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# Scale-Up of Microwave-Assisted Reactions in a Multimode Bench-Top Reactor

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**ABSTRACT:** An evaluation of a new bench-top microwave batch reactor that uses a single 1 L reaction vessel is presented. Several microwave-assisted organic reactions have been scaled-up, including Newman Kwart and Diels−Alder reactions, Pd-catalyzed cross-couplings, heterocycle synthesis, aromatic substitution, and a Knoevenagel condensation. A range of different solvents (high and low microwave absorbing), varying reaction times (4 s up to 2 h), and temperatures (120−250 °C) have been explored in these investigations. For all studied transformations, it was possible to perform a direct scale-up (up to 720 mL reaction volume) without changing the previously optimized reaction conditions achieved in a laboratory-scale single-mode microwave instrument (2−20 mL processing volume), obtaining similar isolated product yields. A scalability up to 360-fold, when moving from 3 mmol up to 1.08 mol, was demonstrated, and isolated product yields up to 300 g (2.5 mol scale) in a single run could be accomplished, providing the potential for a kilogram output per day for specific transformations by performing multiple sequential runs.

## 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 enhance product purities compared to conventionally heated experiments.[1−3] In particular, in the pharmaceutical, agrochemical, and related industries, the utilization of microwave-assisted synthesis for initial discovery and development processes is common practice.[4] While the use of microwave heating for performing reactions in the milligram to gram region is straightforward, scale-up of microwave synthesis from the laboratory to process and production scale has proven more difficult to achieve and is still a challenging area.

Two different approaches for microwave synthesis on a larger scale (>100 mL volume) have emerged: batch synthesis in larger multimode reactors or continuous/stop flow techniques.[5] With respect to scale-up using both methodologies, several issues have to be considered. The big challenge for process scale-up involving microwave technology is to establish a reliable and safe process setup. One of the main limitations of microwave batch 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), the penetration depth is in the order of a few centimeters, depending on the dielectric properties of the medium.[6] In addition, when moving to larger and larger batch reactors, many of the genuine benefits of small-scale microwave chemistry are in fact lost. As the reaction volume increases, it becomes more difficult to heat up—but also to cool down—the reaction mixture at the same rate as on small-scale, and as a consequence, more microwave power is needed. Generally, the most common batch microwave instruments provide a comparatively high microwave power output (>1000 W) from standard air-cooled magnetrons, which prove sufficient to effectively heat up mixtures of up to 500 mL. 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).[3] In the context of organic synthesis, batch scale-up has been successfully demonstrated in microwave instruments using either single reaction vessels with filling volumes of up to 12 L or a parallel multivessel rotor setup (up to 1 L total reaction volume) using commercially available multimode instruments.[5] For the single vessel format, however, to reach such high volumes the microwave instrument has to be very large and will not fit in a standard fume hood. A disadvantage of the parallel setup is that charging and emptying multiple vessels can be tedious without automation, especially if solids are involved.[5]

As a consequence of the apparent limitations of large-scale batch microwave processing, recent efforts have also focused on performing microwave chemistry under continuous- or stop-flow conditions.[5] 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.[5,7,8] Applying a flow regime, many of the advantages of small-scale microwave heating (rapid heating and cooling) are reinstated, with limited penetration depths

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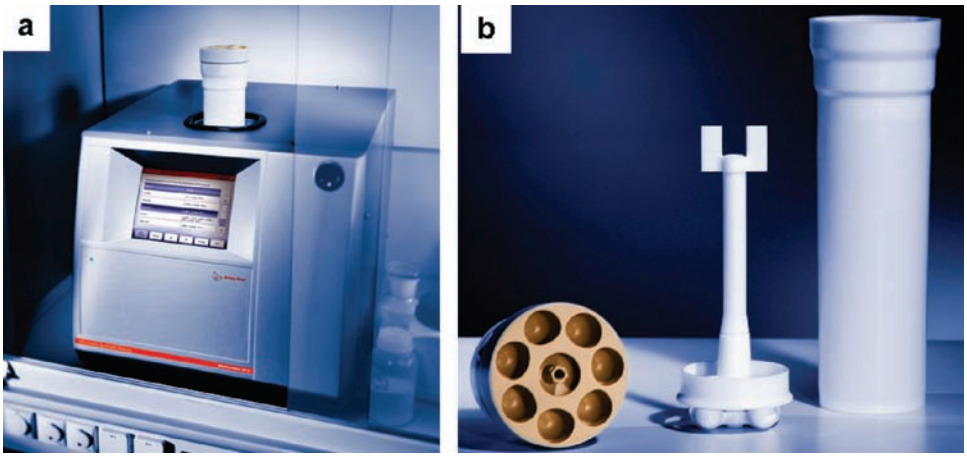


**Figure 1.** (a) Masterwave BTR installed in a standard laboratory fume hood. (b) Masterwave BTR reaction vessel, consisting of a 1 L PTFE liner, agitator, and cap (right to left).

typically not being an issue.[7,8] With the continuous flow approach reactions are rather "scaled-out" than scaled-up. However, the major drawback of continuous flow processing is the incompatibility with heterogeneous reaction mixtures and highly viscous liquids. A further, more general, problem that discourages chemists from applying a continuous flow format for chemical synthesis is that reactions in medicinal chemistry are normally performed in a batch mode, and transferring them into a continuous process requires extensive reoptimization to develop appropriate homogeneous reaction conditions and suitable residence times.[9]

In the past few years, a significant number of microwave protocols have already made their way into scale-up laboratories since microwave technology is increasingly required in early scale-up phases on a ~0.5−5 kg scale, specifically for the synthesis of intermediates and active compounds.[9] Impressive progress has been achieved in translating small-scale protocols from the milligram or gram scale (typically performed in a single-mode instrument) to a larger scale using multimode batch microwave reactors. For example, the Leadbeater group recently introduced a prototype microwave reactor capable of processing up to 12 L in a single vessel format.[10] Using commercially available batch instruments fitted with a single reaction vessel, much lower product quantities in the range of 50−250 g can typically be produced. Several examples have been reported by Leadbeater,[11−13] Moseley,[14] and others[15] employing either the Biotage Advancer or Milestone UltraCLAVE reactor. By performing reactions in a parallel fashion using multivessel rotors, up to ~100 g of product per run can generally be obtained, as has been shown by several authors.[9,13,14,16−19]

Since the majority of small-scale reactions is optimized under batch conditions, the development of a convenient batch microwave reactor that could perform reactions on the kilogram scale on a daily basis and which is not limited to homogeneous reaction mixtures (as a continuous flow instrument) would be desirable. Ideally, the scaling of a protocol from the milligram scale to the kilogram scale should be straightforward with little need for reoptimization. Here, we present the evaluation of a novel benchtop microwave batch reactor that uses a 1 L single reaction vessel. Several transformations, including pharmaceutically relevant syntheses, were studied particularly with respect to direct scalability, but other important scale-up issues such as stirring efficiency, heating and cooling performance, or working at high pressures were also taken into account.

## RESULTS AND DISCUSSION

**Equipment.** The utilized microwave bench-top reactor (Masterwave BTR) manufactured by Anton Paar GmbH[20] serves batch-type scale-up reactions in a 250−750 mL scale following the one-vessel-at-a-time concept. Depending on the specific chemistry, a daily output of several hundred grams of product per day is accessible performing sequential batch processing. The compact-sized reactor fits in any standard laboratory fume hood (see Figure 1a), like common small-scale single-mode reactors. The instrument features a single 1 L PTFE reaction vessel with a bayonet-lock cap comprising a lip-type seal (see Figure 1b). The cap contains a metal safety disk, which opens in case of extensive overpressure, and empties the vessel content in a mandatory expansion tank. Each vessel hosts a magnetic driven PTFE paddle stirrer operating at 0−700 rpm. A software-guided stirring regime provides optimized agitation during the entire process. This is an important feature for scale-up purposes since only proper agitation ensures homogeneous and quick heat distribution within the employed volume. The reaction vessel is immersed into the cavity and positioned directly onto a rising Pt100 sensor for accurate temperature measurement.[21] This simplifies vessel set up and handling since the use of a fragile immersion tube is prevented. Due to an inversed nozzle at the bottom of the PTFE liner (see Figure 2), the temperature sensor measures directly inside the reaction mixture giving immediate feedback of the current temperature. Pressure sensing is achieved by a hydraulic sensor integrated in the sliding cover of the instrument.

The instrument employs two standard industrial 850 W magnetrons providing a maximum microwave power output of 1700 W. The operation limits of the instrument are 250 °C and 30 bar and thus comparable with the small-scale single-mode reactors.[3] The precise reaction temperature measurement by the PT100 sensor allows direct method transfer from small-scale single-mode microwave reactors, thus providing scalability from the discovery to the kilolab scale. Experiment programming as well as parameter control is achieved by an integrated touch screen user interface employing a dedicated software package. Relevant reaction parameters such as temperature, time, and maximum stirrer speed can be modified on the fly during the experiment. The applied microwave power is adjusted automatically by the instrument according to the programmed heating profile and the employed volume.

All collected data are displayed on the screen in a graph as well as in numeric widgets. An optional remote control tool (VNC open source) allows for reaction monitoring and user interaction from the office desk.

Effective cooling after the reaction is performed by an internal closed cooling circuit. A microwave transparent cooling liquid is permanently circulating around the vessel, withdrawing the heat effectively by the aid of a heat exchanger fan in the rear of the instrument. The default cooling temperature is set to 55 °C as a safety measure. However, any temperature between 70 and 30 °C can be individually adjusted for the cooling step. It is recommended to choose a cooling temperature below the boiling point of the solvent since the reaction vessel is not hermetically sealed. The hydraulic piston integrated in the sliding cover provides for smooth release of postreaction overpressure by slowly lifting the bayonet-locked cap to ensure handling of pressureless vessels only. A built-in compressed air vessel ejector simplifies removal of the vessel from the cavity.

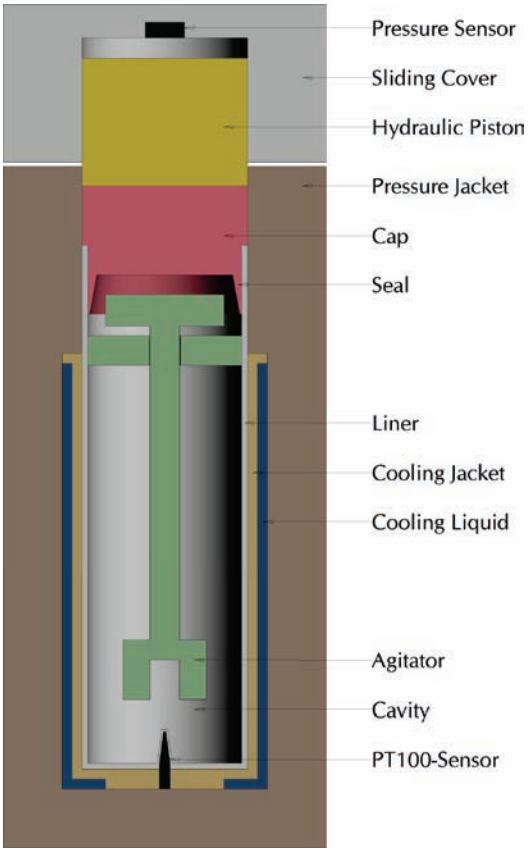


**Figure 2.** Schematic display of the 1 L reaction vessel inside the microwave cavity of the Masterwave BTR.

As protection against overpressure or thermal runaways during the run, the vessel cap is equipped with a metal rupture disk. Depending on the reaction temperature the rupture disk will open at 46−54 bar providing sufficient overpressure tolerance during the entire operation range. In case of a venting action, the vessel content is emptied via a common stainless steel tubing at the rear of the instrument into a mandatory expansion tank. In combination with the comprehensive software-controlled measures, this mandatory setup ensures the utmost safety when processing liter-scale quantities at elevated temperature and pressure conditions.

**Performance Validation.** To demonstrate the general heating performance of the instrument, a variety of common organic solvents have been heated in different volumes. In the initial evaluation phase, water, ethanol (EtOH), *N*-methylpyrrolidinone (NMP), acetonitrile (MeCN), tetrahydrofuran (THF), and dichloromethane (DCM) have been utilized as model solvents to determine the benchmarks of the system. As shown in Table 1, even solvents that interact rather poorly with microwaves (low to moderate loss tangent)[6,22] can be heated satisfactorily with the Masterwave reactor. Since the instrument's dedication is scale-up and enhancement of productivity in kilolab applications, the minimum filling volume has been set to 250 mL. The maximum filling volume depends on the target temperature and the applied solvent as the thermal expansion of the corresponding solvent has to be taken into consideration (see Figure 3). As an average recommendation, a maximum filling volume of 700 mL has been determined to provide sufficient headspace for proper pressure measurement in the system.[20]

According to the physical properties and the employed volume of the solvents, average heating rates of 20 to more than 70 °C/min can be achieved (see Table 1). Whereas in the initial heating phase the heating rates could be even higher, a certain

**Table 1. Heating/Cooling Performance of Masterwave BTR for Model Solvents**

| entry | solvent | volume [mL] | target temperature [°C] | heating rate [°C/min][a] | heating time [min] | cooling rate [°C/min][b] | cooling time [min][b] |
|---|---|---|---|---|---|---|---|
| 1 | water | 400 | 215 | 30.6 | 6.0 | 6.9 | 21.0 |
| 2 | water | 700 | 215 | 19.4 | 9.7 | 6.3 | 23.0 |
| 3 | EtOH | 400 | 200 | 50.3 | 3.4 | 9.6 | 13.5 |
| 4 | EtOH | 600 | 200 | 33.8 | 5.0 | 8.1 | 16.0 |
| 5 | NMP | 400 | 220 | 71.8 | 2.6 | 10.2 | 14.7 |
| 6 | NMP | 700 | 220 | 37.3 | 5.1 | 8.6 | 17.4 |
| 7 | MeCN | 400 | 200 | 42.5 | 4.0 | 12.7 | 10.2 |
| 8 | MeCN | 600 | 200 | 33.3 | 5.1 | 9.7 | 13.4 |
| 9 | THF | 400 | 180 | 30.6 | 4.9 | 9.1 | 13.2 |
| 10 | THF | 700 | 180 | 31.2 | 4.8 | 8.5 | 14.1 |
| 11 | DCM | 400 | 160 | 28.2 | 4.6 | 7.6 | 15.7 |
| 12 | DCM | 650 | 160 | 23.2 | 5.6 | 6.0 | 19.9 |

[a] Calculated from a standardized starting temperature of 30 °C. [b] Referring to 70 °C in general, whereas THF was cooled to 60 °C and DCM was cooled to 40 °C for safety reasons.


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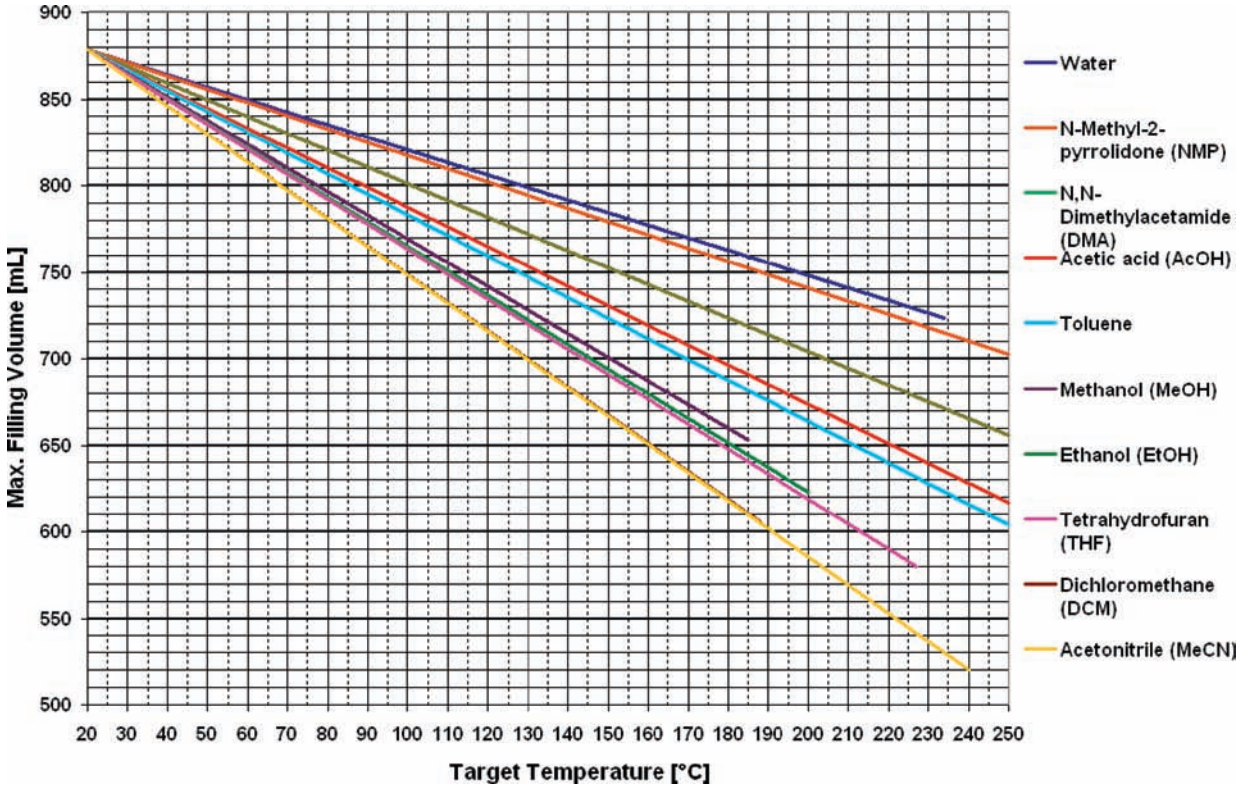


**Figure 3.** Applicable maximum filling volume of a selection of organic solvents in order not to exceed the 30 bar operation limit of the reactor.

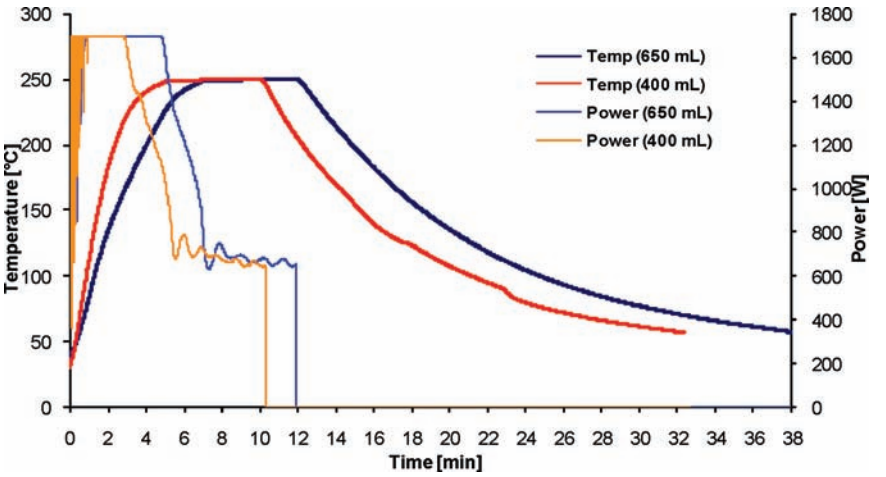


**Figure 4.** Heating profiles for 400 mL (red) and 650 mL (blue) of DMA solvent.

decrease is observed when approaching the target temperature. The instrument's software algorithm reduces the microwave power to avoid thermal overshoot. This results in a slightly extended heating time but enhances the precision of reaction control as demonstrated by heating various volumes of *N*,*N*-dimethylacetamide (DMA) (see Figure 4). Maximum power is only applied for a rather short time; once the temperature is within 20 °C of the target temperature, the power reduction starts. In the hold time period, relatively moderate power levels are required to maintain the target temperature. The required power levels during hold time are very similar since the influence of the filling volume is negligible at this point. More accuracy in achieving the target temperature provides better reproducibility of the reactions, less byproduct formation, and in consequence less effort to isolate the desired compounds. This is a key factor in kilolab processing when several hundred grams of valuable product per batch are generated.

The heating performance of the system was optimized according to the physical properties of THF as representative solvent. This is demonstrated by the fact that there is virtually no difference in the heating rates of THF, regardless of whether the minimum or the maximum filling volume is applied (see Table 1, entries 9 and 10).

The cooling efficiency of the Masterwave BTR is mainly influenced by the heating capacity of the applied solvents. For common organic solvents, an average cooling rate of around 8 °C/min down to 70 °C is typical. In general, the overall cooling


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time is dependent on the employed volume and the final temperature. Whereas cooling down to 80 °C is highly efficient and quick for a broad variety of solvents, the final step to lower temperatures is obviously more time consuming. In general, a period of approximately 15 min for the cooling step can be estimated. Nevertheless, low boiling solvents such as THF, MeOH, or DCM require somewhat longer cooling times since the vessel needs to be cooled significantly below 70 °C before being taken out of the reactor.

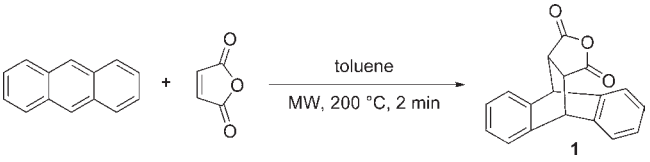
**Chemistry Evaluation Concept.** To investigate the potential of this reactor platform for the direct scalability of previously optimized small-scale microwave protocols to larger scales in the range of several hundred grams, a variety of synthetic organic transformations have been covered in these studies. To explore the limits of this batch reactor regarding magnetron efficiency, a range of solvents have been tested, including toluene—which is known as a weakly microwave absorbing solvent[3,6,22]—at 200 °C. With respect to reaction time, we have chosen experiments with extremely short (4 s) and long (2 h) reaction times. Reactions requiring high temperatures or generating high pressures close to the maximum instrument limit of 250 °C and 30 bar have additionally been evaluated. In terms of stirring efficiency, strongly heterogeneous reactions at different filling volumes have been performed. In addition, transition metal catalyzed C−C cross coupling syntheses using very low Pd concentrations, a multicomponent, and heterocyclic reactions have been carried out in this study.

For these scale-up investigations, we first revisited—and when necessary reoptimized—already existing microwave-assisted procedures on small scale (1−10 mmol) in a 10 mL Pyrex vessel employing a single-mode instrument with internal fiber-optic probe temperature measurement capabilities (Monowave 300, Anton Paar GmbH).[21] Subsequently, the same chemistry was performed on a medium scale (5−80 mmol) using the same single-mode instrument but in a larger (30 mL) Pyrex vessel. The final step was the scale-up (0.2−2.5 mol) in the Masterwave BTR reactor employing the 1 L PTFE vessel. In all cases, the optimized reaction times (hold time at the desired maximum temperature) were translated from small to large scale. However, heating and cooling times were significantly longer on large scale.

**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.[23] Numerous Diels−Alder processes have been studied under microwave conditions due to the long reaction times and elevated temperatures often required.[1,2] This type of reaction is an excellent example to test the heating efficiency of the magnetron since these reactions typically require rather forcing conditions—a poor microwave absorbing solvent at high temperatures. Scale-up studies in toluene at 155 °C were successfully performed by Leadbeater in the Biotage Advancer on a 120 mL scale.[11] Moseley and co-workers have translated the optimized sealed vessel small-scale conditions at 200 °C (see Table 2) to an open vessel approach on 2.5 L scale by performing a solvent change from toluene (tan $\delta$ 0.040)[22] to 1,2-dichlorobenzene (tan $\delta$ 0.280)[22] and by reducing the temperature to 180 °C.[17,24]

For the current study, we have chosen the cycloaddition between anthracene and maleic anhydride in toluene to provide the corresponding Diels−Alder adduct **1** (Table 2). On the basis of our previous experience with this transformation under both microwave and oil bath conditions,[25] we obtained complete conversion for this cycloaddition within 2 min at 200 °C using equimolar amounts of diene and dienophile. The product precipitated directly upon cooling, and for all three experiments on different scale comparable yields were achieved (90%, 93%, 94%, see Table 2), allowing the production of 196 g of the Diels−Alder cycloadduct **1** on the largest scale (0.75 mol, 600 mL).

**Table 2. Comparison of the Scale-Up for the Diels−Alder Cycloaddition of Anthracene with Maleic Anhydride**




| entry | scale | reaction volume [mL] | yield [%][a] | isolated product [g][b] |
|---|---|---|---|---|
| 1 | 2.5 mmol | 2 | 90 | 0.622 |
| 2 | 20 mmol | 16 | 93 | 5.16 |
| 3 | 0.75 mol | 600 | 94 | 196 |

[a] Isolated yield. [b] Purity ≥97% by HPLC (215 nm).

Although, as already stated above, toluene itself is a low microwave absorbing solvent (tan $\delta$ 0.040),[22] the fact that the cycloaddition is executed under fairly concentrated conditions (1.23 M for both the diene and the dienophile) allows the overall reaction mixture to be heated to 200 °C by single-mode microwave irradiation within ca. 1.3 min and within 5 min in the Masterwave BTR reactor.

**Newman−Kwart Rearrangement.** Since we already have tested the heating efficiency for the poor microwave absorbing solvent toluene at 200 °C, we wanted to evaluate the performance of the Masterwave BTR at the temperature limit of 250 °C for prolonged reaction time. Therefore, the Newman−Kwart rearrangement (NKR) proved to be an excellent model reaction, as it presents an example of a first-order, unimolecular rearrangement converting an *O*-thiocarbamate to an *S*-thiocarbamate which generally requires high temperatures in the range of 200−300 °C.[26] Moseley and co-workers have re-evaluated the NKR in detail under both microwave and conventional thermal heating and have shown that there is no difference between the two under well-controlled conditions.[27] Electron-withdrawing group (EWG) substituents are known to aid the rearrangement, either reducing the reaction time or lowering the required temperature, whilst electron-donating group (EDG) substituents tend to require temperatures in the 300 °C region.[26] The reaction solution is typically homogeneous, and when well-stirred, the potential problem of localized superheating due to inefficient agitation under microwave irradiation is prevented.[28] Several scale-up studies on the NKR have been performed by Moseley and co-workers in flow and batch mode employing several commercially available microwave instruments.[8c,14,29]

For the current investigation, we performed the NKR of *O*-thiocarbamate **2** bearing a chloro substituent at the 4-position in NMP as solvent (Table 3). As has been shown previously, for this relatively neutral substrate to reach >95% conversion within 20 min, a temperature of 280 °C is required.[27c] In an initial study we therefore optimized the NKR on a 1 mmol scale toward the ideal reaction time to reach full conversion at 250 °C. As can be seen in Table 3 (compare entries 1−4), the reaction mixture


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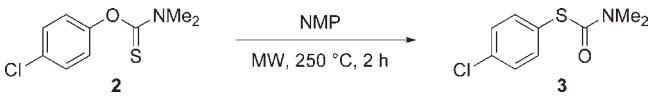
**Table 3. Comparison of the Scale-Up for the Newman−Kwart Rearrangement**



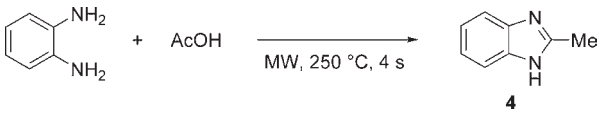

| entry | scale | reaction volume [mL] | time [min] | conversion [%][a] | purity [%][b] | yield [%][c] | isolated product [g] |
|---|---|---|---|---|---|---|---|
| 1 | 1 mmol | 2 | 30 | 50 | - | - | - |
| 2 | 1 mmol | 2 | 60 | 76 | - | - | - |
| 3 | 1 mmol | 2 | 90 | 89 | - | - | - |
| 4 | 1 mmol | 2 | 120 | 95 | 94 | 81 | 0.175 |
| 5 | 9 mmol | 18 | 120 | 94 | 92 | 87 | 1.68 |
| 6 | 0.325 mol | 650 | 120 | 99 | 61 | - | - |
| 7 | 0.3 mol | 600 | 90 | 100 | 79 | 58 | 37.5 |
| 8 | 0.3 mol | 600 | 60 | 74 | 73 | - | - |
| 9[d] | 0.3 mol | 600 | 120 | 99 | 94 | 83 | 53.8 |

[a] HPLC conversion at 215 nm. [b] Product purity in reaction mixture (HPLC at 215 nm). [c] Isolated yield. [d] Reaction mixture was degassed with nitrogen for 1 h prior to microwave heating.

needs to be heated for 2 h to obtain 95% conversion and thus 81% isolated yield after a simple precipitation/filtration workup procedure. Similar results were obtained for the medium scale-up at 9 mmol in the 30 mL vessel (87% yield, entry 5, Table 3). When going to the large-scale experiment at 0.325 mol in the Masterwave BTR applying identical reaction conditions as in small-scale (250 °C, 2 h), indeed a 99% conversion was observed; however, the product purity in the reaction mixture was only 61% (entry 6, Table 3). We initially ascribed this finding to the somewhat longer total reaction time of 2 h 30 min, compared to 2 h 8 min on the 1 mmol scale, indicating that this NKR is rather sensitive to prolonged time at high temperatures, leading to increased formation of impurities. As a first resolution, we reduced the reaction time to 1 h 30 min, which resulted again in full conversion and in an increased purity to 79%, but still the isolated yield was only 58% and thus not satisfactory (entry 7, Table 3). A further time reduction to 1 h only provided 74% conversion. To probe if the longer exposure time at higher temperatures leads to product decomposition, we performed a control experiment on 1 mmol scale for longer reaction times, but even after 4 h heating at 250 °C, the product purity did not decrease below 87%. Our next approach to improve the purity on large scale was to degas the NMP solvent to remove oxygen from the reaction mixture, which is known to improve the purity profile in the NKR, in particular when the reaction is slow and dilute and the solvent more reactive at high temperatures.[30] By performing the NKR again at 250 °C for 2 h with prior degassing of the reaction mixture for ca. 1 h, nearly full conversion could be now obtained, with a product purity of 94% and an isolated yield of 83% (entry 9, Table 3). Apparently, while degassing is not required on small scale using standard Pyrex vessels, it appears to be essential when performing the reaction on larger scale (0.3 mol, 600 mL) in a PTFE reaction vessel.

**Benzimidazole Synthesis.** The next model reaction for probing the instrument's heating efficiency was the generation of 2-methylbenzimidazole (**4**) by condensation of *o*-phenylenediamine with acetic acid (Table 4) since this reaction also requires high temperatures to reach completion in an acceptable time frame, comparable to the Newman−Kwart rearrangement. Benzimidazoles are an important class of heterocycles, and the scaffold is contained in numerous biologically active substances.[31] Although several

**Table 4. Comparison of the Scale-Up for the 2-Methylbenzimidazole Synthesis**




| entry | scale | reaction volume [mL] | yield [%][a] | isolated product [g][b] |
|---|---|---|---|---|
| 1 | 10 mmol | 2.5 | 85 | 1.12 |
| 2 | 80 mmol | 20 | 86 | 9.04 |
| 3 | 2.5 mol | 630 | 91 | 300 |

[a] Isolated yield. [b] Purity ≥99% by HPLC (215 nm).

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.[31] A number of microwave-assisted protocols have already been reported in the literature.[32,33]

A scale-up study for the microwave-assisted synthesis of 2-methylbenzimidazole in a 16-vessel rotor system using the Synthos 3000 instrument (Anton Paar) was recently reported by Kappe and co-workers.[16] A total volume of ~960 mL (3.6 mol) was processed providing an overall combined benzimidazole product yield of 466 g. Although the reaction time is only 5 min at 200 °C, the overall processing time was 50 min, not taking into account the time required to fill, manipulate, close, and open all 16 individual vessels. A kinetic study was performed on small-scale as well, indicating that the reaction could be performed at 270 °C (~29 bar internal pressure) with only 1 s hold time.[16]

We adapted the conditions from this kinetic study for our scale-up evaluation, however, with a decrease in temperature to 250 °C and a slight increase of the nominal hold time to 4 s (Table 4). Note that in the original work a temperature of 200 °C (~10 bar pressure) was selected for the scale-up study since most sealed-vessel microwave instruments do not allow processing above 20 bar of pressure.[3] To increase throughput, a concentration of 5 M was employed. Even at this rather high concentration level the reaction mixture was still homogeneous and not too viscous for microwave processing using magnetic stirring as the agitation method in the small (10 mmol, 2.5 mL) and medium


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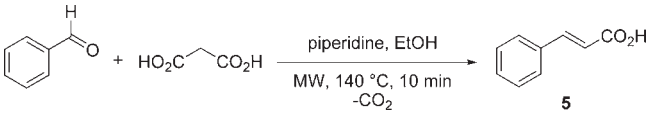
**Table 5. Comparison of the Scale-Up for the Synthesis of Cinnamic Acid via the Knoevenagel Condensation**




| entry | scale | reaction volume [mL] | yield [%][a] | isolated product [g][b] |
|---|---|---|---|---|
| 1 | 5 mmol | 3 | 85 | 0.631 |
| 2 | 15 mmol | 10 | 89 | 1.98 |
| 3 | 0.5 mol | 325 | 86 | 64.1 |

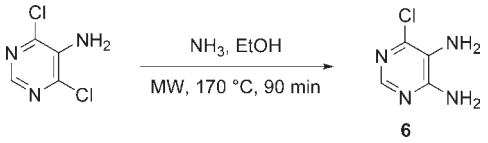
[a] Isolated yield. [b] Purity ≥99% by HPLC (215 nm).

scale (80 mmol, 20 mL). Since acetic acid has a reasonably high loss tangent (tan $\delta$ = 0.174),[22] microwave dielectric heating is comparatively efficient for this transformation. The high-field density Monowave 300 enabled short ramp times of ~0.5−1.5 min for reaching 250 °C for the small and medium scale. The large batch reactor heated the reaction mixture of 630 mL to this temperature in around 7 min by using the full 1700 W magnetron power for ca. 5 min, leading to a total reaction time of 34 min, including cooling to 60 °C. A maximum pressure of 26 bar was reached for a short period during the reaction. A slightly higher yield was achieved on the large scale, 91% compared to 85% and 86% on the 10 and 80 mmol scale, respectively, but still the outcome can be considered in good agreement (see Table 4). From the largest scale experiment at 2.5 mol (630 mL), 300 g of the benzimidazole product **4** was isolated. Although this is a somewhat lower throughput compared to the previous microwave scale-up experiment employing a multivessel rotor system (16 × 60 = 960 mL volume),[16] in the present scale-up experiment only one reaction vessel needs to be manipulated which is a distinct benefit over the multivessel rotor approach.

**Knoevenagel Condensation.** Although there have been a number of reports on microwave-assisted open vessel Knoevenagel reaction protocols (mostly using domestic microwave ovens),[1,34] only one closed vessel microwave procedure has so far been reported.[3,35] With this sealed vessel method, cinnamic acid (**5**) was prepared via the Doebner modification of the Knoevenagel condensation by reacting benzaldehyde and malonic acid with piperidine as base at 140 °C for 10 min (Table 5). In this case, one equivalent of gaseous $CO_2$ is released, and thus care has to be taken when deciding on the reaction scale since enough headspace needs to be left for the pressure buildup in order not to exceed the pressure limit of the instrument. We considered the Knoevenagel−Doebner condensation as a suitable model reaction to test the performance of the Masterwave BTR under high pressure over a longer period, close to the pressure limit of 30 bar. An additional aspect to take into account was the behavior of the pressure release mechanism since a substantial amount of overpressure is left after the cooling phase.

By employing the original protocol[3,35] of 4 mmol benzaldehyde, 1.5 equiv of malonic acid, and piperidine in 1 mL of EtOH in the 10 mL microwave vial, a maximum pressure of 15.3 bar was recorded at 140 °C and 10 min reaction time (Monowave 300), while full conversion was achieved (HPLC at 215 nm). Since the pressure limit of 30 bar was not reached, we scaled the reaction up to 5 mmol with 2 mL of solvent after calculating the expected pressure using the ideal gas law ($pV = nRT$). At this scale, the maximum pressure observed was 26.5 bar, so no further scale-up was possible considering the pressure limit of the instrument. A 3-fold increase in scale for the 30 mL vial was performed; also here the maximum attained pressure was 26.5 bar, and full conversion was achieved similar to the smaller scale experiment. Before we proceeded to the 1 L vessel, the possible maximum pressure was calculated again and resulted in 24.5 bar for a 100-fold scale-up to 0.5 mol scale, which was in fact identical to the pressure observed in the actual experiment (24 bar). Due to the pressure generated during the condensation, a comparatively low filling volume of 325 mL for the 1 L vessel was employed, thus allowing a scale-up from 631 mg to 64.1 g isolated cinnamic acid (Table 5).

**Table 6. Comparison of the Scale-Up for the Synthesis of 4,5-Diamino-6-chloro-pyrimidine (6)**




| entry | scale [mmol] | reaction volume [mL] | yield [%][a] | isolated product [g][c] |
|---|---|---|---|---|
| 1 | 305 | 400 | 86 | 38 |
| 2 | 366 | 540 | n.d.[b] | n.d.[b] |
| 3 | 366 | 540 | 87 | 92 |

[a] Isolated yield. [b] Entry 2 was worked up together with entry 3. [c] Purity ≥99% by HPLC (215 nm).

The integrated hydraulic system of the instrument's cover releases the formed carbon dioxide smoothly without loss of vessel content. The workup procedure involved a precipitation step with 1 M HCl, followed by filtration, and hence product yields for all three examples were virtually identical and comparable with the original reference,[3,35] ranging from 85 to 89% (see Table 5).

**$S_NAr$ with Ammonia.** The $S_NAr$ reaction shown in Table 6 was selected as another example for performing chemistries under high pressure close to the instrument limit of 30 bar, now for prolonged reaction times of more than one hour. In an earlier work, we investigated the synthesis of diamino pyrimidine **6** on an 80 g scale using a Synthos 3000 microwave reactor.[9] This $S_NAr$ reaction is described in the literature on a 5 g scale using ammonia in ethanol in a sealed tube under pressure for 6 h at 125−130 °C with a yield of 76%.[36] We were able to find suitable microwave conditions at 170 °C for 3 h, giving a yield of 83%. Since we knew that during this reaction a high pressure is generated, we chose this substitution reaction to test the performance under relatively harsh conditions (high temperature and high pressure). Further objectives were to test the stirring of suspensions and reproducibility when two or more batches were performed one after another to produce compound **6** on a multihundred gram scale. As shown in Table 6, 170 g of 5-amino-4,6-dichloropyrimidine was reacted with ammonia in EtOH at 170 °C in three batches. In a first run (entry 1), we started with a reaction time of 90 min and a reaction volume of 400 mL and got full conversion to pyrimidine **6** which was isolated after workup in 86% yield. For a further scale-up, two identical batches with a volume of 540 mL each were performed under the same conditions (entries 2 and 3); reaction monitoring by HPLC showed again full conversion for both batches. In total, 130 g of pyrimidine **6** was obtained with a total processing time of less than 6 h and an overall yield of 87%. Compared to the reaction in the Synthos 3000 where


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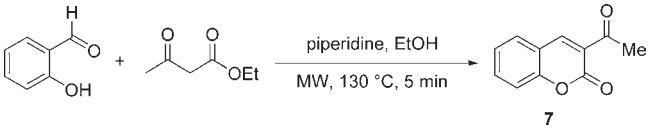
**Table 7. Comparison of the Scale-Up for the Synthesis of 3-Acetylcoumarin**




| entry | scale | reaction volume [mL] | yield [%][a] | isolated product [g][b] |
|---|---|---|---|---|
| 1 | 3 mmol | 2 | 71 | 0.63 |
| 2 | 30 mmol | 20 | 78 | 1.98 |
| 3 | 0.60 mol | 400 | 72 | 80.9 |
| 4 | 0.84 mol | 560 | 73 | 115 |
| 5 | 1.08 mol | 720 | 71 | 145 |

[a] Isolated yield. [b] Purity ≥99% by HPLC (215 nm).

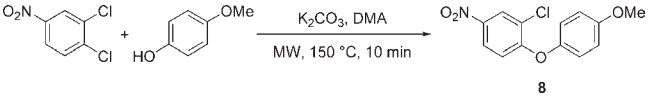
stirring was a limiting factor, we were able to decrease the overall processing time and to increase the productivity significantly.

**3-Acetylcoumarin Synthesis.** Coumarins have attracted intense interest in recent years because of their diverse pharmacological properties; furthermore, they can be prepared using a number of synthetic routes,[37] including microwave heating.[38] Since the Leadbeater group has explored the condensation of salicylaldehyde with ethyl acetoacetate to form 3-acetylcoumarin (7, see Table 7) across a range of scales (up to 18 mol) and in a number of commercial microwave units, including reaction optimization using in situ Raman reaction monitoring,[10,11,39] we have selected this reaction for our reproducibility study at different scales and filling volumes in the Masterwave BTR. In addition, the reaction is homogeneous throughout its course, and the starting materials are readily available and inexpensive.

As a starting point we have performed this transformation according to the original small-scale procedure on a 3 mmol scale using 1 mol % of piperidine catalyst, ethanol as solvent at a concentration of 1.5 M, and heating at 130 °C for 20 min.[10] A 61% isolated yield, which was somewhat lower compared to the Leadbeater protocol, was obtained after a simple filtration step, since the product precipitated directly upon cooling. To reduce the reaction time while maintaining the reported yield, we performed some additional optimization studies. First we increased the temperature up to 140 and 150 °C together and shortened the reaction time to 10 min. However, these modifications only resulted in decreased conversions (73% at 130 °C, 66% at 140 °C, 63% at 150 °C). The next step was to increase the piperidine concentration, and we discovered that 3 mol % is sufficient to reduce the reaction time to 5 min at 130 °C while obtaining a higher isolated yield (71%).

With these reoptimized reaction conditions for the synthesis of 3-acetylcoumarin (Table 7) in hand, we started our scale-up experiments. The transformation was performed on three scales: 0.6, 0.84, and 1.08 mol, which covered filling volumes ranging from low (400 mL), medium (560 mL), to the maximum permitted volume[20] for EtOH at 130 °C (720 mL). The synthesis of 3-acetylcoumarin proved to be very scalable and reproducible, affording isolated yields of 72%, 73%, and 71%, respectively, at the three reaction scales (Table 7). It may be noted that to avoid a spilling of the reaction mixture at very high filling volumes into the cavity during the cooling and pressure release phase it is advisible to reduce the stirring speed to 300−400 rpm under these conditions.

**Table 8. Comparison of the Scale-Up for the $S_NAr$ of 1,2-Dichloro-4-nitrobenzene with 4-Methoxyphenol**



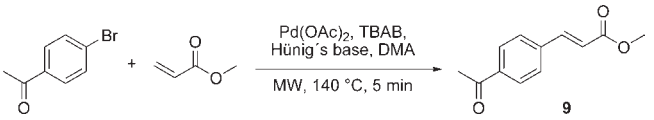

| entry | scale [mmol] | reaction volume [mL] | yield [%][a] | isolated product [g][c] |
|---|---|---|---|---|
| 1 | 1 mmol | 2 | 87 | 0.244 |
| 2 | 8 mmol | 16 | 37[b] | n.d. |
| 3 | 7 mmol | 14 | 44[b] | n.d. |
| 4 | 6 mmol | 12 | 44[b] | n.d. |
| 5 | 5 mmol | 10 | 97 | 1.36 |
| 6 | 0.20 mol | 400 | 97 | 54.4 |
| 7 | 0.315 mol | 630 | 98 | 86.5 |

[a] Isolated yield. [b] Conversion according to HPLC analysis at 215 nm. [c] Purity ≥96% by HPLC (215 nm).

**$S_NAr$ with 4-Methoxyphenol.** The $S_NAr$ reaction shown in Table 8 for the synthesis of diphenyl ether **8** has proven to be a perfect probe in the past for the evaluation of large-scale microwave reactors[17,40] since it is very reliable under standard procedures; any failure in the reaction is, therefore, normally indicative of instrumentation issues.[41] Furthermore, the reaction progress is dependent solely on the temperature since there is no catalyst or initiation period and no evidence of a special microwave effect was found.[40] In addition, the reaction of 3,4-dichloronitrobenzene with 4-methoxyphenol is heavily heterogeneous due to the presence of an inorganic base ($K_2CO_3$) suspended in the polar aprotic solvent DMA. For example, when probing this $S_NAr$ reaction in a continuous flow or stop-flow scaling-out procedure, the solid $K_2CO_3$ had to be exchanged for a soluble organic base.[8c,40] This heterogeneity was a crucial factor in our decision for selecting this transformation for testing the stirring efficiency on larger scales. As it is known, inefficient agitation has a significant implication for microwave-heated reactions, even for homogeneous mixtures, but more gravely when heterogeneous or viscous mixtures are processed, since it leads to temperature gradients within the reaction mixture due to field inhomogeneities in the microwave cavity and thus to misleading presumptions towards possible nonthermal microwave effects.[28]

The original conditions from previous reports were to heat 3,4-dichloronitrobenzene with 1.1 equiv of 4-methoxyphenol in DMA, slurried with 1.5 equiv of $K_2CO_3$ (−325 mesh) at 140 °C for 10 min (Table 8).[17] On cooling and upon addition of water, the diaryl ether product **8** could be readily obtained by filtration. Since stirring was an important issue in this study, the small-scale experiments in the 10 and 30 mL vials were additionally controlled via a built-in prototype camera of the Monowave 300. In our hands, at 1 mmol scale using 2 mL of DMA a 92% conversion was achieved at 150 °C (Table 8), providing an 87% isolated yield of diphenyl ether **8**. The stirring of the reaction mixture at 600 rpm seemed to be efficient for this scale and filling volume according to online monitoring with the built-in camera. Moving to the 30 mL vial it was found that proper agitation of the $K_2CO_3$ slurry—resulting in high conversion—could be obtained using up to 10 mL of solvent (Table 8, entry 5). On higher scale, difficulties in the magnetic stirring were observed resulting in poor conversion (Table 8, entries 2−4).[42]

**Table 9. Comparison of the Scale-Up for the Synthesis of Methyl Cinnamate 9 via the Heck Reaction**




| entry | scale | reaction volume [mL] | yield [%][a] | isolated product [g][b] |
|---|---|---|---|---|
| 1 | 1 mmol | 2 | 86 | 0.176 |
| 2 | 9 mmol | 21 | 90 | 1.66 |
| 3 | 0.25 mol | 590 | 91 | 46.5 |

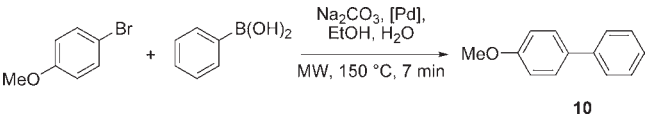
[a] Isolated yield. [b] Purity ≥99% by HPLC (215 nm).

For our tests in the Masterwave BTR, we first decided to perform the reaction on a 0.2 mol scale in 400 mL of DMA. Full conversion was obtained after 10 min at 150 °C, and diaryl ether **8** was isolated in 97% yield. These results encouraged us to go to even larger scales, and not surprisingly, similar results could also be achieved in the higher volume range of 630 mL on a 0.315 mol scale. Here, the product yield was 98%, delivering 86.5 g of diaryl ether **8**. Apparently, the mechanical paddle agitator in the Masterwave BTR is capable to stir even severely heterogeneous reaction mixtures, which may otherwise be difficult to process when stirring has to be conducted via magnetic stirring using stir bars.

**Heck Reaction.** The Heck reaction, the palladium-catalyzed arylation and vinylation of olefins, was discovered about 30 years ago and has since become an important C−C coupling reaction in organic synthesis, due to its high chemoselectivity and mild reaction conditions.[43] Furthermore, transition-metal-catalyzed coupling reactions of this type have seen an increase in utility by pharmaceutical companies over the past 20 years.[44] Therefore, it is not surprising that microwave heating has been used regularly as a tool in Heck coupling reactions with significant success.[45,46] In particular, the Leadbeater group has extensively examined this transformation introducing a ligandless low Pd-catalyst loading protocol (0.5−10 ppm) that uses water as solvent.[47] Since then, several scale-up studies utilizing a variety of scientific microwave instruments have been performed covering scale-up in closed vessels (up to 2 mol),[10,11,13,17,18] in open vessels,[48] and in flow/stop-flow mode.[10,20,29,49]

For the present scale-up investigation involving the Heck reaction of 4-bromoacetophenone with methyl acrylate catalyzed by $Pd(OAc)_2$ to provide cinnamate ester **9** (Table 9), the reaction conditions reported by Moseley and Woodman were adapted.[17] These conditions were slightly different from the aqueous conditions initially reported by Leadbeater,[47] employing DMA as the solvent in combination with Hünig's base, leading to a completely homogeneous reaction mixture, with the Pd catalyst at low concentration levels being soluble in DMA and further solubilized by the phase transfer catalyst tetrabutylammonium bromide (TBAB). When performing the reaction using 1 mmol 4-bromoacetophenone, 1.05 equiv of methyl acrylate, 1.5 equiv of Hünig's base, 0.1 mol % $Pd(OAc)_2$, and 0.4 mol % (TBAB) in 2 mL of DMA at 140 °C for 2 min, a 72% HPLC conversion was obtained. To reach a higher conversion of 97% (86% isolated yield after a precipitation/filtration workup, see Table 9), we had to increase the reaction time to 5 min. When moving to the 30 mL vessel on a 9 mmol scale a similar isolated yield of 90% was achieved. For further scaling of this transformation to the 0.25 mol level, the reaction was conducted in the Masterwave BTR under identical reaction conditions using 500 mL of DMA. Also in this case, we were able to isolate the product in 91% yield, which confirmed the excellent scalability of this Heck coupling,

**Table 10. Comparison of the Scale-Up for the Suzuki−Miyaura Cross-Coupling of 4-Bromoanisole and Phenylboronic Acid**




| entry | scale | reaction volume [mL] | yield [%][a] | isolated product [g][b] |
|---|---|---|---|---|
| 1 | 1.3 mmol | 2 | 99 | 0.237 |
| 2 | 10.4 mmol | 18 | 98 | 1.88 |
| 3 | 0.182 mol | 320 | 96 | 32.3 |

[a] Isolated yield. [b] Purity ≥97% by HPLC (215 nm).

**Suzuki−Miyaura Reaction.** As another example for a transition-metal-catalyzed C−C bond constructing reaction we have chosen the Suzuki−Miyaura cross-coupling.[50] As the resulting biaryl motif is found in a range of pharmaceuticals, herbicides, and natural products, as well as in conducting polymers and liquid crystalline materials, development of improved conditions for the Suzuki−Miyaura reaction has received much attention. Similar to the Heck reaction, the Leadbeater group has devoted considerable effort to the development of microwave-assisted protocols for performing Suzuki−Miyaura reactions in water (or in an ethanol−water mixture) as a solvent and in the presence of "homeopathic" quantities (<5 ppm) of palladium catalysts.[51,52] The power and usefulness of this protocol become increasingly evident at larger scales, as the use of inexpensive solvents, the elimination of expensive phosphine ligands, and the very low palladium loadings make this coupling economically feasible. Therefore, numerous microwave-assisted scale-up studies in open[13,24,53] and closed vessels[10,11] as well as in flow format[54] have so far been reported.

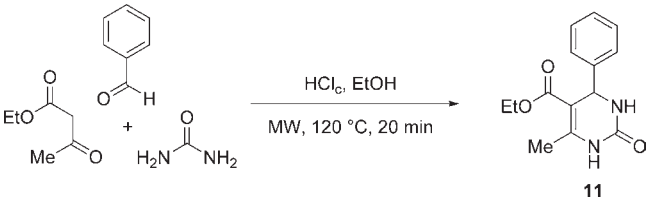
For the small-scale Suzuki−Miyaura cross-coupling of 4-bromoanisole with phenylboronic acid (Table 10), we applied the reaction conditions previously optimized by our group.[25a] This protocol, which was only slightly modified compared to the original Leadbeater conditions,[51,52] also uses a very low Pd concentration of merely 0.0006 mol %. By heating 1.2 mmol of 4-bromoanisole, phenylboronic acid (1.2 equiv), and $Na_2CO_3$ as base (1 equiv), in ethanol/water 5:3 as solvent together with the Pd catalyst at 150 °C for 7 min (Table 10), a nearly quantitative (99%) yield of isolated pure biaryl product **10** was obtained (see Table 10). On a 10-fold increase in scale, a virtually identical yield of 98% was achieved. For the large-scale Masterwave BTR experiment—mainly for economical reasons—we decided to stay at the lower filling volume limit, which on the other hand allowed us to evaluate the stirring and general instrument performance of the instrument at low volumes. By translating the reaction conditions to a 0.182 mol scale (total filling volume of 320 mL), biaryl **10** was isolated in 96% yield (32.3 g), which demonstrated the excellent scalability and stirring performance also at very low filling volumes (Table 10).

**Biginelli Dihydropyrimidine Synthesis.** A direct and simple method for the synthesis of dihydropyrimidines (DHPMs) is the Biginelli multicomponent reaction (MCR), a one-pot

cyclocondensation of a β-ketoester, aldehyde, and (thio)urea under acidic conditions in a solvent such as ethanol, which was first reported by Biginelli in 1893.[55,56] The obtained multifunctionalized DHPM derivatives exhibit a broad range of interesting pharmacological properties which has led to the development of a number of lead compounds based on that structural core.[56−59]

As a model reaction for our scale-up study, we selected the standard Biginelli cyclocondensation, where equimolar amounts of benzaldehyde and urea react with 1.5 equiv of ethyl acetoacetate under acid catalysis to the corresponding DHPM **11** (Table 11). In recent protocols Lewis acid catalysts like $Yb(OTf)_3$,[57,59] $LaCl_3$ for 2-thio-DHPMs,[60] or TMSCl (trimethylsilyl chloride)[61] proved to be superior compared to the traditionally utilized HCl. However, as the scale increases, the use of lanthanide catalysts becomes rather costly; hence, for a closed-vessel scale-up investigation 20 mol % HCl[10] or $FeCl_3$[18] has been used as alternatives. In the past, we have described in detail several high-yielding and rapid microwave-assisted protocols that allow the synthesis of gram quantities of DHPMs utilizing controlled single-mode microwave irradiation.[18]According to the reaction conditions reported in these protocols, we synthesized DHPM **11** on a 4 mmol scale at 120 °C within 20 min employing 20 mol % HCl as catalyst. The product precipitated directly upon cooling and could be isolated in 51% yield (Table 11), which was comparable with previous results obtained by Leadbeater and co-workers.[10] Similar yields were achieved when performing the Biginelli reaction on medium scale (26 mmol, 53%) and large scale (0.9 mol, 55%), showing again the excellent scalability when going from small to large scales. By employing the 1 L vessel, we took advantage of the highest possible recommended filling volume[20] when using EtOH as solvent of ca. 720 mL, therefore providing 129 g of the product.

**Table 11. Comparison of the Scale-Up for the Biginelli Multicomponent Dihydropyrimidine Synthesis**




| entry | scale | reaction volume [mL] | yield [%][a] | isolated product [g][b] |
|---|---|---|---|---|
| 1 | 4 mmol | 3 | 51 | 0.529 |
| 2 | 26 mmol | 21 | 53 | 3.56 |
| 3 | 0.9 mol | 720 | 55 | 129 |

[a] Isolated yield. [b] Purity ≥98% by HPLC (215 nm).

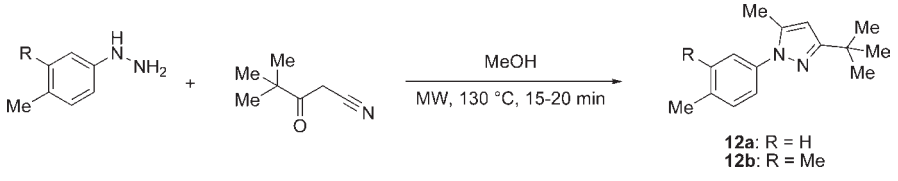
**Aminopyrazole Synthesis.** The formation of aminopyrazoles as shown in Table 12 is part of the synthesis of p38 MAP kinase inhibitors described in the literature with a yield of 60−85% after refluxing in toluene for 24 h.[62] We recently investigated this reaction under microwave conditions and optimized the scale-up to greater than 100 g scale using a Synthos 3000 microwave batch reactor.[9] To compare the performance of the Masterwave BTR especially with focus on reproducibility and productivity, we performed two reactions using different arylhydrazines on various scales. The reaction of *p*-tolylhydrazine and pivaloylacetonitrile was tested first on a 0.25 mol scale in 400 mL of MeOH (entry 1, Table 12) with a reaction time of 20 min at 130 °C. The conversion to product was checked by HPLC and showed no starting materials left. Under the same conditions, we then converted 1 mol of *p*-tolylhydrazine into pyrazole **12a** in two batches with 700 mL of reaction volume each and compared the data for each run (entries 2 and 3, Table 12). The time required for heating and cooling was more or less identical for each run, and reaction control by HPLC showed full conversion for both. All three batches were then combined and worked up together giving 272 g of product **12a** in a total yield of 82% and an overall processing time of less than 2 h.

Similar results were obtained for the cyclization of 3,4-dimethyl phenylhydrazine and pivaloylacetonitrile to give pyrazole **12b**. Again, we started the scale-up on a 0.23 mol scale in 400 mL of methanol (15 min reaction time at 130 °C) followed by two runs on a 0.5 mol scale in 650 mL of MeOH (entries 4−6, Table 12). At the end, 282 g of pyrazole **12b** could be isolated with an average yield of 82%. The overall processing time for all three runs was below 2 h which makes it possible to produce these pyrazoles in quantities of several hundred grams per day.

## CONCLUSION

In summary, we have investigated the scope for the scale-up of several organic transformations using a commercially available bench-top batch microwave reactor.[63] The Masterwave BTR

**Table 12. Comparison of the Scale-Up for the Cyclization of Aryl Hydrazines with Pivaloylacetonitrile**




| entry | R | scale [mol] | time [min] | reaction volume [mL] | yield [%][a] | isolated product [g][c] |
|---|---|---|---|---|---|---|
| 1 | H | 0.25 | 20 | 400 | n.d.[b] | n.d.[b] |
| 2 | H | 0.5 | 20 | 700 | n.d.[b] | n.d.[b] |
| 3 | H | 0.5 | 20 | 700 | 82[b] | 272[b] |
| 4 | Me | 0.23 | 15 | 400 | 88 | 57 |
| 5 | Me | 0.5 | 15 | 650 | 78 | 109 |
| 6 | Me | 0.5 | 15 | 650 | 82 | 116 |

[a] Isolated yield. [b] Entries 1−3 were worked up together. [c] Purity ≥99% by HPLC (215 nm).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provides a 1 L single reaction vessel capable of processing volumes from 250 mL up to 750 mL and has operating limits similar to most common single-mode instruments (250 °C/30 bar).

A range of solvents (high and low microwave absorbing) were tested in an initial study, highlighting the excellent heating efficiency of the instrument,[64] with ramp times of 3−10 min to the desired temperature depending on the filling volume and absorptivity of the solvents. In general, a time period of approximately 15 min for the cooling step can be estimated, which also proved to be acceptable for these rather large volumes.

Although the total reaction time clearly increased on moving from small (single-mode) to large scale in the Masterwave BTR, very similar isolated yields and/or conversions were obtained for small- and large-scale experiments, indicating that the prolonged ramp and cooling times did not affect the efficiency of the scale-up format. In addition, heavily heterogeneous reaction mixtures—where problems occurred on medium scale due to inefficient stirring and thus incomplete conversions—can be processed without difficulty, as a result of the good performance of the paddle stirrer.

Importantly, most of the reactions could be scaled up in a direct fashion from small (2 mL processing volume) via medium (20 mL) to large scale (max. 720 mL), without changing the reaction conditions previously optimized on small scale in a single-mode microwave instrument. Therefore, reaction scales up to 2.5 mol (300 g) for a single run could be accomplished, allowing a daily output in the kilogram range for specific transformations, considering overall cycling times of <1 h.

## 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 8 min, hold at 100% solution B for 1 min. $^1$H NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts ($\delta$) are expressed in parts per million downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. All products synthesized in these studies are known in the literature, and most of them have been previously prepared and characterized in our laboratories using microwave-assisted protocols.

**Microwave Irradiation Experiments.** Small- and medium-scale microwave irradiation experiments were performed using a Monowave 300 single-mode microwave reactor (Anton Paar GmbH) using the standard 10 or 30 mL Pyrex vessel, respectively.[20,21] The reaction temperature was controlled by the FO probe (IR as slave), and stirring speed was set to 600 rpm. The *heat to temperature as fast as possible* mode was chosen for both instruments. For the large-scale experiments the Masterwave BTR with its 1 L PTFE reaction vessel was employed. Similar to the single-mode setup, starting materials have been weighed directly into the reaction vessel and diluted with the appropriate solvent. The readily assembled agitator was inserted and the vessel closed with its bayonet-lock cap after expanding its lip-type seal with the corresponding expansion tool. For optimum results, the stirring speed was set in accordance to the filling volume (rpm equals mL). For the utmost safety when processing large chemical quantities at elevated conditions, the Masterwave BTR must be installed inside a fume hood, and a connection to an appropriate expansion system must be assured. With the provided standard stainless steel tubing with standard Swagelok bulkhead fitting (∅ 10 mm), even a simple stainless steel barrel (ca. 50 L) can be connected as the minimum required expansion tank. In case of an overpressure venting action, the vessel's metal safety disk ruptures and empties the vessel content safely into the expansion tank.

**Diels−Alder Reaction of Anthracene with Maleic Anhydride on a 0.75 mol Scale (Table 2).** To the 1 L reaction vessel was added anthracene (0.75 mol, 134 g), maleic anhydride (0.75 mol, 74 g), and 600 mL of toluene. The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 200 °C for 2 min (ramp time 6.5 min). After cooling to 70 °C (25 min), the resulting precipitate was filtered and washed with ca. 450 mL of cold toluene. The precipitate was dried overnight at 50 °C, and the white cycloadduct **1** was obtained in 95% yield (196 g) and 97% purity by HPLC (215 nm). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$7.50−7.45 (m, 2H), 7.36−7.31 (m, 2H), 7.22−7.15 (m, 4H), 4.87 (brs, 2H), 3.65 (t, $J$ = 1.6 Hz, 2H).[25a]

**Synthesis of 4-Chlorophenyl-*S*-thiocarbamate (3) on a 0.3 mol Scale (Table 3).** To the 1 L reaction vessel was added 4-chlorophenyl-*O*-thiocarbamate (0.3 mol, 65 g) and 600 mL of NMP. The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 250 °C for 2 h (ramp time 5 min 40 s). After cooling to 70 °C (19.5 min), the reaction mixture was transferred to an Erlenmeyer flask and placed into an ice-bath. Cold water (1.5 L) was added slowly while stirring the reaction mixture vigorously. A precipitate was formed which was intensified by scratching with a glass rod. After further 1 h stirring in the ice-bath, the precipitate was filtered, washed with cold water, and dried overnight at 40 °C. The off-white *S*-thiocarbamate **3** was obtained in 83% yield (53.8 g) and 97% purity by HPLC (215 nm). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$7.50−7.43 (m, 4H), 2.98 (brd, $J$ = 30.2 Hz, 6H).[27c]

**Synthesis of 2-Methylbenzimidazole (4) on a 2.5 mol Scale (Table 4).** To the 1 L reaction vessel was added *o*-phenylenediamine (2.5 mol, 270 g) and 500 mL of acetic acid. The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 250 °C for 4 s (ramp time 7 min 20 s). After cooling to 60 °C (26 min), the reaction mixture was transferred to a round-bottom flask to evaporate the excess acetic acid under reduced pressure. A saturated aqueous $K_2CO_3$ solution (1 L) was added, and the resulting precipitate was filtered and washed with cold water until pH ∼ 7. After drying overnight at 50 °C the pink 2-methylbenzimidazole product (**4**) was obtained in 91% yield (300 g) and >99% purity by HPLC (215 nm). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$12.17 (brs, 1H), 7.44 (brs, 2H), 7.12−7.06 (m, 2H), 2.47 (s, 3H).[16]

**Synthesis of Cinnamic Acid (5) by Knoevenagel Condensation on a 0.5 mol Scale (Table 5).** To the 1 L reaction vessel was added benzaldehyde (0.5 mol, 51 mL), malonic acid (0.75 mol, 78 g), piperidine (0.75 mol, 74 mL), and 200 mL of EtOH. The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 140 °C for 10 min (ramp time 4 min). After cooling to 67 °C (8.5 min), the reaction mixture was poured into 1 L of water and acidified under stirring with 450 mL of 2 M HCl, whereupon a white precipitate was formed. The slurry was kept on an ice-bath for 30 min, and then the product was filtered and washed with 800 mL of cold


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water. After drying overnight at 50 °C, cinnamic acid (**5**) was obtained as white powder in 86% yield (64 g) and >99% purity by HPLC (215 nm). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$7.70−7.67 (m, 2H), 7.62 + 7.65 (ds, 1H), 7.42−7.39 (m, 3H), 6.56 + 6.51 (ds, 1H).[35]

**Synthesis of 4,5-Diamino-6-chloro-pyrimidine (6) on a 0.732 mol Scale (Table 6).** To the 1 L reaction vessel was added 5-amino-4,6-dichloro-pyrimidine (0.366 mol, 60 g) and a solution of 10% ammonia in EtOH (2.25 mol, 480 mL). The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 170 °C for 90 min (ramp time 4 min). After cooling to 65 °C (15 min 20 s), a precipitate was formed. In a second run, the same amounts were reacted under the same conditions (ramp time 4 min, cooling to 65 °C in 15 min 13 s). Both reaction mixtures were combined and worked up together. The precipitated solid was filtered, suspended again in water (250 mL), and stirred at ambient temperature for 30 min. The precipitate was filtered, washed with water, and dried overnight in vacuum at 50 °C to give compound **6** as a yellow solid (92 g, 87%) and a purity of 99% by HPLC (215 nm): mp 248−250 °C (decomp.) (lit.[36] 249−250 °C). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.65 (s, 1H), 6.76 (s, 2H), 4.95 (s, 2H).[9]

**Synthesis of 3-Acetylcoumarin (7) on a 1.08 mol Scale (Table 7).** To the 1 L reaction vessel was added salicylaldehyde (1.08 mol, 115 mL), ethyl acetoacetate (1.08 mol, 137 mL), piperidine (3 mol %, 32.4 mmol, 3.2 mL), and 468 mL of EtOH. The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 130 °C for 5 min (ramp time 4 min). After cooling to 70 °C (10 min 40 s), the resulting precipitate was cooled to room temperature, filtered, and washed with cold EtOH. After drying overnight at 50 °C the coumarin product **7** was obtained as a yellow solid in 71% yield (145 g) and 99% purity by HPLC (215 nm). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$8.66 (s, 1H), 7.97 + 7.94 (dd, $J1$ = 1.5 Hz, $J2$ = 7.7 Hz, 1H), 7.78−7.72 (m, 1H), 7.48−7.39 (m, 2H), 2.95 (s, 3H).[10]

**Synthesis of 2-Chloro-1-(4-methoxyphenoxy)-4-nitrobenzene (8) on a 0.315 mol Scale (Table 8).** 1,2-Dichloro-4-nitrobenzene (0.315 mol, 60.5 g) and 4-methoxyphenol (0.347 mol, 43 g) were dissolved in 630 mL of DMA in the 1 L reaction vessel by stirring with a stir bar. The stir bar was removed, $K_2CO_3$ (Sigma Aldrich 347825, −325 mesh, 0.473 mol, 65 g) added, the mechanical stirrer inserted, and the vessel closed with the screw-cap. The reaction mixture was heated at 150 °C for 10 min (ramp time 4 min). After cooling to 60 °C (14 min), the reaction mixture was transferred to an Erlenmeyer flask, and 630 mL of water was added slowly while stirring the reaction mixture vigorously. A precipitate was formed which was intensified by scratching with a glass rod. After further 1 h stirring in the ice-bath, the precipitate was filtered and washed with cold water. After drying overnight at 50 °C, the yellow product was obtained in 98% yield (87 g) and >99% purity by HPLC (215 nm). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$8.44 (d, $J$ = 2.75 Hz, 1H), 8.17 + 8.14 (dd, $J1$ = 2.8 Hz, $J2$ = 9.2 Hz, 1H), 7.21−7.15 (m, 2H), 7.08−7.03 (m, 2H), 6.92 + 6.89 (ds, 1H), 3.79 (s, 3H).[17,40]

**Synthesis of Methyl 4′-Acetyl-cinnamate (9) on a 0.25 mol Scale (Table 9).** 4-Bromoacetophenone (0.25 mol, 50 g) was dissolved in 425 mL of DMA in the 1 L reaction vessel. Methyl acrylate (0.263 mol, 24 mL) and *N*,*N*-diisopropylethylamine (0.375 mol, 65 mL) were added to this solution and thoroughly mixed. In a separate flask, tetrabutylammonium bromide (0.4 mol %, 1 mmol, 322 mg) and $Pd(OAc)_2$ (0.1 mol %, 0.25 mmol, 56 mg) were dissolved in 75 mL of DMA. This solution was added into the reaction vessel, the mechanical stirrer inserted, and the vessel closed with the screw-cap. The reaction mixture was heated at 140 °C for 5 min (ramp time 3 min). After cooling to 60 °C (15 min), any solid HBr salts were decanted. Subsequently, 700 mL of warm water was slowly added to the well-stirred mixture, whereupon a yellow precipitate was formed. The reaction mixture was cooled to room temperature by placing it in an ice-bath, and the precipitate was filtered, washed with 600 mL of cold water, and dried overnight at 50 °C. The cinnamate product **9** was obtained as a light yellow solid in 91% yield (46 g) and >99% purity by HPLC (215 nm). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$7.99−7.96 (m, 2H), 7.88−7.86 (m, 2H), 7.75 + 7.69 (ds, 1H), 6.82 + 6.76 (ds, 1H), 3.74 (s, 3H), 2.59 (s, 3H).[17]

**Synthesis of 4′-Methoxybiphenyl (10) on a 0.182 mol Scale (Table 10).** To the 1 L reaction vessel was added 4-bromoanisole (0.182 mol, 23 mL), phenylboronic acid (0.218 mol, 27 g), $Na_2CO_3$ (0.182 mol, 19 g), 182 mL of EtOH, 112 mL of water, and palladium stock solution (Sigma Aldrich 207349, 970 $\mu$g/mL of Pd in 5 wt % HCl, 0.0006 mol %, 1 $\mu$mol, 126 $\mu$L). The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 150 °C for 7 min (ramp time 3 min 20 s). After cooling to 60 °C (16 min 40 s), a white precipitate was formed which increased after cooling in an ice-bath for 1 h. The precipitate was filtered, washed with cold water, and dried overnight at 50 °C. The biphenyl product **10** was obtained as a white powder in 96% yield (32 g) and 97% purity by HPLC (215 nm). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$7.62−7.58 (m, 4H), 7.45−7.40 (m, 2H), 7.33−7.28 (m, 1H) 7.05−7.00 (m, 2H), 3.79 (s, 3H).[25a]

**Synthesis of Dihydropyrimidinone 11 on a 0.9 mol Scale (Table 11).** To the 1 L reaction vessel was added benzaldehyde (0.9 mol, 91 mL), ethyl acetoacetate (1.35 mol, 171 mL), urea (0.9 mol, 54 g), concentrated HCl (20 mol %, 0.18 mol, 5.5 mL), and 450 mL of EtOH. The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 120 °C for 20 min (ramp time 5 min). After cooling to 65 °C (12 min 20 s), a precipitate was formed. After cooling in an ice-bath for 1 h, the precipitate was filtered, washed with 900 mL of a mixture of cold water/EtOH 2:1, and dried overnight at 50 °C. The pyrimidine product **11** was obtained as a white powder in 55% yield (129 g) and 99% purity by HPLC (215 nm). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$9.19 (s, 1H), 7.74 (brs, 1H), 7.35−7.22 (m, 5H), 5.14 (d, $J$ = 3.1 Hz, 1H), 3.98 (q, $J$ = 7.1 Hz, 2H), 2.25 (s, 3H), 1.09 (t, $J$ = 7.1 Hz, 3H).[18]

**Synthesis of 5-*tert*-Butyl-2-*p*-tolyl-2*H*-pyrazol-3-ylamine (12a) on a 1.25 mol Scale (Table 12).** *p*-Tolylhydrazine hydrochloride (0.25 mol, 40 g) and pivaloylacetonitrile (0.325 mol, 41 g) were dissolved in MeOH (400 mL) and placed into the 1 L reaction vessel. The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 130 °C for 20 min (ramp time 2 min 55 s). After cooling to 55 °C (12 min 12 s), the reaction mixture was combined with run 2 and run 3 which were performed under the same conditions but on a 0.5 mol scale. After combining all three batches, the solvent was evaporated, and the remaining solid was suspended in diethyl ether (1000 mL). The suspension was cooled to 0 °C, stirred for 20 min, and filtered. After filtration and drying overnight in vacuum at 50 °C, 5-*tert*-butyl-2-*p*-tolyl-2*H*-pyrazol-3-ylamine **12a** was isolated as an off-white solid (272 g, 82%) and a purity of 99% by HPLC (215 nm): mp 196 °C (decomp.). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.36−7.50 (m, 4H), 5.67 (s, 1H), 2.38 (s, 3H), 1.29 (s, 9H).[9]

**Synthesis of 5-*tert*-Butyl-2-(3,4-dimethyl-phenyl)-2*H*-pyrazol-3-ylamine (12b) on a 0.5 mol Scale (Table 12).** 3,4-Dimethyl-phenylhydrazine hydrochloride (0.5 mol, 86 g) and pivaloylacetonitrile (0.65 mol, 81.4 g) were dissolved in MeOH (500 mL) and placed into the 1 L reaction vessel. The mechanical stirrer was inserted, and the vessel was closed with the screw-cap. The reaction mixture was heated at 130 °C for 15 min (ramp time 3 min 6 s). After cooling to 55 °C (14 min 44 s), the solvent was evaporated, and the remaining solid was suspended in diethyl ether (400 mL). The suspension was cooled to 0 °C, stirred for 20 min, and filtered. The crystalline solid was filtered and dried overnight in vacuum at 50 °C. Compound **12b** was isolated as a white solid (116 g, 82%) and a purity of 99% by HPLC (215 nm): mp 220 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.32−7.39 (m, 2H), 7.26−7.29 (m, 1H), 5.66 (s, 1H), 2.29 (s, 6H), 1.29 (s, 9H).[9]

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