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Microwave-assisted organic synthesis: scale-up of palladium-catalyzed aminations using single-mode and multi-mode microwave equipment

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Dedicated to the memory of Nancy Verhaert

Abstract—Batch wise scale-up of Buchwald–Hartwig aminations under microwave irradiation has been investigated for the first time. Multi-mode (microSYNTH and MARS) (several vessels irradiated in parallel per batch) as well as single-mode (Discover) (one vessel irradiated per batch) platforms can be successfully used for this purpose with trifluoromethylbenzene (benzotrifluoride: BTF) as amination solvent. The obtained yields indicate a direct scalability in BTF for all the studied aminations. The Voyager equipment (based on a Discover platform) is the most convenient system since it allows an automatic continuous batch wise production without the necessity to manually load and unload reaction vessels.

1. Introduction

Microwave-assisted organic synthesis (MAOS) is a rapidly growing subfield within the area of organic chemistry.[1] Since the first reports in the literature on MAOS in the mid eighties the number of annually published articles using microwave heating has increased continuously.[2] In the early days domestic microwaves were used, often giving only a poor reproducibility. Moreover, accidents were common due to the lack of control. This lack of control and reproducibility is partly responsible for the initial slow take up of microwave heating in organic syntheses. The introduction of dedicated equipment by Prolabo (closed down already), CEM, Milestone, Biotage (formerly Personal Chemistry), Plazmatronika and more recently by Anton Paar allowing the on-line monitoring of temperature, power and pressure had a large impact on the further development of this relatively young research field.[3] The latest trend is to use only microwave equipment designed for organic synthesis and to abandon scientific results for publication obtained using domestic microwaves. The organisation of annual workshops and conferences focusing on MAOS such as the 'MAOS meeting' in Graz and the 'International Microwaves in Chemistry Conference' in Orlando clearly support that microwave-assisted organic synthesis has now reached a mature scientific level. The growing interest, both from industry and academia, for such events indicates that the real impact of microwaves on the field of organic syntheses still has to come! Most of the chemistry hitherto performed in a dedicated microwave system has been executed on a small scale only. Single-mode microwaves are standardly used for this purpose, typically allowing the production of several hundred milligram quantities per run. One of the major current issues is the question whether microwave heating could be used to scale-up these reactions to gram and kilogram scale, preferentially without the requirement to reoptimize reaction parameters tuned for the small scale runs. For the scale-up purpose historically two different approaches, batch[4] and continuous-flow,[5] have been followed taking into account the physical limitations inherent to microwave equipment construction.[1h] Large batch reactors have been developed for a multi-mode or single-mode microwave platform. For these the most important drawback is the limited penetration depth of microwave irradiation. Alternatively, multi-mode equipment supplied with a rotor with several smaller vessels has been launched, which allows the use of a large total volume in one microwave run without the penetration depth issue. Besides batch approaches

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Keywords: Palladium; Homogeneous catalysis; Buchwald–Hartwig amination; Aryl chlorides; Multi-mode cavity; Single-mode cavity; Microwave irradiation.

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continuous-flow systems based on single-mode and multi-mode cavities have been used as well. The major limitation of these continuous microwave reactors is that they are unsuitable for heterogeneous mixtures and viscous liquids. Interestingly, reports on scale-up using dedicated microwave equipment in peer reviewed journals is hitherto rather limited. In particular more complex chemistry, such as transition metal catalyzed reactions, is hardly studied.[6] Based on the limited availability of more complex examples and the background of our research group, we decided to investigate the scale-up of Buchwald–Hartwig aminations under microwave irradiation using dedicated multi-mode (MicroSYNTH, MARS) and single-mode (Voyager) batch reactors.[7,8]

2. Description of microwave equipment used

2.1. Voyager[3]

The Voyager system (stop/flow system) of CEM is based on the Discover single-mode platform equipped with an 80 mL glass vessel (borosilicate), a peristaltic pump and two valves (Fig. 1). The system has a continuous unpulsed microwave output ranging from 0 to 300 W. The temperature in the vessel is controlled internally by a fiber optic probe. On-line pressure monitoring is also provided. The Voyager microwave is designed to automatically fill the 80 mL vessel with reagents (two stock solutions), seal the vessel, perform a microwave experiment, release the vessel, remove the reaction mixture from the vessel and subsequently clean it with solvent (even under microwave irradiation if desired) (Fig. 2). The liquid of the cleaning step can be collected separately via a waste line or can be added to the product if desired. We always chose the latter. The contents of the closed vessel can be released after a microwave experiment at a pre-programmed temperature and pressure (in our experiments we used 95 °C and 10 psi as vessel release parameters), which allows a serious increase of the throughput (number of cycles in a given timeframe) of the system. Cooling to the set temperature value is done using a propelled air flow. When the Voyager platform is based on an older type of Discover microwave an enhanced stirring device is standardly used. This device fits in the small cavity located at the bottom of the microwave cavity (on top of the IR sensor). It consists of a magnet at both ends of the bar, which couples with the magnetic stirring plate located at the bottom of the Discover

Figure 1. Voyager platform (**1**) and 80 mL glass vessel (**2**).

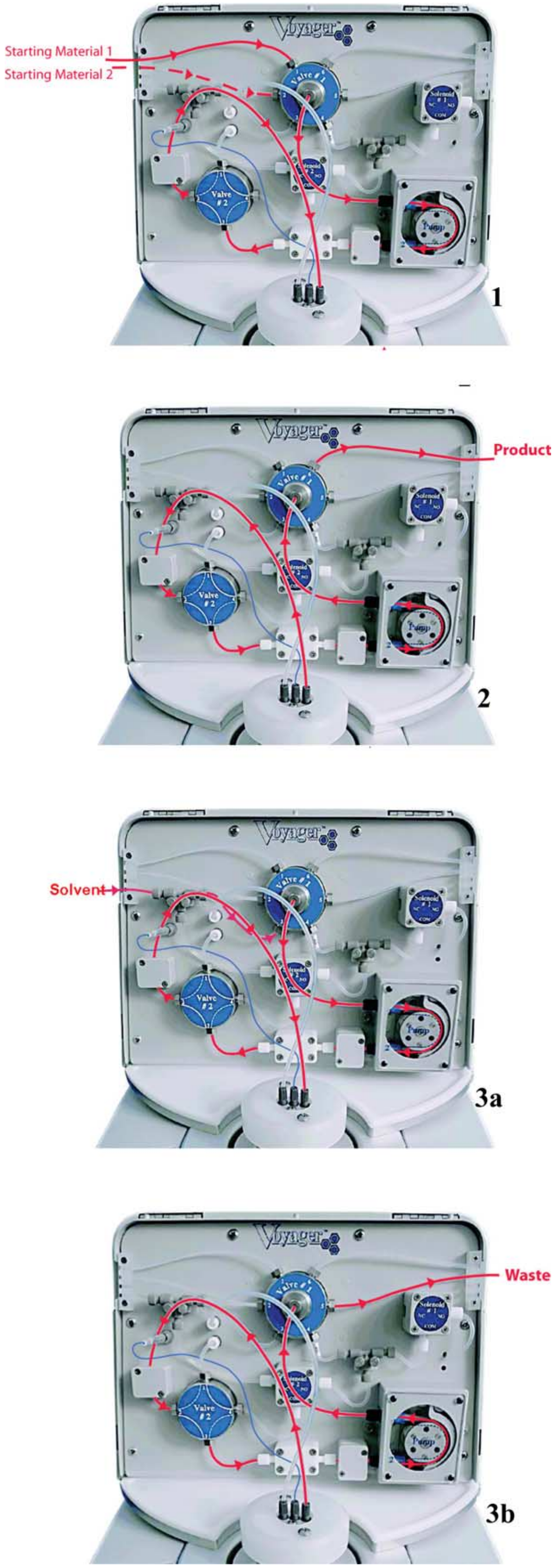


Figure 2. Add step (**1**), remove step (**2**) and clean vessel step (**3**) ((**3a**) fill with solvent, (**3b**) remove solvent to waste).

unit. Two more centrally located magnets couple with the stirring bar in the reaction vessel. The enhanced stirring device gives access to a microwave unit with a more powerful stirring capacity. All our experiments were done using this special device. Recent Discover units are equipped with electromagnetic stirring plates that deliver more stirring power in comparison with the older type of Discover unit. Therefore the enhanced stirring device is not used anymore in this newer unit.

2.2. MicroSYNTH[3]

The MicroSYNTH system of Milestone is a multi-mode platform equipped with a magnetic stirring plate and a rotor that allows parallel processing of several vessels per batch (Fig. 3). We used the high-pressure vessel assembly type based on a rotor with 10 vessel positions (teflon (TFM) inserts) (vessel volume 100 mL, max pressure 1450 psi, max temperature 300 °C). The system has two magnetrons that together deliver a maximum power output of 1000 W. The power supply of the magnetron is pulsed. Temperature is controlled internally by fiber optic probe in one control reference vessel. On-line pressure monitoring of the reference vessel is also provided. All rotor segments are protected by a reclosing (vent and reseal) relief valve mechanism. Additionally, the system is equipped with a solvent sensor detector safety feature. Cooling down of the rotor segments to room temperature is done by an air flow provided by the exhaust fan.

2.3. MARS[3]

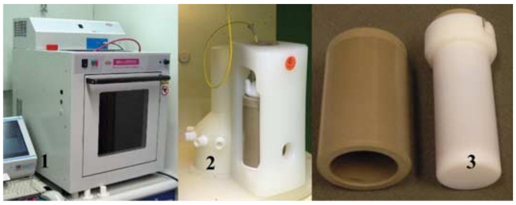


Figure 3. MicroSYNTH platform (**1**), control vessel rotor segment (**2**), high-pressure sleeve, insert and cap of a standard vessel assembly (**3**).

The MARS system of CEM is a multi-mode platform equipped with a magnetic stirring plate and a rotor that allows the parallel processing of several vessels per batch (Fig. 4). We used the HP-500 (teflon (TFA) insert) (vessel volume 80 mL, max pressure 350 psi, max temperature 210 °C) and Greenchem (glass (borosilicate) insert) (vessel volume 80 mL, max pressure 200 psi, max temperature 200 °C) vessel assembly types both based on a fourteen positions rotor. The system delivers a continuous power output between 0 and 1200 W. Temperature is controlled internally by fiber optic probe in one control reference vessel. On-line pressure monitoring of the reference vessel is also provided. All rotor segments are protected by a vent nut that contains a rupture membrane. Additionally, the system is equipped with a solvent sensor detector safety feature. Cooling down of the rotor segments to room temperature is done by an air flow provided by the exhaust fan.

3. Results

Recently our laboratory reported the rapid palladium-catalyzed amination of aryl chlorides under temperature controlled microwave heating using a CEM Discover single-mode microwave unit.[7c,71] In a reaction time of only 10 min using a relatively low catalyst loading (1 mol%) complete conversion of starting material and a good yield could be achieved for the coupling of both electron rich and electron neutral aryl chlorides with all types of amines (anilines, primary and secondary aliphatic amines). For the coupling of anilines and secondary cyclic aliphatic amines palladium precatalyst based on $Pd(OAc)_2$ and 2-(dicyclohexylphosphanyl)biphenyl[9] (DCPB) ligand worked smoothly while for the amination reactions using acyclic secondary and primary aliphatic amines $Pd(OAc)_2$ in combination with 2-(di-*t*-butylphospanyl)biphenyl[9] (DTPB) ligand was found to be optimal. All the reported examples were performed on a 1 mmol scale of aryl chloride allowing the production of hundred milligram quantities of *N*-substituted anilines.

First we investigated the direct scalability going from a 10 mL vessel to an 80 mL vessel in a Discover apparatus. We selected the coupling of electron rich 4-chloroanisole with morpholine, which we previously performed on a 1 mmol scale as a test case.[71] Unfortunately, running this reaction on a 20-fold scale (20 mmol 4-chloroanisole, 24 mmol morpholine, 28 mmol NaO*t*–Bu, 20 mL toluene) using the same microwave program (initial set power 300 W, 150 °C, 10 min (total reaction time including ramp time to set temperature)) as for the small scale reaction was unsuccessful. The reaction mixture heated up relatively slowly and the obtained final temperature after 10 min of microwave irradiation was only 128 °C, which is substantially lower than the desired set temperature of 150 °C. Consequently, an incomplete conversion of starting material and an isolated yield of 4-(4-methoxyphenyl)-morpholine of only 38% was obtained (Table 1). In contrast,

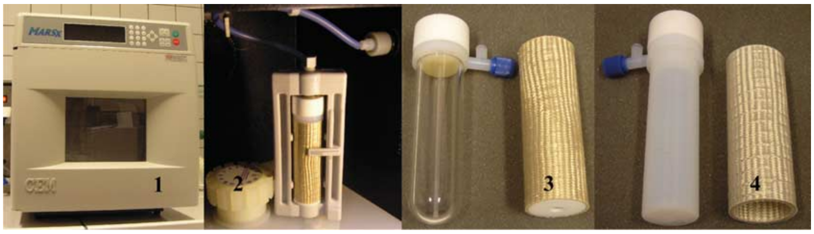
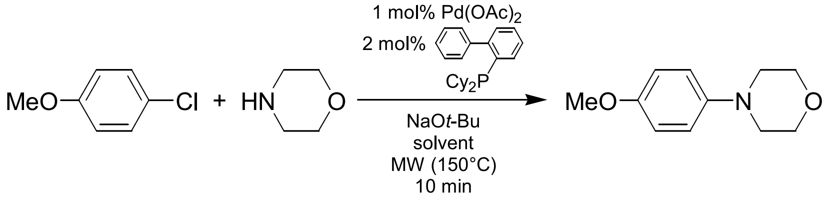


Figure 4. MARS platform (**1**), control vessel rotor segment (**2**), Greenchem insert, cap and sleeve of a standard vessel assembly (**3**) and HP-500 insert, cap and sleeve of a standard vessel assembly (**4**).

Table 1. Scale-up of the Pd-catalyzed amination of 4-chloroanisole with morpholine



Microwave	4-Chloroanisole (mmol)	Vessel		Initial set power (W)	Solvent	Yield (%)[a]
		Volume (mL)	Type			
Discover	1	10	Glass	300	Toluene	76
Discover	20	80	Glass	300	Toluene	38[b]
Mars	20	80	Greenchem	1200	Toluene	78
Discover	1	10	Glass	300	BTF	78
Discover	20	80	Glass	300	BTF	85
Voyager	3×20	80	Glass	300	BTF	78[c]
microSYNTH	6×20	100	High-Pressure	600	BTF	77[c]
Mars	6×20	80	Greenchem	600	BTF	80[c]

[a] 4-Chloroanisole (y mmol), morpholine ($1.2y$ mmol), NaO*t*-Bu ($1.4y$ mmol), toluene or BTF (y mL).
[b] 150 °C could not be reached in 10 min.
[c] Average yield.

for the 1 mmol scale experiment in a 10 mL vessel the set temperature was reached in 2 min allowing a full conversion of starting material in 10 min.[7l] Although polar reagents are present in the reaction mixture we realized the poor coupling characteristic of the solvent (tan δ toluene = 0.04) is responsible for the failure of the scale-up experiment.[10]

Due to this failure we became interested to investigate whether there is a substantial difference between single and multi-mode microwaves when solvents with low tan δ are used. Therefore, we performed power/time experiments (temperature is slave of the power) using 20 mL of pure toluene at full power in several commercial available microwave platforms (Discover, max power 300 W)[11] (MARS, max power 1200 W)[11] (microSYNTH, max power 1000 W)[11] (Fig. 5). The vessels used were either from glass (borosilicate) or teflon (PTFE or TFM). In all

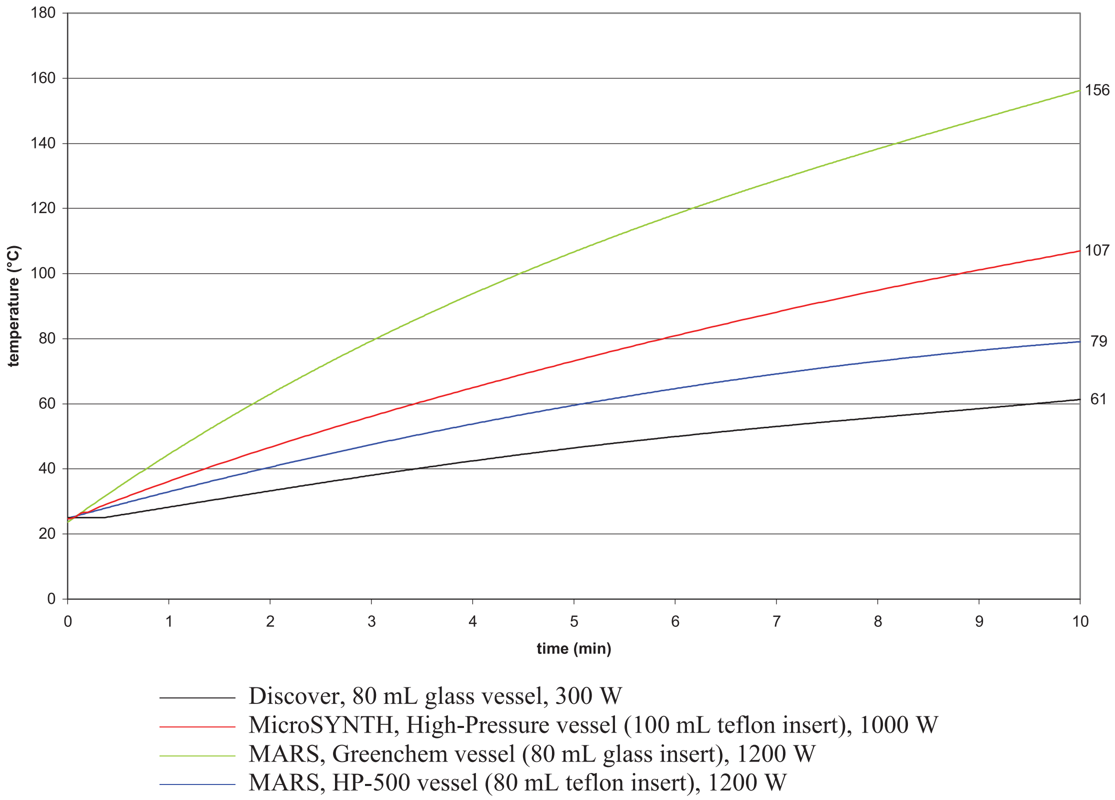


Figure 5. Heating profile of 20 mL of toluene in several commercial available microwave systems, irradiated in a power/time experiment at a constant maximum power output for 10 min.

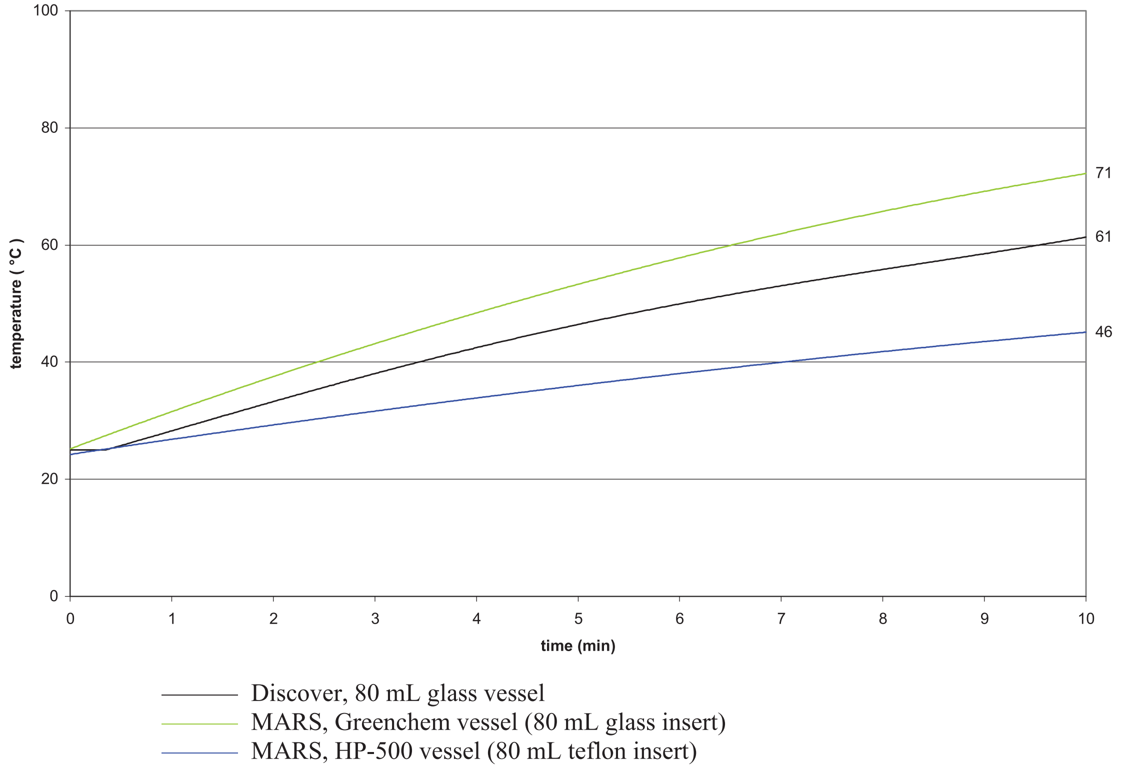


Figure 6. Heating profile of 20 mL of toluene in several commercial available microwave systems, irradiated in a power/time experiment at a constant power of 300 W for 10 min.

cases, the temperature was measured internally using a fiber optic probe. Interestingly, 20 mL of toluene could be heated to 156 °C in 10 min in a Greenchem vessel in the MARS platform. In contrast, 20 mL of toluene could only be heated to 61 °C in a similar 80 mL glass vessel in the Discover system. Important to mention is that even if the same

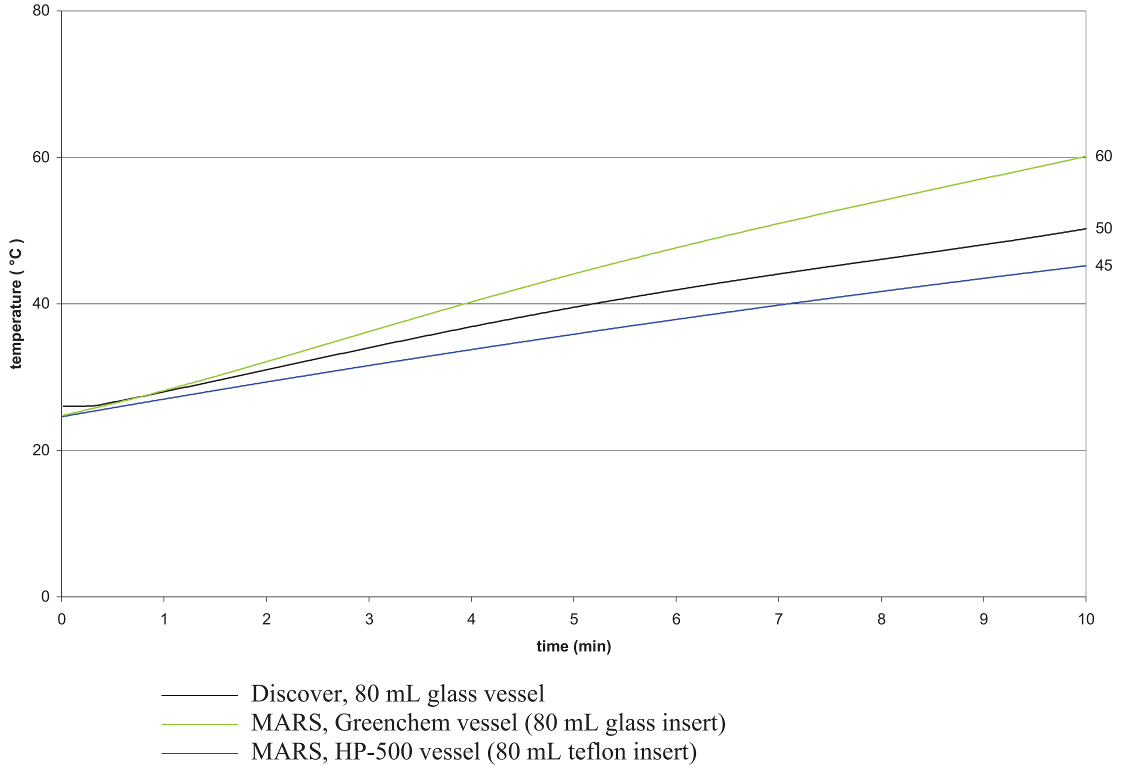


Figure 7. Heating profile of 20 mL of tetrachloromethane in several commercial available microwave systems, irradiated in a power/time experiment at a constant power of 300 W for 10 min.

constant power output is used in all microwave systems the final temperature of toluene is not the same (Fig. 6).[11] Heating the same volume of solvent in the three selected microwaves allows a direct comparison of the heating efficiency of these machines for that specific volume by simply comparing the obtained final temperatures of the heated solvent.[11] However, one should be very careful since the differences observed are also related to the specific material used for the vessel construction. This can be clearly deduced from a comparison of the heating profiles of toluene in the Greenchem and HP-500 vessel in the MARS at the same constant power (Fig. 6).[11] A simple heating experiment with 20 mL of microwave transparent tetrachloromethane clearly showed that the vessel material itself (sleeve and/or insert) is not completely microwave transparent and is at least partially responsible for the heating up of the irradiated solvent via conduction (Fig. 7).[12] This process becomes more and more important the more microwave transparent the irradiated solvent is. Remarkably, toluene and tetrachloromethane can not be heated in the high-pressure vessel of the microSYNTH at a constant power of 300 W since the system shuts down after a few minutes. The heating profiles of pure toluene confirm that our failure with the scale-up of the amination of 4-chloroanisole with morpholine is related to the use of toluene as solvent in that specific microwave platform. Importantly, the heating profiles also indicate that in the Greenchem vessel of the MARS multi-mode microwave, scale-up of the desired amination might be possible. Indeed, performing the amination on a 20 mmol scale of substrate at 150 °C using an initial set power of 1200 W and for a total reaction time of 10 min gave a complete conversion of starting material and an isolate yield of 4-(4-methoxyphenyl)morpholine of 78% (Table 1). This is similar to the result obtained on a 1 mmol scale in the 10 mL glass vessel of the Discover (76%). Although we were able to successfully perform scale-up in one glass vessel we realized that the further scale-up making use of the possibility to process multiple Greenchem vessels (rotor) in one microwave run would be problematic using toluene as solvent. Indeed, Figure 8 clearly shows that the final temperature of toluene in power/time experiments performed at 1200 W for 10 min drops each time a rotor segment that contains a glass vessel with 20 mL of toluene is added. This is obvious since the total volume to be heated increases each time a rotor segment is added. Therefore we looked for an alternative solvent for palladium-catalyzed aminations to allow scale-up in single-mode as well as multi-mode platforms. Possible candidates were screened by performing power/time experiments with 20 mL of solvent at 300 W for 10 min in each microwave system. 300 W was chosen as set power since it is the maximum power output of the Discover. First we looked at tetrahydrofurane (tan $\delta = 0.047$),[10] which has already been used frequently as solvent in Buchwald–Hartwig aminations (Fig. 9).[8f,8j] In comparison with toluene at the same power (Fig. 6), tetrahydrofurane significantly increased the obtained final temperatures in all microwave platforms (Fig. 9) although the tan δ is only slightly higher than that of toluene. Even though the heating profile of tetrahydrofurane is certainly a lot better, the solvent reaches a final temperature of only 94 °C upon heating at maximum power output for 10 min in the Discover. Therefore we looked for other alternatives. Inspired by a lecture where

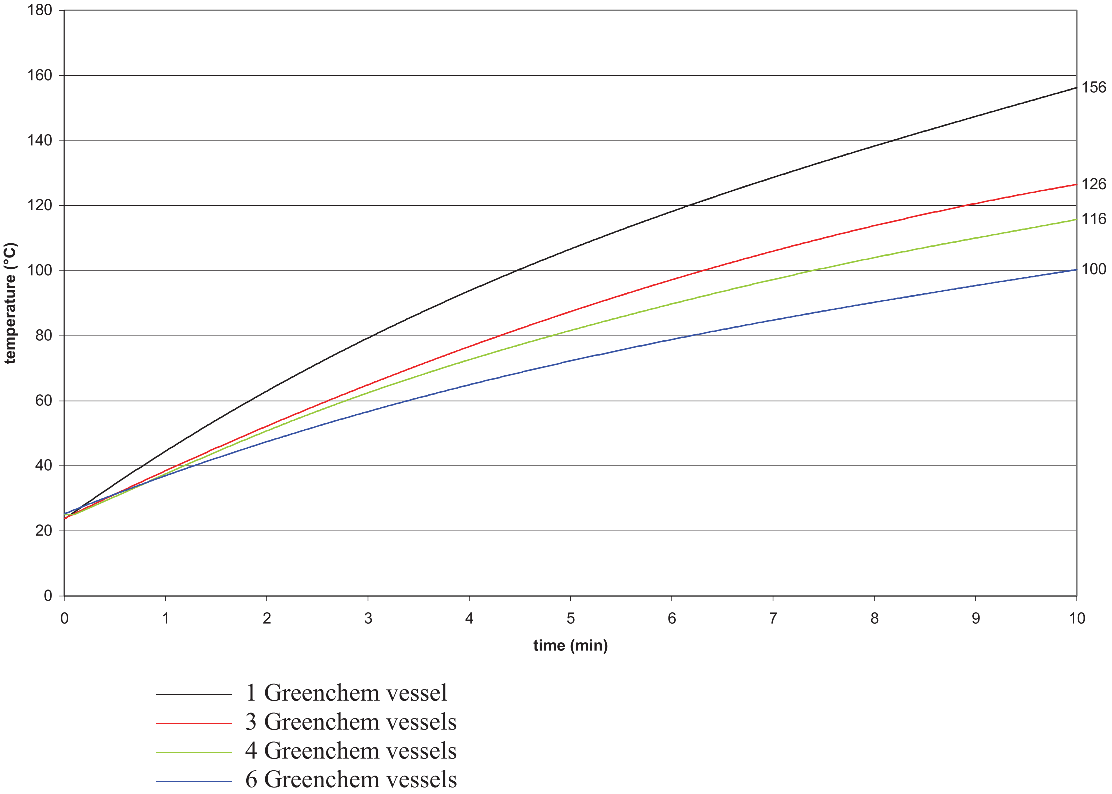


Figure 8. Heating profile of 1, 3, 4 and 6 Greenchem vessels, each filled with 20 mL of toluene, irradiated in the MARS system for 10 min in a power/time experiment at a constant power of 1200 W.

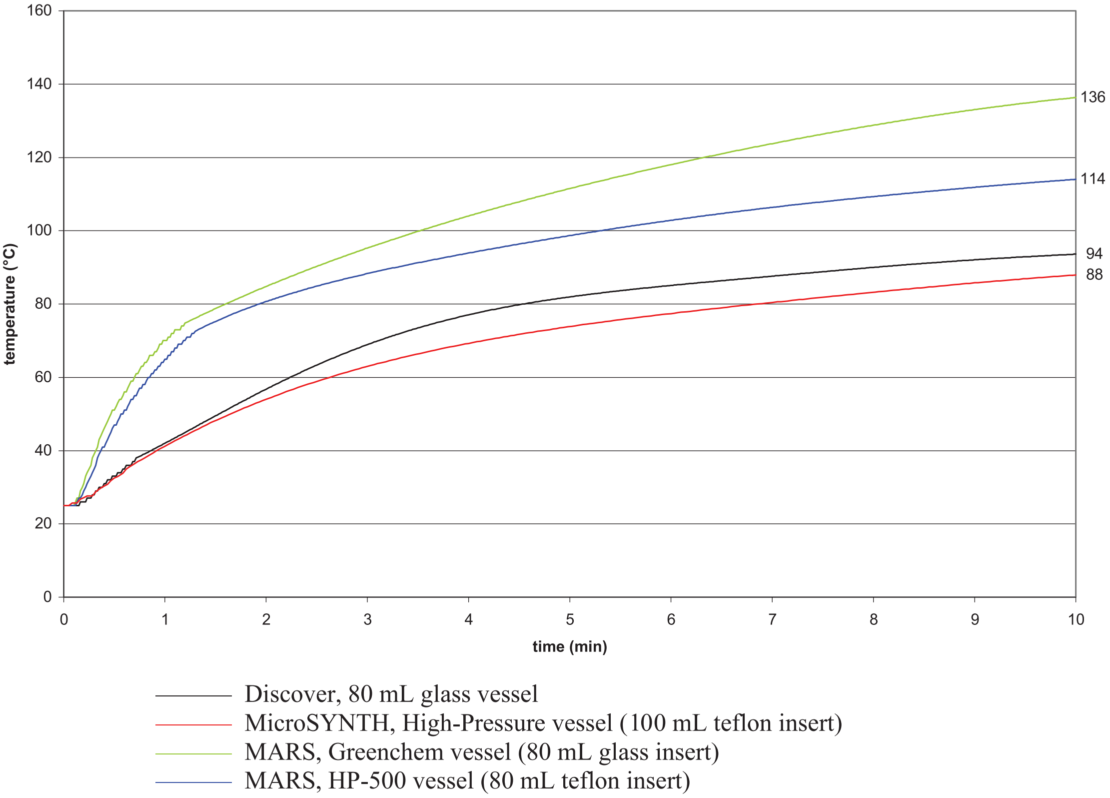


Figure 9. Heating profile of 20 mL of tetrahydrofurane in several commercial available microwave systems, irradiated in a power/time experiment at a constant power of 300 W for 10 min.

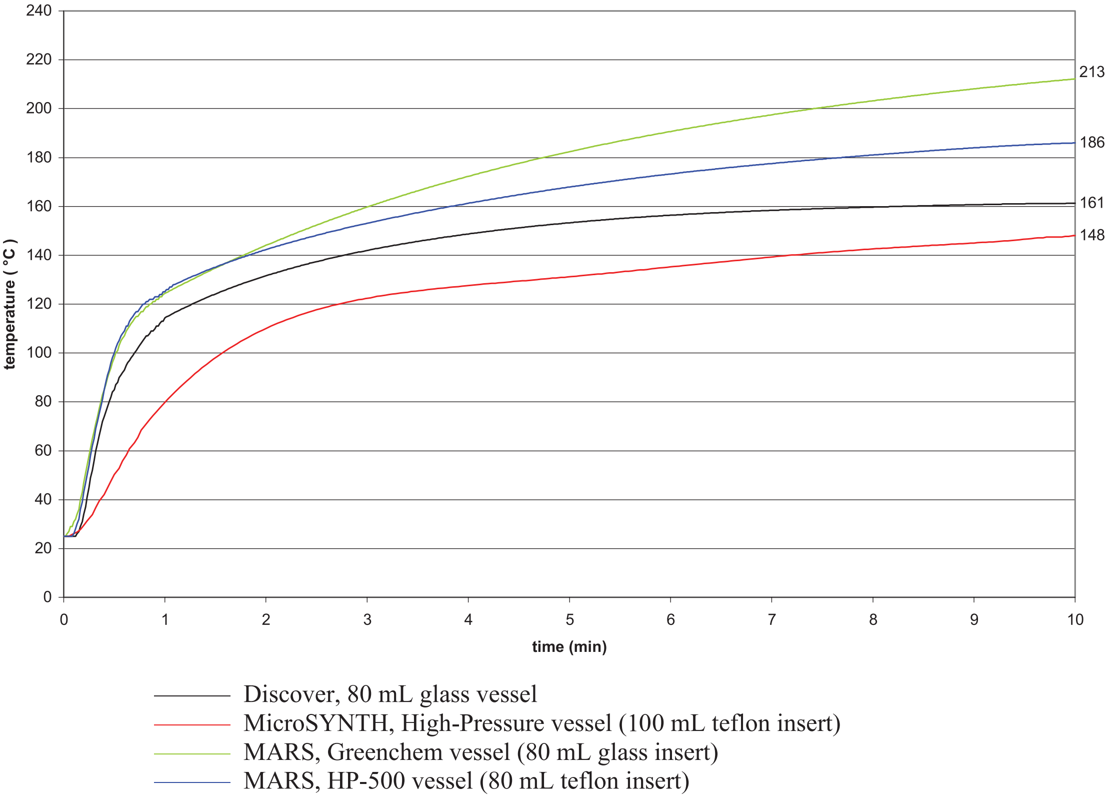


Figure 10. Heating profile of 20 mL of trifluoromethylbenzene (BTF) in several commercial available microwave systems, irradiated in a power/time experiment at a constant power of 300 W for 10 min.

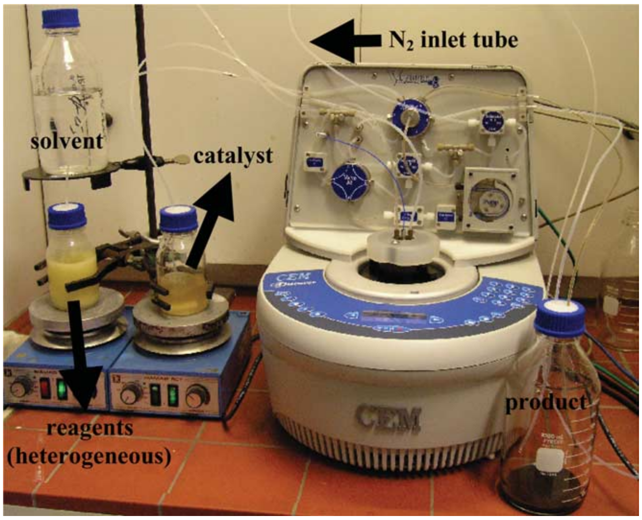
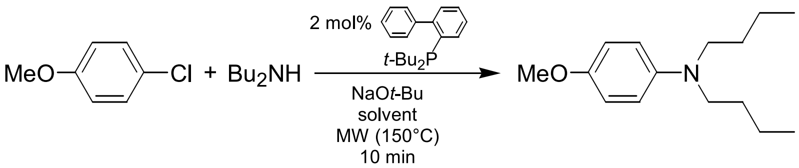


Figure 11. Experimental setup for the scale-up of Pd-catalyzed aminations using the Voyager platform.

Claisen rearrangements were executed using trifluoromethylbenzene (benzotrifluoride: BTF) as the solvent and a review stating the stability of this solvent under strongly basic conditions at high temperature we investigated the heating profile of 20 mL of this solvent at a constant power of 300 W.[13,14] Interestingly, we found that BTF heats up very rapidly, including in the Discover system at maximum power output, since all vessel-microwave combinations gave a final solvent temperature equal or higher than 148 °C (Fig. 10). Since in the real experiments our vessel contains in addition to solvent also polar reagents that will couple with microwaves we can expect that the required 150 °C will certainly be reached in one to two minutes as desired. Therefore we considered BTF as a good solvent candidate for scale-up of Buchwald–Hartwig aminations in single-mode as well as multi-mode platforms. Since BTF has hitherto never been used in palladium-catalyzed reactions we checked its potential as an amination solvent. Rewardingly, when we coupled 4-chloroanisole with morpholine at small scale in a 10 mL glass vessel in the Discover we found that in the same reaction time at the same final temperature a similar isolated yield was obtained using this solvent as a toluene substitute (Table 1).

For the scale-up experiments we first evaluated the Discover single-mode microwave of CEM. An attempt to scale-up our test case amination of 4-chloroanisole with morpholine with a factor 20 (20 mmol 4-chloroanisole, 24 mmol morpholine, 28 mmol NaO*t*-Bu, 20 mL BTF) in an 80 mL vessel proceeded smoothly since a complete conversion of starting material and an isolated yield of 85% of 4-(4-methoxyphenyl)morpholine could be achieved in the same reaction time (10 min) as when 1 mmol of the aryl chloride was used in BTF (Table 1).[15] Next we looked at the possibility to perform this experiment in a completely automized batch wise process. For this purpose we used the Voyager (stop/flow system) system of CEM. For our automized scale-up experiment we made a stock solution of catalyst ($Pd(OAc)_2$/2 DCPB) in BTF and a second solution containing 4-chloroanisole, morpholine and NaO*t*-Bu in BTF. The latter is a heterogeneous mixture due to the low solubility of NaO*t*–Bu in BTF. Therefore this stock solution was put on a magnetic stirring plate, which prevented precipitation of the base at the bottom of the bottle and, which allowed the creation of a more or less homogeneous suspension. The whole setup can be seen in Figure 11. When we programmed the Voyager for three cycles of 20 mmol aryl chloride the average yield was similar as the one obtained in the previously mentioned one batch experiment (Table 1). Even when we performed 12 cycles the yield did not drop significantly since an average yield of 76% for batches 10–12 was obtained. When one takes into account that a complete cycle takes only 16 min, the stop/flow system gives the opportunity to make 1.35 mol (around 261 g) of 4-(4-methoxyphenyl)morpholine in one day. Next we attempted to scale-up the most challenging coupling we previously published namely the amination of 4-chloroanisole with *N*,*N*-dibutylamine using DTPB as ligand for the palladium catalyst. Performing the experiment on a 20 mmol scale of 4-chloroanisole in an 80 mL glass vessel in the Discover gave the same yield as on a 1 mmol scale in a 10 mL glass vessel in toluene (Table 2). Further scale-up in the Voyager gave an average yield of 44% over three cycles and clearly illustrates the power of the Voyager system. Finally, we also tried to use a heteroaromatic substrate namely 3-chloropyridine. Pd-catalyzed amination of 3-chloropyridine (20 mmol) with benzylamine (30 mmol) using DTPB as ligand gave a 85% isolated yield in a one batch experiment in the 80 mL vessel

Table 2. Scale-up of the Pd-catalyzed amination of 4-chloroanisole with *N*,*N*-dibutylamine

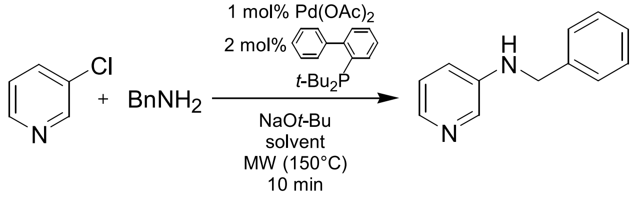


Microwave	4-Chloroanisole (mmol)	Vessel		Initial set power (W)	Solvent	Yield (%)[a]
		Volume (mL)	Type			
Discover	1	10	Glass	300	Toluene	50
Discover	20	80	Glass	300	BTF	45
Voyager	3×20	80	Glass	300	BTF	44[b]

[a] 4-Chloroanisole (*y* mmol), *N*,*N*-dibutylamine (1.2*y* mmol), NaO*t*–Bu (1.4*y* mmol), toluene or BTF (*y* mL).

[b] Average yield.

Table 3. Scale-up of the Pd-catalyzed amination of 3-chloropyridine with benzylamine



Microwave	3-Chloropyridine (mmol)	Vessel		Initial Set Power (W)	Solvent	Yield (%)[a]
		Volume (mL)	Type			
Discover	1	10	Glass	300	Toluene	87
Discover	20	80	Glass	300	BTF	85
Voyager	3×20	80	Glass	300	BTF	81[b]

[a] 3-Chloropyridine (y mmol), benzylamine ($1.5y$ mmol), NaO*t*-Bu ($1.4y$ mmol), toluene or BTF (y mL).
[b] Average yield.

in the Discover, which is essentially the same as the result obtained on a 1 mmol scale in toluene (Table 3). Running three cycles in the Voyager also gave a similar result (average yield of 81%) (Table 3).

Secondly, we looked at the scale-up possibilities (6× 20 mmol) of the MARS (Greenchem vessels) and microSYNTH (high-pressure vessels) multi-mode microwaves of the companies CEM and Milestone, respectively. To get an idea about the set power required to heat up multiple vessels we performed power/time experiments with 6 vessels each containing 20 mL of BTF. We decided to execute these power/time experiments in the microSYNTH (high-pressure vessels) since we already found that heating one Greenchem vessel with 20 mL of BTF at a constant power of 300 W for 10 min in the MARS system gives a higher final temperature than when a similar experiment is performed in a high-pressure vessel in the microSYNTH (Fig. 10). Heating 6 high-pressure vessels with 20 mL of BTF at a constant power of 300 W gave a final solvent temperature of 127 °C, which is 21 degrees lower than when one vessel is heated at the same constant power in the same time (Fig. 10). Increasing the power to 600 W increased the final temperature of the solvent for the 6 high-pressure vessels to a similar value as with one high-pressure vessel at 300 W and therefore 600 W was selected as the set power for the large scale amination experiments. Irradiating a rotor with 6 high-pressure vessels each containing 20 mmol 4-chloroanisole, 24 mmol morpholine, 28 mmol NaO*t*–Bu and 1 mol% $Pd(OAc)_2$/2 mol% DCPB catalyst in 20 mL BTF to 150 °C using an initial set power of 600 W gave a complete conversion of starting material in 10 min and an average isolated yield of 77% of 4-(4-methoxyphenyl)-morpholine (Table 1). A similar experiment with 6 Greenchem vessels in the MARS using the same microwave parameters gave 80% reaction product (Table 1). Both large scale (6×20 mmol) experiments performed in a microSYNTH and MARS multi-mode system gave a similar yield as the small scale (1 mmol) experiment in a 10 mL glass vessel in the Discover (Table 1).

4. Conclusion

Rapid Pd-catalyzed amination of aryl chlorides under microwave irradiation can be easily scaled-up without yield decrease if trifluoromethylbenzene (BTF) is used as solvent. Single-mode as well as multi-mode platforms can be used for this purpose. Although similar yields could be obtained in the Voyager, microSYNTH and MARS equipment, we prefer the Voyager since it is a completely automized unit that allows the continuous production of reaction product without the necessity to manually load and unload reaction vessels. Moreover, the Voyager allows pumping of heterogeneous mixtures, which is problematic in continuous-flow units.

5. Experimental

5.1. General

For column chromatography Kieselgel 60 (ROCC, 0.040–0.063 mm) was used. $Pd(OAc)_2$ (Acros), DCPB (Strem Chemicals or Acros), DTPB (Strem Chemicals or Acros), BTF (Acros) as well as all the amines and (hetero)aryl chlorides were obtained from commercial sources and used as such. The characterization data of 4-(4-methoxyphenyl) morpholine, *N*,*N*-dibutyl-4-methoxyaniline and *N*-benzylpyridin-3-amine were identical with those previously reported in the literature.[71,16] For the microwave-assisted amination experiments in toluene extra dry (<30 ppm water) toluene of Acros was used. The toluene (Acros) used to determine the heating profiles was p.a. quality.

5.2. Scale-up of palladium-catalyzed aminations of (hetero)aryl chlorides using the Voyager platform

5.2.1. Preparation of the stock solutions. *Stock solution one*. A 250 mL bottle (Schott) was charged with (hetero)aryl chloride (70 mmol), amine (morpholine or *N*,*N*-dibutylamine: 84 mmol) (*N*-benzylamine: 105 mmol) and NaO*t*–Bu (9.42 g, 98 mmol) and BTF (35 mL) in air. Subsequently, the bottle was flushed with Ar for a few minutes under magnetic stirring. The stock solution of reagents (including base) is heterogeneous. Therefore it was placed on a magnetic stirring plate, which prevented precipitation of the base at the bottom of the bottle. This allowed the creation of a more or less homogeneous suspension.

Stock solution two. A 250 mL bottle (Schott) was charged with $Pd(OAc)_2$ (0.157 g, 0.70 mmol), 2-(dicyclohexylphosphanyl)biphenyl (DCPB) or 2-(di-*t*-butylphospanyl) biphenyl (DTPB) (1.4 mmol) and BTF (35 mL) in air. Subsequently, the bottle was flushed with Ar for 10 min under magnetic stirring. When DTPB was used as ligand for the catalyst the stock solution was stirred for 16 h before using it.[17]

5.3. Remarks

- * The viscosity of the stock solutions influences the actual volume that will be pumped out of the stock solutions in the reaction vessel of the Voyager system in a certain timeframe. Therefore one needs to calibrate the system first by determining the pumping time necessary to pump in the desired volume (#mmol of reagents and base, catalyst).
- * We coupled the Voyager platform to a nitrogen cylinder (Fig. 11). In this way flushing of the tubing during loading, unloading and cleaning of the reaction vessel is performed with N_2 gas instead of air.
- * The set power for all amination experiments using the Voyager or Discover system was 300 W, the set temperature 150 °C. The total irradiation time (including the ramp time to the set temperature) was 10 min. Crude reaction mixture was filtered over Celite and rinsed well with dichloromethane. The filtrate was subsequently evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel.

5.4. Scale-up of the palladium-catalyzed amination of 4-chloranisole with morpholine using the MARS and microSYNTH platform

A Greenchem or high-pressure vessel was charged with 4-chloranisole (20 mmol), morpholine (24 mmol) and NaO*t*–Bu (2.69 g, 28 mmol) in air. Subsequently the vial was flushed with Ar for one minute. Then, 20 mL of a stock solution of catalyst[†] was added via a syringe and the resulting mixture stirred and flushed with Ar for a few minutes. Next, the Greenchem or high-pressure vessel was sealed. 6 Greenchem or high-pressure vessels filled in this way were then heated to 150 °C in a MARS or microSYNTH platform, respectively. The set power was 600 W. The total irradiation time (including the ramp time to the set temperature) was 10 min. After the rotor was cooled down to room temperature the vessels were opened, the contents of the 6 vessels combined, filtered over Celite and rinsed well with dichloromethane. The filtrate was subsequently evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel.

[†] Stock solution of catalyst, A 250 mL bottle (Schott) was charged with $Pd(OAc)_2$ (0.314 g, 1.40 mmol), 2-(dicyclohexylphosphanyl)biphenyl (DCPB) (0.981 g, 2.8 mmol) and BTF (70 mL) in air. Subsequently, the bottle was flushed with Ar for 10 min under magnetic stirring.

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References and notes

1. For recent reviews and books on microwave-assisted organic synthesis: (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283. (b) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406–416. (c) Kappe, C. O. *Am. Lab.* **2001**, *33*, 13–19. (d) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727. (e) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105. (f) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314–320. (g) Hayes, B. L. Microwave Synthesis: Chemistry at the Speed of Light; CEM: Matthews, 2002. (h) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002. (i) Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66–77. (j) *Microwave-Assisted Organic Synthesis*; Lindström, P., Tierney, J. P., Eds.; Blackwell: Oxford, 2004. (k) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
2. (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279–282. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945–4958.
3. http://www.cem.com/; http://www.milestonesrl.com/; http://www.biotage.com/; http://www.plazmatronika.pl/eng/index.html; http://www.anton-paar.com/.
4. (a) Raner, K. D.; Strauss, C. R.; Trainor, R. W.; Thorn, J. S. *J. Org. Chem.* **1995**, *60*, 2456–2460. (b) Perio, B.; Dozias, M.-J.; Hamelin, J. *Org. Process Res. Dev.* **1998**, *2*, 428–430. (c) Cléophax, J.; Liagre, M.; Loupy, A.; Petit, A. *Org. Process Res. Dev.* **2000**, *4*, 498–504.
5. (a) Cablewski, T.; Faux, A. F.; Strauss, C. R. *J. Org. Chem.* **1994**, *59*, 3408–3412. (b) Kazba, K.; Chapados, B. R.; Gestwicki, J. E.; McGrath, J. L. *J. Org. Chem.* **2000**, *65*, 1210–1214. (c) Khadilkar, B. M.; Madyar, V. R. *Org. Process Res. Dev.* **2001**, *5*, 452–455. (d) Esveld, E.; Chemat, F.; van Haveren, J. *Chem. Eng. Technol.* **2000**, *23*, 279–283. (e) Esveld, E.; Chemat, F.; van Haveren, J. *Chem. Eng. Technol.* **2000**, *23*, 429–435. (f) Shieh, W.-C.; Dell, S.; Repi, O. *Tetrahedron Lett.* **2002**, *43*, 5607–5609.
6. For the scale-up of Heck and Negishi reactions in a prototype multi-mode microwave of Anton Paar GmbH see: Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C. O. *Org. Process Res. Dev.* **2003**, *7*, 707–716. For the scale-up of Suzuki reactions in a single-mode microwave of CEM (Discover) using a 50 mL round-bottomed flask see: Leadbetter, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888–892.

7. For small scale microwave-assisted Pd-catalyzed amination of aryl halides see: (a) Sharifi, A.; Hosseinzadeh, R.; Mirzaei, M. *Monatsh. Chem.* **2002**, *133*, 329–332. (b) Wan, Y.; Alterman, M.; Hallberg, A. *Synthesis* **2002**, 1597–1600. (c) Maes, B. U. W.; Loones, K. T. J.; Lemière, G. L. F.; Dommisse, R. A. *Synlett* **2003**, 1822–1824. (d) Wang, T.; Magnin, D. R.; Hamann, L. G. *Org. Lett.* **2003**, *5*, 897–900. (e) Antane, S. *Synth. Commun.* **2003**, *33*, 2145–2149. (f) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* **2003**, *5*, 4373–4376. (g) Weigand, K.; Pelka, S. *Mol. Divers.* **2003**, *7*, 181–184. (h) McCarroll, A. J.; Sandham, D. A.; Titcomb, L. R.; de K. Lewis, A. K.; Cloke, F. G. N.; Davies, B. P.; de Santana, A. P.; Hiller, W.; Caddick, S. *Mol. Divers.* **2003**, *7*, 115–123. (i) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814–6816. (j) Jensen, T. A.; Liang, X. F.; Tanner, D.; Skjaerbaek, N. *J. Org. Chem.* **2004**, *69*, 4936–4947. (k) Harmata, M.; Hong, X.; Ghosh, S. K. *Tetrahedron Lett.* **2004**, *45*, 5233–5236. (l) Maes, B. U. W.; Loones, K. T. J.; Hostyn, S.; Diels, G.; Rombouts, G. *Tetrahedron* **2004**, *60*, 11559–11564. (m) Poondra, R. R.; Turner, N. J. *Org. Lett.* **2005**, *7*, 863–866.
8. For reviews on palladium-catalyzed amination see: (a) Barañano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287–305. (b) Frost, C. G.; Mendonça, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615–2623. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2047–2067. (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146. (e) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000; pp 195–262. (f) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209. For reviews containing a part on recent progress made in palladium-catalyzed amination see: (g) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. (h) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075. (i) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625–655. For a review dealing with palladium-catalyzed aminations seen from an industrial point of view see: (j) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.
9. For pioneering literature on Buchwald's monodentate phosphine ligands based on a biphenyl backbone see: (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174.
10. Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–223.
11. The maximum power measurement method the manufacturers (CEM, Milestone) use to determine the power output of their multi-mode system (MARS, microSYNTH) is different. If the IEC method is used for the MARS platform it delivers a maximum power output of 1500 W instead of 1200 W. The microSYNTH platform delivers a maximum power output of 1000 W following the IEC method. This means one should take into account that the compared heating profiles, resulting from power/time experiments performed at the same constant power output in the MARS and microSYNTH platform, give only a rough indication of the difference in performance of both multi-modes. Working at the same set constant power output in both multi-mode platforms is in reality actually not working at the same power. The maximum power measurement method used to determine the power output of the single-mode Discover unit (CEM) is also different so comparing heating profiles, resulting from power/time experiments performed at the same constant power output in a multi-mode or single-mode platform, gives also only a rough indication of the difference in performance of the microwave systems. Working at the same set constant power output in both platforms is in reality actually not working at the same power. In addition, for all commercial microwaves (single-mode and multi-mode) there is a 'nominal' power. Not all units of a certain type produce exactly the same power so even comparison between two units can be tricky (MARS $\pm 15\%$, microSYNTH $\pm 10\%$, Discover $\pm 10\%$). Microwave power measurement: (1) MARS (1200 W): heat 1 L of water (T_{initial}: 18–22 °C) in a beaker for 2 min at the maximum power of the microwave and determine the temperature difference of the water; power in Watts $= 35\ (T_{\text{final}} - T_{\text{initial}})$; (2) microSYNTH (1000 W): heat 1 L of water (T_{initial}: around 10 °C) for 1 min in a beaker at the maximum power of the microwave and determine the temperature difference of the water; power in Watts $= 70\ (T_{\text{final}} - T_{\text{initial}})$; (3) Discover (300 W): heat 50 mL of water (T_{initial}: 18–22 °C) for 30 s in a 100 mL round-bottomed flask at the maximum power of the microwave and determine the temperature difference of the water; Power in Watts $= 7\ (T_{\text{final}} - T_{\text{initial}})$.
12. For the heating profiles (IR) of quartz and glass vessels filled with microwave transparent CCl_4 measured in a Smith Synthesizer (Personal Chemistry) see: Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136–9139.
13. Lecture of N. Moorcroft presented at the '2nd International Microwaves in Chemistry Conference', Orlando (USA), 4/3–7/3 2004.
14. Use of BTF as solvent in organic synthesis: Maul, J. J.; Ostrowski, P. J.; Ublacker, G. A.; Linclau, B.; Curran, D. P. *Top. Curr. Chem.* **1999**, *206*, 79–105.
15. For the amination of 4-chloroanisole with morpholine we also attempted to scale-up with a factor 36 (36 mmol 4-chloroanisole, 43.2 mmol morpholine, 50.4 mmol NaO*t*-Bu, 36 mL BTF) in the 80 mL vessel of the Discover apparatus. In the same reaction time as for the 1 mmol and 20 mmol experiments (10 min) an isolated yield of 73% of 4-(4-methoxyphenyl)morpholine could be obtained. This is similar to the yield obtained on a 1 mmol scale (78%) but lower than the isolated yield of the 20 mmol experiment (85%).
16. (a) Trifonov, L. S.; Orahovats, A. S. *Helv. Chim. Acta* **1987**, *70*, 1732–1736. (b) O'Connor, S. J.; Barr, K. J.; Wang, Le.; Sorensen, B. K.; Tasker, A. S.; Sham, H.; Ng, S.-C.; Cohen, J.; Devine, E.; Cherian, S.; Saeed, B.; Zhang, H.; Lee, J. Y.; Warner, R.; Tahir, S.; Kovar, P.; Ewing, P.; Alder, J.; Mitten, M.; Leal, J.; Marsh, K.; Bauch, J.; Hoffman, D. J.; Sebti, S. M.; Rosenberg, S. H. *J. Med. Chem.* **1999**, *42*, 3701–3710.
17. Recently, Buchwald and co-workers reported that by stirring a mixture of $Pd(OAc)_2$ and DTPB in toluene for 16 h at room temperature a palladacycle is formed. In consequence of this report, we always stirred our stock solution of $Pd(OAc)_2$ and DTPB for at least 16 h before using it: Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413–2415.