microwaves in this area include combinatorial chemistry (solid- and fluorous-phase synthesis, parallel processing, use of polymer-supported reagents),[7] biochemical processes such as high-speed polymerase chain reaction (PCR)[8] and rapid enzyme-mediated protein mapping,[9] electrochemistry,[10] photochemistry,[11] and simultaneous ultrasound/microwave processing.[12]

Processing techniques employed in microwave chemistry involve solventless (dry-media) procedures where the reagents are adsorbed onto either a microwave transparent (i.e., silica, alumina or clay) or strongly absorbing (i.e., graphite) inorganic support, which additionally can be doped with a catalyst or reagent.[13] Alternatively, microwave-assisted synthesis can be carried out using phase-transfer catalysis (PTC),[14] under heterogeneous catalytic gas-phase conditions[15] or, most commonly, in solvents. Using the latter technique, standard organic solvents, high-temperature (near critical)

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water,[16] or ionic liquids[17] have been employed as reaction media in open[18] or closed vessel systems.[19]

Regardless of the specific chemistry or processing technique, the main benefits of performing reactions under microwave conditions are the significant rate enhancements and the higher product yields that can frequently be observed. While different hypotheses have been proposed to account for the observed rate enhancements under microwave irradiation, a generally accepted rationalization remains elusive.[20] Regardless of the origin/existence of a special microwave effect, microwave-enhanced chemistry can be extremely efficient and is applicable to a broad range of practical synthesis.

Although most of the early pioneering experiments in microwave-enhanced organic synthesis have been carried out in unmodified domestic microwave ovens, the current trend clearly is to use dedicated instruments for chemical synthesis, in particular for processes involving organic solvents. Beginning in the late 1980s, dedicated multimode[21] and monomode[22] microwave reactors for organic synthesis were designed and later became commercially available. Most recently, the focus in the published literature from both academic and industrial laboratories has shifted toward the use of small commercially available monomode (also called single-mode) microwave applicators, that typically allow the safe processing of up to 10 mL of reaction volume in a single reaction vessel with a pressure limit of ca. 20 bar.[23,24] These reactors feature built-in magnetic stirrers, direct temperature control of the reaction mixture aided by fiber-optic probes or IR sensors, and software that enables on-line temperature/pressure control by regulation of microwave power output. Such applicators have been proven suitable and reliable for the safe and controlled microwave synthesis of gram-scale quantities of materials using organic solvents.

While the above-mentioned techniques are very successful for small-scale organic synthesis, in particular for the rapid optimization of reaction conditions and in the context of the drug discovery process, there is a clear need to develop larger-scale MAOS techniques, which can ultimately provide products on a kilogram scale.[25] With some of the physical limitations of microwave heating technology (magnetron power, penetration depth) under consideration,[5,26] two different approaches for microwave synthesis on a larger scale (>100 mL volume) have emerged. While some groups have employed larger batch-type multimode[21] or monomode reactors,[27] others have used continuous flow techniques (multi- and monomode)[28] to overcome the inherent problems associated with MAOS scale-up. In general, one should note that published examples of MAOS scale-up experiments are rare, in particular those involving complex organic reactions.

An important issue for the process chemist is the potential of direct scalability of microwave reactions, allowing rapid translation of previously optimized small-scale conditions to a larger scale. Keeping these issues in mind, we herewith report our findings on the microwave scalability of a range of organic transformations typically from a less than 1 g to 100 g scale employing a dedicated multimode batch reactor.

Results

General Considerations. One of the main limitations of microwave scale-up technology is the restricted penetration depth of microwave irradiation into absorbing materials, that is, solvents or reaction mixtures. At the typical operating frequency of most microwave reactors of 2.45 GHz, the penetration depth is generally in the order of a few centimeters, depending on the dielectric properties of the medium.[5,26] This means that 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 are heated by convection and not by direct "in core" microwave dielectric heating.[29] This physical limitation is one of the main reasons for the development of continuous flow reactors,[28] where the reaction mixture is passed through a relatively small microwave heated flow cell, avoiding penetration depth problems. On the other hand, continuous flow reactors with pumping systems may not be appropriate for processing solids, highly viscous liquids, or heterogeneous reaction mixtures.

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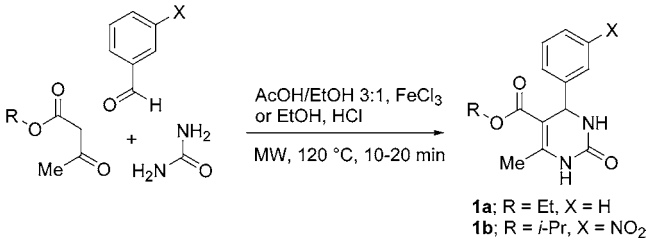
Scheme 1



Having these issues in mind, we here report on MAOS scale-up experiments involving up to 500 mL of reaction volume in a dedicated multimode cavity, employing an eight-position rotor system. This parallel batch processing technique not only circumvents the issue of penetration depth but also allows for genuine parallel synthesis, that is, performing different chemical reactions simultaneously in one irradiation experiment. The reaction vessels (ca. 60 mL filling volume each) used in the current studies are made of either PTFE-TFM or quartz glass and are dedicated for reactions at high pressures and temperatures (80 bar, 300 °C). The 1400 W multimode microwave reactor is equipped with magnetic stirring, on-line temperature and pressure control, and various safety features. The technical details of this prototype reactor are presented in the Experimental Section.

Case Studies. To test the general suitability of this reactor platform to perform larger-scale microwave-assisted reactions, and specifically to investigate the potential for direct scalability of previously optimized small-scale microwave protocols, a variety of organic reactions have been covered in these proof-of-principles studies. These include multicomponent chemistries (Biginelli and Kindler reactions), transition metal-catalyzed carbon−carbon cross-coupling protocols (Heck and Negishi reactions), solid-phase organic synthesis, and Diels−Alder cycloaddition reactions using gaseous reagents in prepressurized reaction vessels. A range of solvents (strongly and poorly microwave absorbing), catalysts (homogeneous and heterogeneous), and varying reaction times and temperatures have been studied to rationalize general conclusive trends from these experiments.

A. Biginelli Dihydropyrimidine Synthesis. Multicomponent reactions (MCRs) in general are of increasing importance in organic and medicinal chemistry. In times where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses. The Biginelli protocol (Scheme 1) is particularly attractive, since the resulting dihydropyrimidine (DHPM) scaffold displays a wide range of biological activities which has led to the development of a number of lead compounds based on that structural core.[30] In general, the standard procedure for the Biginelli condensation involves one-pot condensation of the three building blocks in a solvent such as ethanol using a strongly acidic catalyst, that is, hydrochloric acid.[30] One major drawback of this procedure, apart from the long reaction times involving reflux temperatures, are the moderate yields frequently observed when using more complex building blocks. We have recently described a high yielding and rapid microwave-assisted protocol that allows the synthesis of gram quantities of DHPMs utilizing controlled single-mode microwave irradiation.[31]

As the first model reaction for our scale-up experiments, we selected the standard Biginelli cyclocondensation,[30] where in a one-pot process equimolar amounts of benzaldehyde, ethyl acetoacetate, and urea react under Lewis acid ($FeCl_3$) catalysis to the corresponding dihydropyrimidine **1a** (Scheme 1). Utilizing single-mode microwave irradiation, the reaction can be carried out on a 4.0 mmol scale in AcOH/EtOH 3:1 at 120 °C within 10 min, compared to 3−4 h using conventional thermal heating, providing DHPM **1a** in 88% isolated yield and high purity (>98%) (Figure 1).[31]

Adapting this chemistry to scale-up in the multimode reactor, we filled four vessels of the eight-position rotor with 80 mmol of reagents each (0.32 mol in total), solvents, and the catalyst in identical concentrations as in the small-scale experiment. Microwave heating was performed under the same conditions as in the small-scale run (120 °C for 10 min) providing the desired DHPM **1a** in a slightly lower, but still comparable overall isolated yield (73%). Importantly, the product yields in the individual four vessels of the eight-position rotor were virtually identical (70−74%), demonstrating the good homogeneity of the microwave field in the cavity.[32] In contrast to the small-scale experiments a heating ramp was programmed for the large-scale run (3 min to 120 °C) to have better control and reproducibility over the heating profile.

To demonstrate the full range of scalability possible in the eight-position rotor, another Biginelli condensation was performed using different building blocks employing two, four, or eight vessels of the rotor leading to a maximum scale of 8 × 80 mmol in one single run (0.64 mol, ca. 400 mL of total reaction volume). As a model reaction, we chose the synthesis of DHPM **1b** (Scheme 1), an important intermediate in the preparation of the orally active antihypertensive agent SQ 32926.[33] For this particular Biginelli condensation, a 20 min reaction time at 120 °C using HCl as a catalyst in EtOH provided the best yield (52%) that could be obtained in the small-scale optimization experiments (data not shown). Similar to the first example, the results of the small-scale run performed in the monomode cavity were comparable to the scale-up runs in the multimode instrument using the same set of conditions (in addition to a 3 min linear heating ramp to 120 °C). There was no significant difference between the isolated total yields of experiments carried out in two, four, or eight vessels (43%, 46%, and 48%, respectively of combined overall yields; for details, see the Experimental Section). The magnetron power of the reactor (1400 W) is sufficient to allow the linear heating from room temperature

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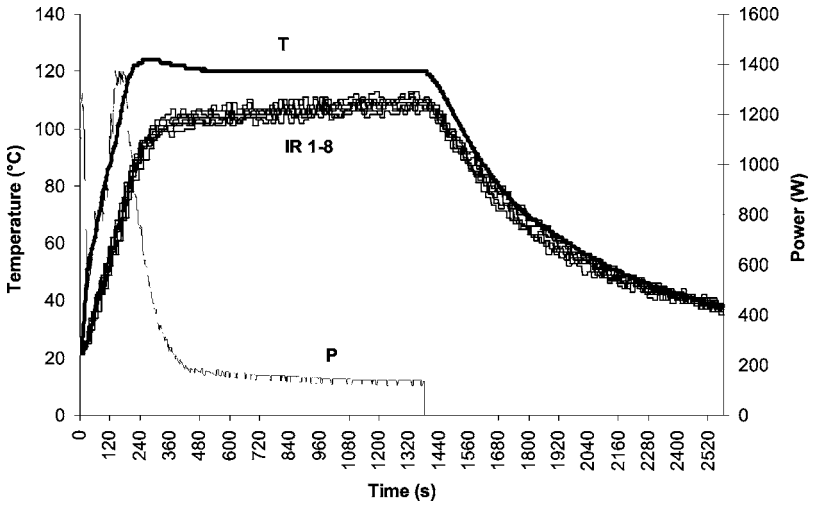
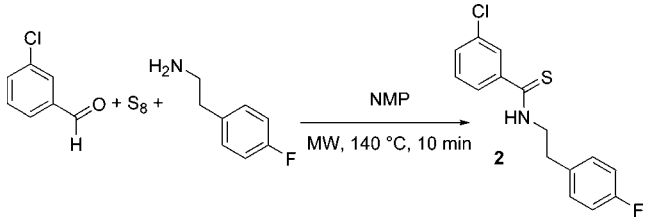


Figure 1. **Temperature and power profiles for a typical Biginelli condensation (1b, Scheme 1) in AcOH/EtOH (3:1) under sealed quartz vessel/microwave irradiation conditions. Linear heating ramp to 120 °C (3 min), temperature control using the feedback from the reference vessel temperature measurement (constant 120 °C, 20 min), and forced air cooling (20 min). The reaction was performed in eight quartz vessels, each containing 40 mL of reaction volume. Shown is the temperature measurement in one reference vessel via internal gas balloon thermometer (T), the surface temperatures monitoring of the eight individual vessels by IR thermography (IR 1−8), and the magnetron power (P, 0−1400 W). Note that the power of the magnetron suffices to follow a linear heating ramp from 20 to 120 °C in 3 min. After the maximum temperature has been reached, <200 W power is used to keep the reaction temperature at 120 °C. Also note that the individual IR vessel surface temperatures deviate by less than 10 °C. For clarity, the pressure graph is not shown.**

to 120 °C within 3 min (ramp) of all eight vessels, even when filled with ca. 50 mL each (total of 400 mL) of reaction mixture.

B. Kindler Reaction. Thioamides are essential building blocks for the preparation of a number of biologically relevant heterocyclic scaffolds (i.e., utilizing the Hantzsch thiazole synthesis). While many different methods to prepare thioamides have been reported in the literature, the three-component coupling of an aldehyde, elemental sulfur, and an amine (Kindler reaction) has so far received comparatively little attention.[34] This is despite the fact that this one-pot process allows for an easy introduction of diversity into the thioamide backbone by simple variation of the aldehyde and amine components in the condensation step. Since a large number of aldehydes and primary/secondary amines are commercially available, a diverse set of synthetically useful thioamide products can potentially be prepared in one step using this method. While conventional Kindler condensations require long reaction times and high temperatures, sealed vessel microwave synthesis allows the rapid preparation of thioamide building blocks in a comparatively short time frame. Recently, we have reported a rapid microwave Kindler protocol for the preparation of thioamide libraries on a 4.0 mmol scale in single-mode cavities, using 1-methyl-2-pyrrolidone (NMP) as solvent employing microwave heating at 110−180 °C for 2−20 min.[35] As a model reaction for the present scale-up studies, we have chosen the condensation of elemental sulfur with 3-chlorobenzaldehyde and 4-fluorophenethylamine to form the corresponding thioamide **2**

Scheme 2



(Scheme 2), an interesting building block for, for example, heterocycle synthesis.[34] The previously optimized 4 mmol microwave conditions (140 °C, 10 min)[35] were directly applied to a large-scale run (3 min ramp to 140 °C), using four vessels filled with 40 mmol of reagents each. As in the previous cases, the isolated yield of 90% for the large-scale run nicely compared with the 95% yield of thioamide **2** obtained in the previously published small-scale experiment.

C. Heck Reactions. The Heck reaction, the palladium-catalyzed arylation and vinylation of olefins, was discovered about 30 years ago and has since become an important carbon−carbon coupling reaction in organic synthesis, due to its high chemoselectivity and mild reaction conditions.[36] The Heck coupling reaction requires a catalyst and usually also a phosphine ligand (when a homogeneous catalyst is used), to stabilize the catalyst−substrate complex. The presence of an appropriate base is also necessary, and the reaction is usually performed in a dipolar, aprotic organic solvent, for example, acetonitrile (MeCN) or 1-methyl-2-pyrrolidone (NMP). Under conventional heating, temperatures between 60 and 120 °C for several hours are routinely used with standard catalysts. Recently, it has been demonstrated that Heck couplings can be dramatically enhanced

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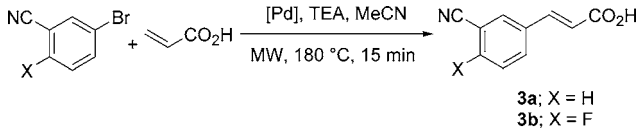
Scheme 3

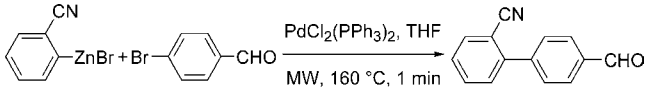


3a; X = H
3b; X = F

by microwave heating, reducing reaction times from hours to minutes.[37] For the present scale-up study, the Heck coupling of aryl bromides with acrylic acid leading to cinnamic acids has been investigated (Scheme 3). A variety of related aryl bromide/acrylic acid coupling procedures have been reported in the literature, in most cases using $Pd(OAc)_2$/tri(*o*-tolyl)phosphine as the catalytic system under conventional heating conditions.[38] Optimization of the reaction conditions under small-scale (2 mmol) single-mode conditions led to a protocol that employed acetonitrile as solvent, 1 mol % $Pd(OAc)_2$/tri(*o*-tolyl)phosphine as catalyst/ligand system, triethylamine (TEA) as base, and a 180 °C reaction temperature for 15 min. For the cyano bromobenzene substrate, 82% yield of the corresponding cinnamic acid **3a** was isolated, and for the fluoro/cyano substrate, the yield of **3b** was considerably lower (55%), under otherwise identical reaction conditions. Several recent reports in the literature have dealt with the use of heterogeneous palladium on carbon (Pd/C) as an alternative, simple, and inexpensive catalyst system for Heck coupling reactions.[39] In this context, we have discovered that the homogeneous $Pd(OAc)_2$/tri(*o*-tolyl)-phosphine catalyst system can be replaced for 5% Pd/C[40] (<0.1 mol % concentration of Pd catalyst) without the need to change any of the other reaction parameters. Yields for the Heck reaction providing cinnamic acid **3a** were very similar using either homogeneous or heterogeneous Pd catalysis (see Experimental Section for details).

For scale-up, the homogeneous Pd coupling conditions were employed for experiments on a 4 × 20 mmol scale in the multimode batch reactor (ca. 30 mL reaction volume per vessel). An overall yield of 79% of cinnamic acid **3a** was obtained. In a different run, cinnamic acid **3b** was synthesized from the corresponding aryl bromide in 56% yield. Both yields closely agree with the yields obtained in the small-scale microwave experiments (see above), demonstrating once more the direct scalability of these reactions. Importantly, it was also possible to prepare both cinnamic acids simultaneously in one single microwave irradiation experiment by using all eight vessels in the rotor, charging four vessels each with the two different arylbromide building blocks (Scheme 3).

Scheme 4



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Similarly, the Pd/C mediated coupling experiment for the synthesis of **3a** was performed without any problems on a 4 × 20 mmol scale providing an identical isolated yield (79%) of cinnamic acid as compared to the homogeneous run.

D. Negishi Reactions. Another important carbon−carbon bond forming reaction is the Negishi reaction, involving the transition metal-catalyzed coupling of an arylhalide with an arylzinc reagent.[41] Despite the importance of this general carbon−carbon bond forming reaction, reports on microwave-induced Negishi couplings are limited.[42,43] For the present scale-up work, we have selected an example that was recently reported on a 1.0 mmol scale in the literature with a single-mode microwave reactor.[42] The optimized reaction conditions involved heating to 160 °C for 1 min in THF in the presence of $PdCl_2(PPh_3)_2$ as catalyst providing an isolated yield of 90% of the desired biaryl product **4** (Scheme 4). This example was specifically selected to address the issue of very short reaction times. In our hands, the previously published small-scale method was reproducible (84% yield) despite the fact that a different method for the preparation of the arylzinc reagent was used (see Experimental Section for details).

The large-scale synthesis was carried out in two vessels on a 2 × 20 mmol scale under an argon atmosphere in the multimode batch reactor. The reaction was heated to 160 °C, employing a heating ramp of 2 min, and kept at 160 °C for an additional minute, otherwise using identical reaction conditions as in the published small-scale experiment. Purification of the combined reaction mixtures by flash chromatography provided biaryl **4** in 77% isolated yield.

E. Solid-Phase Synthesis. Solid-phase organic synthesis (SPOS) shows several advantages compared with classical protocols in solution. To accelerate reactions and to drive them to completion, a large excess of reagents can be used, as these can easily be removed by filtration and subsequent washing of the solid support. In addition, SPOS can easily be automated using appropriate robotics. Furthermore, SPOS can be applied to the powerful split-and-mix strategy, which turned out to be an important tool for combinatorial chemistry.[44] However, solid-phase organic synthesis exhibits several shortcomings due to the nature of the heterogeneous reaction conditions. Nonlinear kinetic behavior, slow reactions, solvation problems, and degradation of the polymer support due to the long reaction times are some of the

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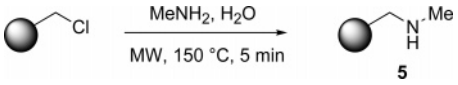
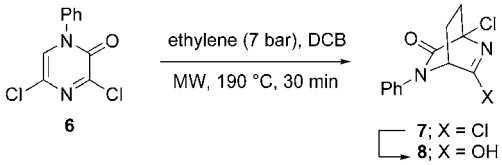
Scheme 5



5

Scheme 6



6

7; X = Cl
8; X = OH

problems typically experienced in SPOS.[45] Performing solid-phase organic synthesis under microwave irradiation conditions has become an increasingly popular technology.[7] Many examples of this high-speed technique have been reported in the literature for small-scale reactions, in most instances using cross-linked polystyrene resins as solid supports.

As a model reaction for solid-phase synthesis scale-up under microwave conditions, we have chosen a recently published protocol, describing the amination of chloromethylated polystyrene resin (Merrifield resin) with methylamine at 150 °C within 5 min (Scheme 5).[46] Interestingly, this transformation was carried out in water as a solvent, which is a highly unusual solvent for SPOS because of the inferior swelling properties of most cross-linked resins in water (in particular polystyrene resins).[45]

In contrast to the other scale-up work described in this report, here dedicated PTFE-TFM reaction vessels have been used instead of quartz vessels, to allow a more convenient handling of the polymer beads. The amination of Merrifield resin with commercially available aqueous methylamine (40% w/w) according to Scheme 5 was carried out in four vessels containing 5.0 g of resin each (0.84 mmol/g loading). Microwave heating for 5 min at 150 °C provided the same degree of amination (loading 0.74 mmol/g of amine functionality as determined by combustion analysis), comparable with the small-scale experiment.

F. Diels−Alder Cycloadditions with Ethylene. The readily accessible and broadly functionalized 2-azadiene system of the 2-(1*H*)-pyrazinone scaffold (e.g., **6**, Scheme 6) has been shown to offer unique opportunities for inter- and intramolecular cycloaddition reactions with electron-rich and electron-poor dienophiles.[47] A particularly interesting cycloaddition route in the 2-(1*H*)-pyrazinone series involves Diels−Alder cycloaddition reaction of the heterocyclic pyrazinone heterodienes with ethylene, leading to bicyclic cycloadducts of type **8**, which can be elaborated further to conformationally restricted dipeptide analogues, useful as β-turn mimetics.[48] Under conventional conditions, these cycloaddition reactions have to be carried out in an autoclave applying 25 atm of ethylene pressure before the setup is heated to 110 °C for 12 h.[49] We have recently demonstrated that it is possible to perform such cycloadditions under microwave conditions using 1,2-dichlorobenzene (DCB) as solvent, saturated with ethylene. For 2-(1*H*)-pyrazinone **6**, for example, the ethylene addition was carried out in 140 min at 190 °C on a 0.2 mmol scale to provide 89% of the final bis-lactam product **8**.[50] Interestingly, it was not possible to further increase the reaction rate by raising the temperature. At temperatures above 200 °C, an equilibrium between the cycloaddition **6** → **7** and the competing retro-Diels−Alder fragmentation process was observed.[50] To perform microwave-assisted protocols utilizing gaseous reagents as described herein, it would clearly be desirable to have a setup where a microwave compatible reaction vessel could be pressurized with a gaseous reagent before irradiating with microwaves. For small-scale single-mode reactors,[23,24] such equipment is not available at the present time.[51] The multimode instrument described in the present study allows the prepressurization of one or more individual reaction vessels in the eight-position rotor.

For the experiment involving prepressurized ethylene conditions, a solution of 1.0 mmol of 2-(1*H*)-pyrazinone **6** (Scheme 6) in 25 mL of DCB in a single quartz vessel was first flushed with ethylene at atmospheric conditions and then pressurized to ca. 7 atm with ethylene (see Experimental Section for details). After irradiation at 190 °C for 30 min, the solvent was removed under reduced pressure and the crude cycloadduct **7** was hydrolyzed by treatment with dilute NaOH at 70 °C for 30 min (microwave irradiation) to furnish bis-lactam **8** in 77% isolated yield. Clearly, here the increased pressure is driving the reaction along the desired pathway, shifting the equilibrium to the cycloadduct side.

Discussion

An overall analysis of the scale-up results presented in this study demonstrates the general direct scalability of microwave-assisted transformations optimized under small-scale single-mode conditions to a larger scale, using multimode batch reactors. By keeping the previously optimized reaction parameters (time, temperature) constant, very similar results in terms of reaction conversions and isolated product yields/purities have been obtained. One critical point in scaling up the volume of microwave-heated transformations is the reproducibility of heating and cooling profiles. Since the power density in single-mode microwave reactors is much higher than those in multimode cavities,[5a] it is possible to obtain very rapid heating (microwave flash heating) of comparatively small volumes (1−5 mL) in these small-scale reactors (with temperature increases of 10 °C s^{-1} not being uncommon). In multimode cavities, it is generally not possible to duplicate those heating profiles for larger volumes (500 mL).[52] With the current 1400 W multimode reactor

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system, it was nevertheless possible to follow the programmed heating ramps (see above), that is, reaching desired reaction temperatures of up to 180 °C within 2−3 min, even for runs involving eight reaction vessels with close to 500 mL of reaction volume. Cooling in single-mode microwave reactors is achieved by active gas-jet cooling of the reaction vessel by compressed air.[23,24] For larger reaction vessels as used in the present study, this technique is significantly less effective and the rapid cooling times of typically 2−3 min achieved on a small scale could not be reproduced. Typically 20−30 min were necessary to bring down the reaction temperature to ca. 40 °C.[53] However, this had no effect on the specific chemistries presented herein.

The transformations described herein were conducted in a parallel fashion. Therefore, rather than exposing one large reaction vessel to microwave irradiation, up to eight vessels can be placed in a rotor system and irradiated simultaneously. Apart from avoiding potential problems related to microwave penetration depth (see above), this method allows one to conduct genuine parallel synthesis, that is, to perform eight different chemical synthesis at the same time. To ensure similar temperatures in a parallel setup, however, the same amount of the identical solvent has to be used in each reaction vessel due to the dielectric properties involved. Since the maximum suggested filling volume of each the reaction vessels is ca. 50−60 mL, a total volume of ca. 500 mL can be processed. In addition, in case of an unexpected vessel failure, only the contents of one vessel are lost and the risk of an explosion is significantly reduced.

Conclusion

The feasibility of direct scale-up from small single-mode microwave reactors to larger multimode systems has been demonstrated. A number of different organic transformations involving different solvents and reaction conditions have been investigated. In all cases, it was possible to achieve similar yields of products on varying reaction scales from 1 to 4 mmol (5 mL processing volume) to a ca. 100−500 mmol scale (max 500 mL volume) without changing the previously optimized conditions (direct scalability). All reactions were repeated several times showing very small deviations in yield. The prototype laboratory-scale multimode microwave reactor used in the present study allows parallel processing in either quartz or PTFE-TFM vessels with maximum operating limits of 300 °C and 80 bar of pressure (quartz vessel). The system allows magnetic stirring in all vessels, full on-line monitoring of temperature, microwave power and pressure and, therefore, seems ideally suited for conducting microwave-assisted transformations on up to a 1000 mL scale.

Experimental Section

General Methods. All starting materials were purchased from commercial sources or were synthesized as described in the cited references. TLC analysis was performed on Merck precoated 60 F_{254} plates. Flash column chromatography was performed using silica gel 60 (0.040−0.063 mm, Merck). Melting points were obtained on a Gallenkamp melting point apparatus, model MFB-595 in open capillary tubes. ^{1}H NMR spectra were recorded on a Bruker AMX360 or AMX500 instrument in $CDCl_3$ or DMSO-d_6, operating at 360 or 500 MHz, respectively, using TMS as reference. On-bead FTIR spectra were recorded on a Unicam Galaxy Series FTIR 7000 (Mattson Instruments Inc.) using mashed resin beads in KBr pellets. Conventional IR spectra were taken on a Perkin-Elmer 298 spectrophotometer in KBr pellets. Mass spectra were obtained on a Hewlett-Packard LC/MSD 1100 series instrument in the atmospheric pressure chemical ionization (negative or positive APCI) mode. Microanalyses were performed on a Carlo Erba 1106 elemental analyzer.

Small-Scale Microwave Chemistry. All reactions described herein were initially run and carefully optimized on a typically 1.0−4.0 mmol scale (max reaction volume 5 mL) using an Emrys Synthesizer single-mode microwave reactor (Personal Chemistry AB). Inside the cavity, the ca. 10 mL reaction vials can be exposed to 20 bar of pressure and 250 °C. Temperature is measured by infrared thermometry on the outer surface of the process vial. After the irradiation period, the reaction vessel is cooled rapidly (approximately 1−2 min) to ambient temperature by compressed air (gas jet cooling). Further details of this instrument have been reported elsewhere.[31]

Large-Scale Microwave Synthesis. The experiments on a large scale described herein (500 mL reaction volume) have been carried out in a prototype multimode batch reactor (Anton Paar GmbH, Graz).[54] The instrument is equipped with two magnetrons, operating at a frequency of 2.45 GHz with continuous microwave output power from 0 to 1400 W. The cavity (dimensions: W × D × H, 45 × 42 × 35 cm^3) is equipped with an eight-vessel rotor, employing either 100 mL PTFE-TFM or 80 mL quartz glass vessels (max filling volume ca. 50−60 mL), both types dedicated for reactions at high pressure (60 or 80 bar controlled pressure, respectively) and temperatures (260 and 300 °C, respectively). The PTFE-TFM vessels are inserted into a ceramic vessel jacket, which provides structural strength and dimensional stability. The ceramics, respectively, the quartz vessels rest inside protecting air cooling jackets made of PEEK. Both types are capped with special seals and a protective PEEK cap. The seals comprise a release valve, which can be manually operated and allows the prepressurization of the vessel via a connection port with a syringe adapter. The individual vessels are placed in the corresponding rotor, fixed by screwing down the upper rotor plate, and finally the rotor is closed with a protection hood (Figure 2). Accurate temperature measurement is achieved by inserting a gas balloon thermometer in one reference vessel. Additionally, the surface temperature of all vessels can be monitored by IR thermography. Pressure is monitored by a load-cell type simultaneous hydraulic pressure sensing system for all vessels, monitoring

(53) Previoulsy described microwave batch reactors possess a coldfinger inside the reaction vessel for rapid cooling after completion of irradiation (see refs 21 for details).

(54) The prototype microwave reactor used for synthesis in this study is based on the Multiwave 3000 microwave digestion system (www.anton-paar.com). For applications and further details, see: Kettisch, P. *Int. Labmate* **2003**, *27*, 39−41.

Figure 2. **View of the eight-position rotor system. Visible are the protecting air cooling jackets made of PEEK containing the quartz or PTFE-TFM vessels and the pressure release valves. The protection hood is shown in the back. This rotor system is placed in the cavity of the reactor.**

the highest pressure level and pressure increase. Both, pressure and temperature data are transferred to the microwave oven wireless by an infrared LED on the rotor. The ovens built-in electronics allows reaction control in a temperature versus time mode. Alternative rotor types for the simultaneous treatment of 16 vessels are available but have not been used for this work. After irradiation, the rotor is cooled to approximately 40 °C within 20 min by venting air through cooling gaps which are surrounding the reaction vessels. The system is equipped with various safety features/devices, including a solvent detection system, and shut-down mechanisms in case of a too rapid temperature or pressure increase in one of the reaction vessels. Each vessel is equipped with a pressure release seal that is designed to vent at 120 bar of pressure, avoiding rupture of the vessel.

CAUTION: Performing chemical synthesis with organic solvents in sealed vessels under pressure constitutes a safety hazard. Proper care must be taken in the event of any unexpected vessel rupture or explosion (exothermic reactions, thermal runaways, arcing phenomena in electromagnetic fields). In our synthetic attempts with the reactor system described above, such experimental hazards were not experienced.

Ethyl 4-Phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a). Four 80 mL quartz reaction vessels equipped with Teflon-coated stirring bars (2.5 cm) were individually charged with 4.80 g (80 mmol) of urea and 2.40 g (8 mmol) of $FeCl_3 \cdot 6H_2O$. To each of these vessels was added 32 mL of a 3:1 (v/v) mixture of AcOH and EtOH, followed by stirring at room temperature for approximately 10−15 min to enable the starting materials to dissolve. Subsequently, 8.49 g of benzaldehyde (80 mmol) and 10.40 g (80 mmol) of ethyl acetoacetate were added. All four quartz reaction vessels were sealed and inserted into the eight-position rotor. The reaction mixtures were heated to 120 °C employing a 3 min linear heating ramp and then irradiated for an additional 10 min at 120 °C. After cooling to 40 °C by an air flow (20 min), individual vessels were removed from the rotor and kept at 4 °C for ca. 1 h. The precipitates were filtered by suction and washed with cold EtOH to provide DHPM **1a** in 70%, 72%, 71%, and 74% yield, respectively. In every case, the purity determined by HPLC and ^{1}H NMR was >98%. The combined yield was 59.80 g (72%). ^{1}H NMR (DMSO-d_6) δ 1.12 (t, J = 7.5 Hz, 3H), 2.28 (s, 3H), 4.03 (q, J = 7.5 Hz, 2H), 5.17 (d, J = 3 Hz, 1H), 7.22−7.41 (m, 5H), 7.78 (br s, 1H), 9.22 (br s, 1H). The spectroscopic and analytical properties of this material were in agreement with an authentic sample.[31]

Isopropyl 4-(3-Nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1b). This DHPM derivative was synthesized in a similar way as described above for **1a**, in two, four, and eight quartz reaction vessels. For the eight vessel run, all eight vessels were filled with the appropriate reagents as described below: 4.80 g (80 mmol) of urea and 32 mL of EtOH were placed in a quartz vessel and stirred for approximately 10−15 min to enable the urea to dissolve. Subsequently, 12.10 g (80 mmol) of 3-nitrobenzaldehyde, 11.50 g (80 mmol) of isopropyl acetoacetate, and 1.50 mL of HCl concd were added. All eight quartz reaction vessels were sealed and inserted into the eight-position rotor. The reaction mixtures were heated to 120 °C employing a 3 min linear heating ramp and then irradiated for an additional 20 min at 120 °C. After cooling to 40 °C by an air flow (20 min), individual vessels were removed from the rotor and the contents combined, treated with 150 mL of water and stirred for ca. 30 min at room temperature. Subsequent cooling at 4 °C for 1 h and filtration provided 98.1 g (48%) of DHPM **1b** in >95% purity (HPLC). ^{1}H NMR (DMSO-d_6) δ 1.00, 1.18 (2d, J = 6.0 Hz, 6H), 2.28 (s, 3H), 4.84 (m, 1H), 5.31 (d, J = 3.0 Hz, 1H), 7.65−7.77 (m, 2H), 7.91 (br s, 1H), 8.09−8.19 (m, 2H), 9.38 (br s, 1H). The spectroscopic and analytical properties of this material were in agreement with an authentic sample.[31]

2-Chloro-*N*-[2-(4-flurophenyl)ethyl]thiobenzamide (2). The reaction was carried out in four 80 mL quartz vessels, each charged with 1.44 g (45 mmol) of elemental sulfur (S_8), suspended in 40 mL of NMP. Subsequently, 6.96 g (50 mmol) of 4-fluorophenethylamine and 5.62 g (40 mmol) of 3-chlorobenzaldehyde were added (in that order). The vessels were sealed, put into the eight-position rotor system, and inserted into the cavity. The reaction mixtures were heated to 140 °C employing a 3 min linear heating ramp and then irradiated for an additional 10 min at 140 °C. After irradiation, the vessels were cooled to 40 °C within 20 min. The dark brown solutions were combined, poured onto crushed ice and stirred for 20 min. The formed precipitate was filtered and purified by redissolving the crude material in acetone, followed by filtration and reprecipitation with ice−water. This protocol afforded 42.2 g (90%) of thioamide product **2** in excellent purity (>98%, HPLC). ^{1}H NMR ($CDCl_3$) δ 3.08 (t, J = 6.5 Hz, 2H), 4.07 (q, J = 6.0 Hz, 2H), 7.03−7.53 (m, 8H), 7.65 (s, 1H). The spectroscopic

and analytical properties of this material were in agreement with an authentic sample.[35]

3-Cyano-*trans*-cinnamic Acid (3a). 1. Small Scale. (A) Homogeneous Catalysis. In a typical procedure for homogeneous catalysis, 1.0 mol % of Pd(II) acetate (4.5 mg, 0.02 mmol), 2.2 mol % of tri(*o*-tolyl)phosphine (13.4 mg, 0.044 mmol), and 2.0 mmol (275 μL) of TEA were dissolved in 3.0 mL of MeCN and stirred for approximately 15 min in the microwave process vial. Then 2.0 mmol (364 mg) of 3-bromobenzonitrile was added, and the mixture stirred for an additional 5 min at room temperature. Finally, 2.0 mmol (137 μL) of acrylic acid was added, and the vial was sealed and subsequently irradiated at 180 °C for 15 min. After cooling, the precipitate was filtered off and treated with 5 mL of water for an initial purification (removal of the TEA HBr). The mother liquor was evaporated, and the residue also treated with water to provide additional product. The combined solid crude products were dissolved in EtOH and filtered to remove residual Pd(0). Evaporation led to a colorless, crystalline product in 82% yield (280 mg) and excellent purity (>98%, HPLC), mp = 230−232 °C (lit.[55] 236−238 °C). ^{1}H NMR (DMSO-d_6) δ 6.70 and 7.61 (2d, J = 16.0 Hz, 1H each), 7.61 (t, J = 8.0 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 8.22 (s, 1H), 12.6 (br s, OH); MS (pos. APCI): m/z 174 (M + 1). **(B) Heterogeneous Catalysis.** Utilizing heterogeneous catalysis, the catalytic system of phosphine ligand and Pd(II)-acetate was substituted by 5.0 mg of Pd/C (5% Pd, 56% water, Degussa AG),[40] removing the need for prestirring. The reaction was carried out under identical conditions as described above (180 °C, 15 min), and identical workup led to the desired product in comparable yield (270 mg, 79%) and purity (>98%). The spectroscopic and analytical properties of this material were identical to the product isolated from a homogeneous run. **2. Scale-Up Experiment.** In a typical procedure for homogeneous catalysis, 1.0 mol % of Pd(II) acetate (0.2 mmol, 45 mg), 2.2 mol % tri(*o*-tolyl)phosphine (0.44 mmol, 134 mg), and 20 mmol (2.75 mL) TEA were dissolved in 25 mL of MeCN and stirred for approximately 15 min in an 80 mL quartz reactor vessel. Then, 20 mmol (3.64 g) of 3-bromobenzonitrile were added, and the mixture stirred for an additional 5 min. Finally, 20 mmol (1.37 mL) of acrylic acid was added, and the vessel was sealed and inserted into the eight-position rotor system. The rotor was equipped with four vessels prepared according to the above protocol and then inserted into the cavity. The reaction mixtures were heated to 180 °C employing a 3 min linear heating ramp and then kept for an additional 15 min at 180 °C. After cooling to 40 °C within a period of 20 min, the vessels were opened and the contents from individual vessels combined. The formed precipitate was filtered, and the filtrate was evaporated. The combined crude products were treated with 50 mL of water, stirred for 20 min, and then filtered by suction. To eliminate traces of Pd, the residue was dissolved in hot ethanol (approximately 50 mL per g) and filtered. Evaporation of the solvent left 10.8 g of off-white product (79%) in excellent purity (>98%). Carrying out the large-scale reaction under heterogeneous conditions on the same scale (four vessels) led to an identical overall product yield of 79%.

3-Cyano-4-fluoro-*trans*-cinnamic Acid (3b). 1. Small Scale. The reaction under homogeneous conditions is carried out as described above for **3a** on a 2.0 mmol scale, employing 3-bromo-4-fluorobenzonitrile (2.0 mmol, 400 mg) as starting material. Identical workup lead to 210 mg (55%) slightly greenish product in high purity (>95%, HPLC), mp = 203−205 °C; ^{1}H NMR (DMSO-d_6) δ 6.64 and 7.58 (2d, J = 16.0 Hz, 1H), 7.56 (m, 1H), 8.12 (d, J = 7.5 Hz, 1H), 8.32 (d, J = 7.5 Hz, 1H), 12.58 (s, OH). MS (neg. APCI): m/z 190 (M-1). **2. Scale-Up Experiment.** The reaction was carried out as mentioned above under homogeneous conditions employing four 80 mL quartz vessels on a 4 × 20 mmol scale each according to the general protocol described above. Identical workup led to 8.6 g (56%) of product **3b** in high purity (>95%).

4-(2-Cyanophenyl)benzaldehyde (5). 1. Preparation of 2 M Stock Solution of $ZnBr_2$ in THF. Anhydrous $ZnBr_2$ (Fluka 96465) was fused at 15 mbar for ca. 15 min in a round-bottomed flask utilizing a heating gun. This reagent (10.0 g, 44.4 mmol) was dissolved in 22 mL of dry THF (distilled from sodium benzophenone ketyl) by vigorous shaking of the flask. **2. Preparation of 0.38 M Stock Solution of 2-Bromozinc Benzonitrile.** A two-necked round-bottomed flask was filled with a solution of 9.10 g (50 mmol) 2-bromobenzonitrile in 40 mL of dry THF under argon atmosphere. The flask was equipped with a stirring bar, a thermometer, and a septum. The flask was immersed into a Dewar vessel cooled by an ethanol/liquid N_2 slush. After cooling the solution to −100 °C, 35 mL (56 mmol) of 1.6 M n-BuLi in hexanes was added carefully, keeping the reaction temp < −78 °C. The addition took approximately 30 min, and afterwards, the mixture was kept at −78° for an additional 3 min. The solution was cooled again to −100−110 °C, and 30 mL of 2 M $ZnBr_2$ in THF was added slowly, keeping the temp < −78 °C. After addition (∼30 min), the flask was allowed to warm to ambient temp within ca. 30 min under vigorous stirring. A sample was taken from the vigorously stirred biphasic mixture, quenched with diluted HCl, and extracted with ether. The etheral extract was analyzed by HPLC (210 nm), showing 76% conversion to the desired 2-bromozinc benzonitrile. **3. Negishi Coupling.** The microwave scale-up was conducted in two 80 mL quartz vessels, equipped with stirring bars. A melted mixture of 3.30 g (17.8 mmol) of 4-bromobenzaldehyde and 250 mg (0.36 mmol) of $PdCl_2(PPh_3)_2$ was poured under argon into each vessel. Subsequently, both vessels were temporarily sealed with rubber septa and charged with 50 mL (corresponding to 19 mmol of 2-bromozinc benzonitrile) of organozinc reagent using a syringe. Both vessels were warmed (ca 50 °C) to ensure dissolution of the substrate. The vessels were then permanently sealed and placed into the eight-position rotor. The reaction was heated to 160 °C, employing a heating ramp of 2 min, and kept at 160 °C for additional 1 min. The cooling period required ca. 20 min to

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reach approximately 40 °C. The contents of both vessels were combined, and after evaporation of the solvent, the crude mixture was purified by silica gel flash column chromatography, employing EtOAc/hexane 1:2.5 as eluent to yield 5.70 g (77%) of product in high purity (>98% by ^{1}H NMR). ^{1}H NMR ($CDCl_3$): δ 7.52−7.84 (m, 6H), 8.03 (d, J = 7.0 Hz, 2H), 10.12 (s, 1H); FT-IR (KBr): 2215 cm^{-1} (CN), 2840−2950 cm^{-1} (CH); MS (pos. APCI): m/z 208 (M + 1). The spectroscopic and analytical properties of this material were in agreement with an authentic sample.[42]

Methylaminomethyl Polystyrene Resin. Washed and dried Merrifield resin (5.0 g, 0.84 mmol/g loading, Nova-Biochem No. 01-64-0104, washed with H_2O, THF/H_2O, DCM, and MeOH (20 mL each) before use) was filled, respectively, into four dedicated 100 mL Teflon vessels and suspended with 50 mL of commercially available aqueous $MeNH_2$ (40% w/w). The vessels were capped, coated with ceramics tubes and a PEEK sheath, and inserted into the rotor system. The rotor was closed and placed inside the cavity of the reactor. The reaction mixtures were heated at 150 °C for 5 min (no heating ramp) and afterwards cooled to ca. 40 °C within 20 min. The combined resins were washed 3 times with H_2O, DCM, and MeOH (20 mL each) and dried at 70 °C to furnish 20.0 g of methylaminomethyl polystyrene resin. The loading was calculated to 0.74 g/mol based on the N content determined by elemental analysis of 1.03%. The reaction progress was also monitored by on-bead FTIR measurement observing the C−Cl stretch at 1270 cm^{-1}, which decreased due to substitution of the chlorine functionality.

Pyrazinone/Ethylene Diels Alder Reaction. Pyrazinone **6**[48] (227 mg, 1.0 mmol) was placed in a 80 mL quartz vessel and dissolved in 25 mL of 1,2-dichlorobenzene. The vessel was flushed several minutes with ethylene and inserted into the rotor, together with three dummy vessels, each filled with 25 mL of solvent. After the vessels were fixed, the reaction vessel containing the pyrazinone precursor was prepressurized with 7 bar of ethylene from a lecture bottle via the gas inlet system of the vessel. Then the rotor was placed inside the cavity and irradiated, employing a 1.5 min heating ramp to reach 190 °C and additional irradiation time at 190 °C for 30 min. After cooling to 40 °C (ca 20 min), the solvent was removed by distillation under reduced pressure. The crude cycloadduct **7** was suspended in 10 mL of 1 M NaOH/dioxane (1:2) and irradiated at 70 °C for 30 min. After cooling, the mixture was neutralized with 1 M HCl and evaporated. The crude bis-lactam product **8** was dissolved in $CHCl_3$ and extracted with water. The organic layer was separated and evaporated, and the residue was purified by silica gel flash chromatography (DCM/ethyl acetate 1:2) to furnish 206 mg (77%) of adduct **8** as a colorless solid. ^{1}H NMR ($CDCl_3$): 2.52−1.94 (m, 4H), 4.97 (m, 1H), 7.25−7.54 (m, 5H). The spectroscopic and analytical properties of this compound were in agreement with authentic material.[50]

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