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Approaches for Scale-Up of Microwave-Promoted Reactions

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Abstract:

In this report, we look at a range of classes of reaction involving microwave heating and show how different processing techniques can be used to address scale-up needs. We look at both batch and continuous-flow processing. We have shown that when using batch methodologies working using an open reaction vessel offers operational advantages while still giving good yields of desired products. In cases where open-vessel conditions are not amenable or where particularly volatile or toxic reagents are used, parallel sealed vessels can offer an alternative approach. For continuous-flow processing, homogeneity of the reaction mixture is key. When the mixture is homogeneous, it is possible to move from small-scale sealed-vessel conditions to the continuous-flow apparatus without any modification of reaction conditions or loss in product yield. When either the starting materials or the product mixture contains particulate matter, continuous processing can prove a challenge, but reoptimization of reaction conditions as well as reduction of the concentration may allow these difficulties to be overcome.

Introduction

The use of microwave heating as a tool for preparative chemistry is continuing to grow. By using microwave irradiation it is often possible to reduce reaction times significantly as well as improve product yields.[1–3] The vast majority of the publications in the area of microwave-promoted organic synthesis relate to small-scale chemistry. Within the chemical industry, the technology is well established at the discovery level, and potential drug candidates are being prepared using microwave heating in at least one step. An area of increasing research interest now is the scale-up of microwave-promoted chemistries.[4,5] This clearly is an area that needs to be addressed if the technology is going to impact process chemistry. There are two possible scale-up options. The first is to use a continuous-flow microwave cell, this technology being used successfully for a number of different reactions.[6–13] The drawbacks of a continuous-flow microwave apparatus are that it can be difficult to process solids, highly viscous liquids, or heterogeneous reaction mixtures. Also, adaptation of conditions from simple small-scale reactions to the continuous-flow cell could end up being time-consuming. The other option is to use a batch-type process. This could either involve using one large vessel[14–20] or parallel batch reactors.[21–23] One of the key advantages of batch processing is that heterogeneity does not prove an issue. However, there are problems when moving to larger and larger batch reactors due to the limited penetration depth of microwaves into the sample. Indeed, depending on the reaction mixture, microwave penetration is usually in the order of just a few centimeters.

There are two main categories of scientific microwave apparatus. Monomode microwave units have been used with great success for small-scale reactions using sealed glass tubes up to a working volume of approximately 50 mL or open round-

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¶ Major contributor to this study.

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bottom flasks to a volume of up to 125 mL. The cavity of a monomode microwave apparatus is designed for the length of only one wave (mode). By placing the sample in the middle of the cavity, it can be irradiated constantly with microwave energy. These units are excellent for optimisation of reaction conditions safely and efficiently. For scale-up, larger apparatus is required. Multimode units have a larger microwave cavity, and with these it is possible to perform reactions in one or multiple sealed vessels or an open vessel. In sealed-vessel configuration, for safety reasons there is a limit to the maximum working volume that can be processed in a single vessel. By using a carousel of reaction vessels it is possible to run a reaction using the same substrates in each vessel, this allowing for more material to be processed than in a single sealed vessel. Alternatively, different substrates could be run in each vessel, but it is often necessary to add a moderating agent when doing this in order to obtain even microwave heating in each vessel.[24] When using an open-vessel configuration, regular glassware can be employed. It is possible to use round-bottom flasks up to 5 L in capacity, and the flask can be attached to a reflux condenser by means of an extender tube passing from inside the microwave cavity to the outside via an attenuator to prevent microwave leakage.

When moving from batch to continuous-flow processing, the same microwave apparatus can be used. Using a monomode microwave unit, it is possible to pass material through a 10 mL glass tube. The tube can be loaded with glass beads[25] or sand[26] to enhance mixing of the reaction mixture and, in the case of the latter, ensure uniform heating. Another option when using monomode microwave apparatus is to use a stop-flow approach. The reaction mixture is pumped into and out of a reaction vessel by a peristaltic pump, these functions, as well as running the reaction, being controlled using a computer. The reaction mixture can be processed using the same conditions as for the batch reaction.[27,28] When using multimode apparatus, material can be passed through a cylindrical reactor located inside the microwave cavity.

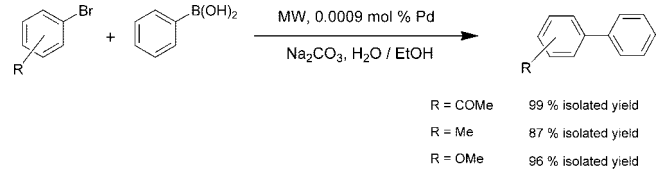
In this report, we look at a range of classes of reaction involving microwave heating and show how different processing techniques can be used to address scale-up needs. Issues such as batch versus continuous-flow approaches, the processing heterogeneous mixtures and the use of gases as reagents are discussed.

Results and Discussion

Batch Processing. *(a) Translation from Sealed-Vessel to Open-Vessel Reaction Conditions.* Looking in the literature, the majority of reactions performed using microwave heating are undertaken in sealed vessels at elevated temperatures. When scaling up reactions in a batch mode, the use of sealed vessels can pose safety issues as the vessel volume increases in size. An alternative we and others have investigated is translating from a sealed to an open reaction vessel, thus removing the need to work at elevated pressures.[29] A transformation we have focused some considerable attention on is the Suzuki coupling. It was possible to translate our original sealed-tube conditions for use in an open vessel with little reoptimization required.[30] This was achieved initially by using the same monomode microwave apparatus as employed for the sealed-vessel experiments, since as mentioned it has the capability to run reactions in open round-bottom flasks of capacity up to 125 mL. The apparatus (CEM Discover) has an opening in the top through which a glass tube can be placed connecting the flask in the microwave cavity with a reflux condenser located outside the microwave. Working on the 5 mmol scale, we found that to move from sealed to open vessel conditions it was necessary to extend the total reaction time from 5 to 20 min and also increase the palladium loading slightly to 1–5 ppm (0.0009–0.0045 mol %). These changes were needed we believe because of the difference in volume of material we were heating and the fact that the bulk temperature was 86 °C in the open vessel as opposed to 150 °C in the sealed tube experiments. With optimized conditions in hand we moved to the larger multimode microwave apparatus (CEM MARS) and performed the reaction on the 1 mol scale and obtained an almost identical yield as to when we worked on the 5 mmol scale (Scheme 1). In all of our open vessel reactions we measured temperature using a fiber-optic temperature probe inserted into a thermal well that was itself-inserted into the reaction mixture. This accurate temperature measurement is key both to control the reaction while running but also to give reproducibility from run to run.

We wanted to determine whether other reactions could be readily converted from sealed- to open-vessel processing, so to initiate this current study, we turned our attention to the Hantzsch synthesis of 1,4-dihydropyridines (Scheme 2). This multicomponent reaction involving condensation of an aldehyde with a β-dicarbonyl compound and ammonia[31] has attracted considerable attention due to the biological properties of many

Scheme 1. **Open-vessel microwave-promoted Suzuki reactions on the 1 mol scale**



Scheme 2. **Hantzsch synthesis of 1,4-dihydropyridines**

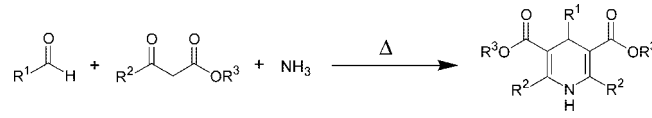


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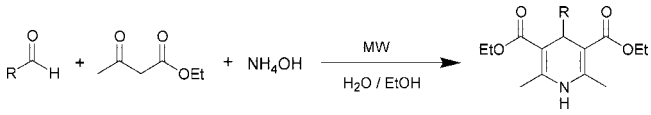
Table 1. **Open-vessel microwave-promoted synthesis of 1,4-dihydropyridines[a]**

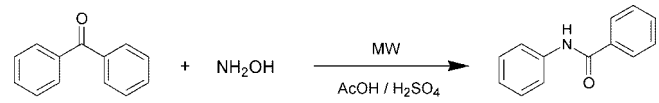


entry	R	ratio of aldehyde: β-dicarbonyl:NH_4OH	scale	solvent	yield (%)[b]
1	Ph	1:5:10	5 mmol	water	40
2	Ph	1:5:10	5 mmol	water/ethanol	71
3	Ph	1:3.4:10	5 mmol	water/ethanol	72
4	Ph	1:3.4:10	1 mol	water/ethanol	76
5	Cy	1:3.4:10	17 mmol	water/ethanol	95
6[c]	Ph	1:3.4:10	0.5 mol	water/ethanol	96

[a] Reaction mixture was heated to reflux and held at this temperature until a total time of 20 min had elapsed. [b] Isolated yield. [c] Using 5,5-dimethyl-cyclohexanedione as β-dicarbonyl component.

of the dihydropyridine products.[32] Microwave heating has been used as a tool for preparing dihydropyridines.[33] In the first report in the area, a series of 4-aryl derivatives were prepared in a domestic microwave with yields ranging from 15% to 52% for a reaction time of 4 min.[34] Other protocols based around these conditions but still using domestic apparatus have been reported.[35,8] More recently a scientific monomode microwave apparatus has been used to prepare a series of dihydropyridines from various, aldehydes (1 equiv), alkyl acetoacetates (6 equiv), and 25% aqueous ammonium hydroxide (10 equiv).[36,37] Reaction times ranged from 10 to 20 min and yields from 53% to 95%. We chose this report as our starting point for development of an open-vessel protocol and then scale-up of the reaction. Working in the CEM Discover on the 5 mmol scale using benzaldehyde (1 equiv), ethyl acetoacetate (5 equiv), and 28% aqueous ammonium hydroxide (10 equiv) as reagents and water (20 mL) as solvent, we found it was possible to obtain the desired dihydropyridine product in 40% yield after a total reaction time of 20 min in an open vessel (Table 1, entry 1), this comparing to a yield of 72% after 15 min using a sealed tube. We attributed our lower yield to the fact that the reaction mixture was biphasic, the organic substrates being insoluble in water, and to loss of ammonia over time. We found that by changing the solvent from water to a water/ethanol mixture it was possible to improve the yield considerably to 71% (Table 1, entry 2). The maximum temperature reached during the run was 84 °C. We wanted to reduce the quantity of the dicarbonyl added, since the 5 equiv we were using was a significant excess. We found we could reduce this to 3.4 equiv without a sacrifice in product yield (Table 1, entry 3). We then took our optimised conditions to the multimode CEM MARS apparatus and scaled the reaction to 1 mol. Performing the reaction in a 3 L flask and using a water/ethanol mix as solvent, we heated the reaction mixture to reflux and held it at this temperature until a total time of 20 min had elapsed (Table 1, entry 4). A 76% isolated yield was obtained. We performed the reaction with two variations in substrate to confirm the generality of the procedure and again obtained yields similar to those using sealed vessels (Table 1, entries 5 and 6).

Scheme 3. **Open-vessel microwave-promoted Beckmann rearrangement**



sealed vessel (10 mmol): heat to 140 °C and hold for 20 min - 74 % yield

open vessel (5 mmol): heat to reflux (120 °C) and hold for 20 min - 95 % yield

open vessel (1 mol): heat to reflux (120 °C) and hold for 20 min - 90 % yield

The Beckmann rearrangement was our next reaction of choice. This acid-catalyzed conversion of ketoximes to *N*-substituted amides accomplishes in one pot both the cleavage of a carbon–carbon bond and the formation of a carbon–nitrogen bond.[38] It represents a powerful method particularly for manufacturing γ-caprolactam. Amides can be prepared directly from ketones in a two-step one-pot process, the first step involving the reaction of the ketone substrate with hydroxylamine as its hydrochloride salt followed by Beckmann rearrangement of the resultant ketoxime to the amide. The reaction generally requires high reaction temperatures and strongly acidic and dehydrating media; thus it is not surprising that several microwave-promoted approaches have been reported, the majority of which focus on the use of microwave heating in conjunction with a solid-supported acid catalyst.[39] In a sealed tube benzophenone can be converted to *N*-phenylbenzamide in 74% yield on the 5 mmol scale using 2 equiv of hydroxylamine hydrochloride and acetic acid/sulfuric acid as solvent. The reaction mixture is heated to 140 °C and held at this temperature for 20 min. We found it was simple to convert this to an open-vessel methodology using the CEM Discover (Scheme 3). The only modification required, other than the open-vessel glassware, was that the maximum temperature was set at 120 °C, this corresponding to the reflux temperature. Working on the 5 mmol scale, we obtained a 95% yield of *N*-phenylbenzamide, which was substantially higher than that obtained in a sealed vessel. We scaled this to 1 mol using the

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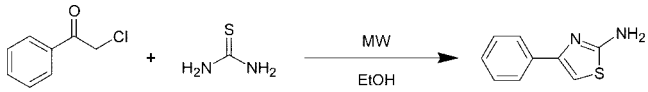
Scheme 4. **Open-vessel microwave-promoted synthesis of a 2-aminothiazole**



sealed vessel (0.5 mmol): heat to 140 °C and hold for 5 min - 80 % isolated yield

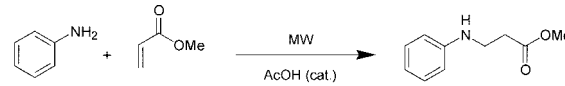
open vessel (12.5 mmol): heat to reflux (85 °C) and hold for 5 min - 71 % isolated yield

same conditions and obtained a 90% yield of the desired product, showing again that reactions can be scaled directly from monomode to multimode apparatus.

Our final reaction of choice in this category was the preparation of 2-aminothiazoles from α-haloketones and thioureas. Compounds bearing a 2-aminothiazole motif have found broad application in the treatment of a range of human health conditions.[40] There are a range of synthetic routes to 2-aminothiazoles but the condensation of α-haloketones with monosubstituted thioureas is one of the most common,[41] and the use of microwave heating to facilitate this reaction has been reported.[42] Our interest was directed towards the use of α-chloroketones as substrates and translation from a sealed vessel to an open vessel methodology (Scheme 4). We found that, using a 1:1.5 stoichiometric ratio of phenacyl chloride to thiourea as reagents and ethanol as the solvent, the reaction was complete within 5 min at 140 °C in a sealed vessel and an 80% isolated yield of the desired product obtained. For translation to an open-vessel methodology we kept the stoichiometry of the reagents the same as well as the concentration and moved to a 125 mL reaction vessel in the CEM Discover. Working on a 12.5 mmol scale, we obtained a quantitative conversion (71% isolated yield) of the desired 2-aminothiazole product after a total reaction time. This was a little lower than when using the sealed vessel, but this could easily be attributed to the lower reaction temperature of 85 °C. In this case, we decided not to scale-up the reaction further using the multimode apparatus but instead would later focus attention on continuous-flow processing.

(b) Reactions Requiring Sealed-Vessel Conditions. Not every reaction can be performed using open-vessel conditions. An example of such a case is when a substrate is particularly volatile and high temperatures are required to affect the desired transformation. In this case performing the chemistry under sealed-vessel conditions is preferable. We have recently reported the rapid, simple, microwave-promoted synthesis of *N*-aryl-functionalized *β*-amino esters using a Michael addition protocol.[43] Reactions are performed neat at 200 °C for 20 min and

Scheme 5. **Synthesis of an *N*-aryl-functionalized *β*-amino ester by an aza-Michael addition reaction**



sealed vessel (13 mmol): heat to 200 °C and hold until a total time of 20 min has elapsed - 81 % yield

sealed vessel (2.8 mol): irradiate for 20 min (maximum temperature reached is 198 °C) - 78 % yield

are catalyzed by acetic acid. The pressure of the reaction mixture during the run peaks at around 200 psi. Because of the volatility of the methyl acrylate, the relative toxicity of both reagents, and the fact that the reaction is performed solvent-free, as a scale-up strategy we chose to use multiple smaller vessels as opposed to one larger vessel. The chemistry is also highly temperature-dependent. Insufficient heating leads to very poor yields, and too much heating leads to side-product formation and decomposition. Most carousels designed for multiple reaction vessels are built such that each individual glass or Teflon vessel sits in its own protective cover. As a result it is not possible to measure the temperature of every vessel simultaneously. One rotor designed for overcoming this problem is the Milestone Q-20, which is used in conjunction with the Milestone MicroSynth unit. The rotor comprises 20 quartz reaction vessels of working volume up to 30 mL. These sit in vessel covers that each have a small window towards the bottom through which it is possible to record the actual vessel temperature using an infrared temperature sensor located in the side of the microwave cavity. Thus, it is possible to control the reaction temperature using a fiber-optic probe inserted into one vessel while at the same time recording the temperature of each vessel as they rotate in the microwave cavity. We scaled up the reaction to 2.8 mol by placing 20 mL (0.14 mol) of reaction mixture into each of the 20 vessels, thus processing a total substrate volume of 0.4 L. We heated the reaction mixtures for 20 min using a microwave power of 1000 W, the final recorded temperature being 198 °C. Upon cooling, we analyzed the contents of representative vessels before combining the contents of them all. We obtained an overall 78% yield with very little variation from vessel to vessel (Scheme 5).

Another reaction of interest to us is the Heck coupling. There have been a number of recent reviews of the scope and versatility of the reaction.[44–48] We have reported a methodology for the reaction based around the use of water as a solvent, very low concentrations of a palladium catalyst, and the application of microwave heating. On the 1 mmol scale, it is possible to perform the reaction in 5–20 min at 170 °C using 1–10 ppm Pd catalyst loadings, the exact conditions being dependent on the substrates used.[49] However, unlike our analogous Suzuki coupling procedure, the low-catalyst loading Heck coupling is not amenable to scale-up using open-vessel conditions, as the elevated temperature obtained under sealed-vessel conditions are required. We have circumvented this

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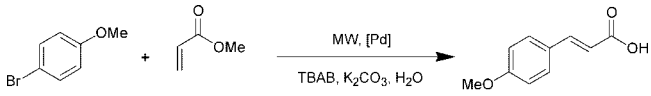
(49) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2005**, *70*, 1786.

Scheme 6. **Heck coupling of 4-bromoanisole with methyl acrylate**



sealed vessel (0.1 mol): heat to 170 °C over 5 min and hold for 15 min - 93 % yield

problem by using an automated stop-flow approach[28] and, more recently, by developing an alternative open-vessel procedure.[50] There has been one report of the scale-up of a Heck coupling performed using microwave heating in a multimode microwave unit with four sealed reaction vessels, each containing 20 mmol of substrate and using 1 mol % palladium as catalyst.[21] Our open-vessel approach involves using 0.1 mol % palladium acetate as the catalyst, sodium carbonate and tributylamine as bases, and tetrabutylammonium bromide as an additive. The reaction is performed solvent-free, and it was when scaled up to the 0.5 mol level, problems were encountered with the exothermic nature of the Heck coupling once initiated. As a result, in this study we wanted to revisit the low-level Heck coupling protocol but using a microwave unit capable of processing one large sealed vessel. The apparatus chosen (Biotage Advancer) comprised a 1200 W microwave unit with a dedicated Teflon reaction vessel of 50–300 mL working volume.[51] Reaction mixtures can be stirred mechanically meaning that heterogeneity is not a problem. The unit is equipped with an adiabatic cooling mechanism so that the product mixture can be cooled rapidly at the end of the reaction. Using this unit we performed the Heck coupling between 4-bromoanisole and methyl acrylate as a test reaction. Since the coupling would be performed in basic aqueous medium, the product of the reaction would be expected to be 4′-methoxycinnamic acid. On the basis of our smaller-scale protocol, we used a 1:2 stoichiometric ratio of aryl bromide (0.1 mol) to methyl acrylate (0.2 mmol), 1 equiv tetrabutylammonium bromide as phase-transfer agent, 3.7 equiv potassium carbonate as base, a palladium loading of 0.002 mol %, and water as the solvent. We knew that, in the heat-up stage, the reaction would generate significant pressure inside the vessel, and thus we decided to ramp to the desired temperature of 170 °C over the period of 5 min before holding it at this point for a further 15 min, stirring continuously. After adiabatic cooling followed by collection and purification of the product, we obtained a quantitative conversion to 4′-methoxycinnamic acid and an isolated yield of 93% (Scheme 6).

(c) Equilibrium Reactions Liberating Volatile Components. Recently, our group has become interested in esterification reactions because these elementary yet multifaceted reactions find wide application in organic synthesis.[52] They are used on small and large scales in the chemical industry, in particular the fine chemicals, flavor, and fragrance businesses.[53] Microwave heating has been used to facilitate acid-, base-, and enzyme-catalyzed esterification reactions.[54,55] It has also been the subject of previous scale-up attempts.[6,10,56,57] A problem with esterification reactions are that they are equilibrium processes and in order to drive them to completion, either the ester product or the water generated needs to be removed as the reaction proceeds or else an excess of one of the reagents needs to be used. We have recently reported a multigram scale microwave-promoted esterification reaction protocol using an apparatus that allows for the removal of water generated during the course of the reaction.[58] As a result the process can be driven towards completion. While this apparatus is useful in this capacity, it is not what it was originally designed for, and there are some complications associated with ensuring removal of just the water and not substrates or products. To overcome these problems and to extend the scope of the method, we decided to modify our general open-vessel apparatus to incorporate a Dean–Stark trap. This was a simple task since all we needed to do was place the trap between the glass tube connecting the flask in the microwave cavity and the reflux condenser mounted externally. With this in place we attempted a test esterification reaction on a 2 mol scale with the objective of running the reaction until such time that the accumulation of water in the trap stopped. We chose as our test reaction the esterification of acetic acid with butanol, using a 1:1 molar ratio of the reagents and sulfuric acid (1 wt %) as catalyst. We heated the mixture until water started to accumulate in the Dean–Stark trap and then held the reaction at this temperature (103 °C) until water stopped being generated (10 min). An 82% conversion to butyl acetate was obtained. We then scaled up the reaction to 6 mol and, using the same protocol, obtained an 89% conversion to the ester product. We performed two further esterification reactions on the 2 mol scale, this time using secondary alcohols. In the reaction of acetic acid with cyclohexanol, we obtained an 80% conversion and with 2-octanol, an 86% conversion. The results are summarized in Scheme 7.

Our attention turned to other reactions that would benefit from being performed in an open-vessel arrangement with the capacity to collect either a product or byproduct by distillation. Use of microwave heating in conjunction with distillation has found uses in, for example, the purification of ionic liquids,[59] the preparation of preparation of pyranoquinolines[60] and the

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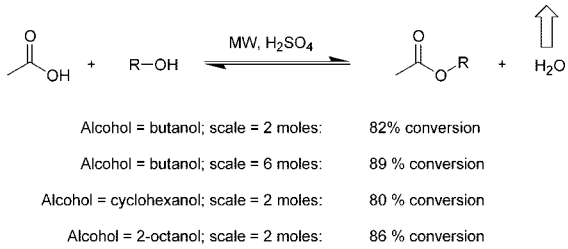
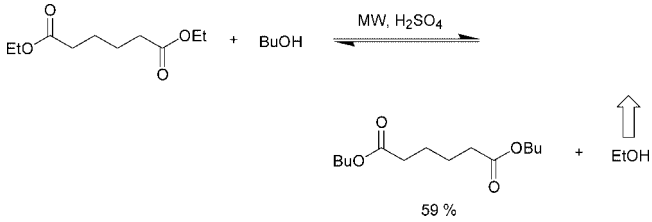
(60) Razzaq, T.; Kappe, C. O. *Tetrahedron Lett.* **2007**, *48*, 2513.

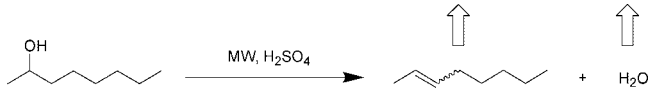
Scheme 7. **Esterification of acetic acid with primary and secondary alcohols**



Scheme 8. **Transesterification reaction of diethyl adipate with butanol**



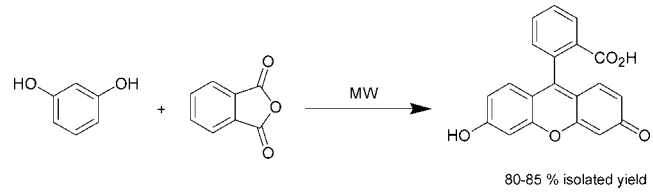
Scheme 9. **Preparation of octene from octanol**



extraction of components from plants.[61] Due to our work in the biofuels area[62] we had an interest in transesterification reactions, these again being equilibrium processes. We chose the reaction of butanol with diethyl adipate as a model, the product being dibutyl adipate (Scheme 8). The reaction could be driven towards completion by removing the ethanol byproduct. Working with a 2:1 molar ratio of butanol to diethyl adipate (1 mol) and using sulfuric acid (1 wt %) as a catalyst, we heated the reaction mixture to 105 °C, holding it at this temperature until a total time of 10 min had elapsed. We then raised the temperature to 115 °C, holding until a further 10 min had elapsed. By this time all the ethanol produced in the reaction had been removed. We then raised the temperature to 145 °C to strip off any butanol remaining in the reaction mixture. A 59% yield of dibutyl adipate was obtained.

We next studied the acid-catalysed dehydration of 2-octanol to yield octene (Scheme 9). In this reaction the alkene products are considerably more volatile than 2-octanol and thus can be collected by direct distillation. Using 1 wt % sulfuric acid as catalyst, we found that the alkene formation commenced once the reaction mixture reached a bulk temperature of 145 °C. Using a Dean–Stark trap, we collected the octene and water produced in the reaction. Starting from 2-octanol we obtained a mixture of *cis*- and *trans*-2-octene together with a trace of 1-octene. In order to allow us to scale up the reaction, we decided to attempt semicontinuous processing whereby we performed the reaction using the same experimental setup but this time added 2-octanol to the reaction vessel as the octene was produced. We achieved this using a variable-speed peristaltic pump and found that the optimum flow rate of 2-octanol into the vessel was 15 mL/min; this allowed us to maintain a steady bulk reaction temperature of 145 °C. Using this apparatus we were able to process 460 mL of alcohol in 30 min (160 mL initial vessel volume and 15 mL/min additional feedstock for 20 min).

Scheme 10. **Preparation of fluorescein**



(d) Reactions Involving Solid Reagents. Moving away from reactions involving liquid reagents, we turned our attention to the preparation of fluorescein (Scheme 10). It is made from phthalic anhydride and resorcinol, both of which are solids at room temperature. We wanted to try to prepare fluorescein using a solvent-free approach,[63] and to achieve this, we initially had to design an appropriate reaction vessel. We wanted to be able to load the solid starting materials into the vessel and, more importantly, remove the hard solid product formed at the end of the reaction. This was not possible using a round-bottomed flask, and so we decided to use a 500 mL capacity reaction pot. These are regularly used in process chemistry but those that are commercially available use a metal fastener to hold the top and the bottom of the reaction pot together. When using microwave heating, it is not possible to use metal, and so we designed a stand made from Teflon into which the pot could sit. We held the top of the reaction pot in place using screws made from PEEK. The components are shown in Figure 1.

The starting materials (2 mol of resorcinol and 1 mol of phthalic anhydride) were first ground in a mortar and pestle to give an intimate mixture before loading into the reaction pot. Using an initial microwave power of 800 W, the solid reactants were heated to 100 °C over the period of 5 min, this being the temperature at which a melt was formed. Then, using a microwave power of 1600 W, the melt was heated from 100 to 220 °C and held at this temperature for 10 min. Upon cooling the product mixture resolidified at around 70 °C. The solid was treated with aqueous potassium hydroxide to solubilize it, and then the basic solution was poured slowly into dilute sulfuric acid to precipitate out the fluorescein product. The crude product was filtered and then added to water in a round-bottom flask. The mixture was then boiled for 10 min using the microwave apparatus; the aim of this was to remove any remaining resorcinol and phthalic anhydride, both of which are water-soluble. Upon cooling and filtration, an 80% isolated yield of pure fluorescein was obtained.

A problem encountered in this reaction was that it was not possible to stir the reaction mixture during the course of the microwave irradiation. This was a particular issue in the initial melting stage and while the reaction mixture was then heated to the desired temperature of 220 °C. To overcome these problems we turned to a microwave apparatus that is specifically designed for processing solids, the Milestone SPMR.[64] It incorporates a tilted glass vessel inside the microwave cavity in which the reaction takes place. Different size reaction vessels

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(63) For another report of a solvent-free approach to fluorescein, see: Nüchter, M.; Ondruschka, B. Application note: www.milestone.com.
(64) For a description of the equipment, see ref 58.

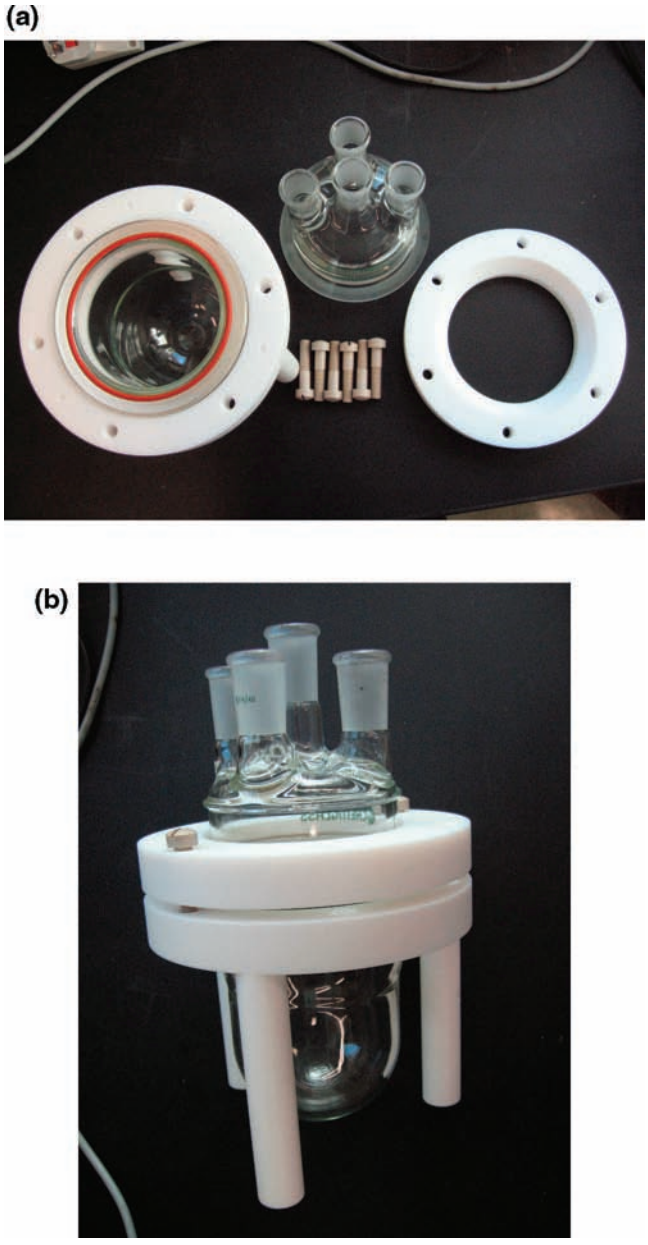

Figure 1

can be used with this system, starting from 300 mL up to 4 L in capacity. The rotation of the vessel assures good mixing of even large amounts of solid material. Using this equipment we performed the synthesis of fluorescein starting from 3 mol of resorcinol and 1.5 mol of phthalic anhydride. We heated an intimate mixture of the solids in a 3 L capacity vessel to 220 °C over the period of 15 min and held it at this temperature for a further 15 min. Once cooled, a modified purification process was performed. This time, water was added directly to the reaction vessel containing the crude product and boiled using microwave heating for a total time of 15 min On cooling, filtration of the remaining solid gave an 85% yield of pure fluorescein, similar to that obtained using the pot reactor.

(e) Reactions Involving Gaseous Reagents. There are only a few reports of organic synthesis in prepressurized vessels using microwave heating.[65–68] This is due to the fact that, until recently, equipment has not been available to preload reaction vessels. Also, commercially available microwave systems have a pressure limit of 20–30 bar, and with the combination of a pressure of reactive gas and the autogenic pressure of solvents at elevated temperatures, there is a limit to the temperature to which reaction mixtures can be heated. We have reported the use of microwave heating in small-scale carbonylation reactions using gaseous CO as a reagent.[69,70] The palladium-catalysed carbonylation of aryl halides is a reaction of both academic and industrial relevance since a range of products including amides, esters and carboxylic acids can be prepared in one step.[71–74] When transferring this chemistry from conventional to microwave heating, a number of approaches have been developed to circumvent the problem of working with gaseous carbon monoxide.[75] Larhed and co-workers have used $Mo(CO)_6$ as a source of carbon monoxide in conjunction with microwave heating.[76] Advantages of using $Mo(CO)_6$ as a replacement for gaseous CO include the fact that it is a solid and is easily used on a small scale with commercially available monomode microwave apparatus with no modification required. However, $Mo(CO)_6$ is toxic, and its use results in metal waste, this being a particular problem if the reaction is to be scaled up. For easy optimization of reaction conditions using gaseous CO, we modified a monomode microwave unit for gas loading. The gas is introduced directly into an 80 mL reaction vessel, and the pressure sensor is connected to the vessel in parallel. As a result, the exact loading pressure can be monitored in real time. This apparatus allowed us to perform hydroxy- and alkoxycarbonylation reactions on scales up to 2 mmol using aryl iodides. For this current study, we turned to a multimode microwave reactor (Anton Paar Synthos 3000) equipped with heavy-walled quartz reaction vessels with operating limits of 80 bar in order to scale up the reaction. This gives us the capability to load up to eight reaction vessels and run them simultaneously by means of a reaction carousel. We chose as our test reaction the ethoxycarbonylation of iodobenzene (Scheme 11). The minimum working volume in the quartz vessels is approximately 15 mL, so we performed a rudimentary calculation to determine the quantity of CO that could be placed in the remaining 65

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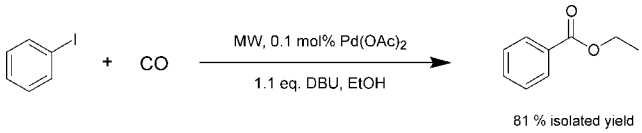
(74) For an example of the use of this chemistry on a multikilogram scale, see: Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101.
(75) For a general review of alternatives to CO gas, see: Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int Ed.* **2004**, *43*, 5580.
(76) (a) For examples, see: Lagerlund, O.; Larhed, M. *J. Comb. Chem.* **2006**, *8*, 4. (b) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327–3329. (c) Wu, X. Y.; Nilsson, P.; Larhed, M. J. *J. Org. Chem.* **2005**, *70*, 346. (d) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750.

Scheme 11. **Alkoxycarbonylation of iodobenzene**



mL volume of the vessel, assuming an initial pressure of 250 psi (~17 bar). This suggested that we could load approximately 45 mmol of CO into the vessel. We decided to perform the reaction on the 32 mmol scale and so, in a trial, loaded a vessel with iodobenzene, 15 mL ethanol as solvent, 1.1 equiv DBU as base, and 0.1 mol % palladium acetate as catalyst. Working on the 32 mmol scale we obtained a 60% yield of product after heating to 125 °C and holding at this temperature until a total time of 20 min had elapsed. This compares to a 91% yield when the reaction is performed on the 1.5 mmol scale. The reduction in yield could be attributed to the limited solubility of CO in ethanol as well as the relatively high concentration of the reaction mixture. By reducing the quantity of iodobenzene used from 32 to 12.5 mmol but keeping all other parameters the same, we were able to obtain a significantly higher yield of 90% of the desired product. We performed the reaction in all eight vessels and found very good vessel-to-vessel consistency. Starting with 0.1 mol of iodobenzene across the eight reaction vessels, we obtained an overall conversion of 91% and an isolated yield of 81% after chromatography.

Continuous-Flow Processing. Batch processing, while allowing us to use open reactors and handle heterogeneous reaction mixtures, does have some disadvantages. Reaction vessels cannot be very large because of microwave penetration issues, throughput can be limited, and if reactions are performed in large sealed vessels, safety may be a concern. The use of continuous flow rather than batch processing means that significant quantities of reagents can be processed and only a relatively small quantity of material is in the microwave field at any one time. Our objectives when starting out with our work with continuous-flow apparatus were to determine if it was possible to process homogeneous, heterogeneous, and highly viscous reaction mixtures and to use directly the reaction conditions from small batch runs without need for reoptimization. We also wanted to compare batch and continuous-flow processing for the same reactions.

For continuous-flow processing where reactants are not heated above their boiling points, an ambient pressure apparatus can be used. We took this approach when converting our biodiesel preparation from a batch protocol to continuous flow.[77] Biodiesel is prepared from vegetable oil by transesterification with methanol using a base catalyst, the byproduct being glycerin. In our protocol, the reaction mixture only needs to be heated to around 50 °C; the key being continuous application of significant microwave power to the reaction mixture while it is in the reactor. Using a 4 L reaction vessel it was possible to process feedstock at flow rates of up to 6 L/min. The reagents were premixed in a holding tank and then pumped into the microwave unit through a tube located near the bottom of the reaction vessel and out at the top. The reaction temperature was measured using a fiber-optic probe located in the upper quadrant. Addition of a Teflon-coated magnetic stir bar allowed us to agitate the contents of the vessel by means of a rotating magnetic plate located below the floor of the microwave cavity, this being required to prevent separation of the mutually immiscible biodiesel and glycerin.

The prerequisite that the reaction be performed under ambient pressure conditions limits the scope of continuous-flow processing so, for the work performed in the study we turned to a microwave unit equipped with a dedicated flow reactor capable of performing chemistry at elevated temperatures and pressures; the Milestone FlowSynth. A technical overview of the unit, together with assessment of its use in the Newman-Kwart reaction has been published recently.[78] The reaction chamber of 200 mL working volume is made from PTFE strengthened by a PEEK outer casing and is mounted vertically in the microwave cavity. Material is pumped in at the bottom of the reactor and out at the top and, as it comes out of the microwave cavity it passes through a cooler heat-exchanger which is attached to a chiller unit. The reaction mixture is stirred mechanically while in the microwave cavity by means of a stir shaft equipped with three paddles. As material passes into the cooler it is aided out of the unit by an Archimedean screw mounted on the upper part of the stir shaft. The temperature of the reaction mixture is measured both in the microwave cavity and also after exiting the cooler by means of thermocouples. The maximum working conditions for the reactor are 200 °C and 30 bar. Autogenic pressure upon heating is maintained by means of a variable back-pressure regulator mounted on the exit of the cooler unit. The flow rate is adjustable from 12 to 200 mL/min.

In employing this unit, we first returned to the esterification of acetic acid with butanol since this was a simple reaction that was monophasic and homogeneous, thus serving as a sharpening stone for subsequent reactions. Another reason for starting with this is that esterification reactions have been the subject of previous reports relating to continuous-flow microwave processing.[79–82] In small-scale sealed-vessel trials we found that near quantitative conversion was possible when using a 2.5: 1 ratio of acetic acid to butanol and 1 wt % sulfuric acid as catalyst. However, the conversion dropped significantly when equimolar quantities of the reagents were used, presumably because the water formed during the course of the reaction can not be removed using sealed-vessel conditions. For the purposes of our flow-through experiments we decided initially to work at a 2:1 stoichiometric ratio of acetic acid to butanol and at a reaction temperature of 150 °C. To perform the reaction we first passed acetic acid through the vessel while irradiating at the full microwave power of 1000 W with the objective of raising the reactor temperature to that desired for passing through the feedstock. With a flow rate of 200 mL/min, it took

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(78) Moseley, J. D.; Lawton, S. J. *Chem. Oggi* **2007**, *25*, 16.

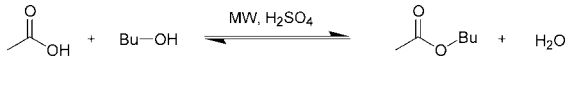
(79) Esterification of acetic acid with 1-propanol: see ref 7.

(80) Esterification of stearic acid with stearyl alcohol: Esveld, E.; Chemat, F.; van Haveren, J. *Chem. Eng. Technol.* **2000**, *23*, 279.

(81) Esterification of carboxylic acids with dimethyl carbonate: Shieh, W.-C.; Dell, S.; Repič, O. *Tetrahedron Lett.* **2002**, *43*, 5607.

(82) Esterification of linalool with carboxylic acid anhydrides: Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128.

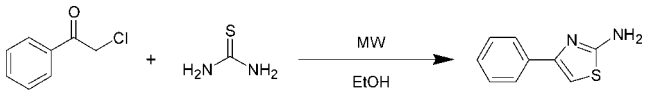
Scheme 12. **Esterification of acetic acid with butanol using continuous-flow processing**



2 : 1 molar ratio of reagents, temperature = 150 °C, 78 % conversion

flow rate = 200 mL / min, residence time = 1 min

Scheme 13. **Synthesis of a 2-aminothiazole using continuous-flow processing**



1 : 1.5 molar ratio of reagents, temperature = 140 °C, 97 % isolated yield

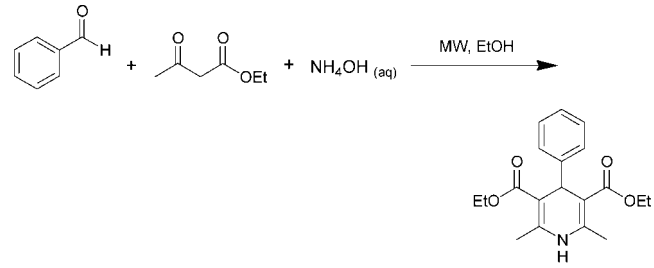
flow rate = 34 mL / min, residence time = 6 min

approximately 5 min to raise the temperature of the reactor to 150 °C. Once this point was reached, we started the flow of the acetic acid/butanol mixture at a rate of 200 mL/min. We processed 21.9 mol of acetic acid and obtained 78% conversion of the desired butyl ester (Scheme 12). We subsequently repeated the reaction using a 1:3 stoichiometric ratio of butanol to acetic acid, but the conversion improved only slightly (80%).

We turned next to the synthesis of the 2-aminothiazole from phenacyl chloride and thiourea. From our sealed-vessel work we knew that the reaction reaches completion within a total time of 5 min and a temperature of 140 °C using ethanol as solvent. In moving to the continuous-flow apparatus, we decided to use the same reagent stoichiometry and concentration of reagents as before (1:1.5 molar ratio of phenacyl chloride to thiourea). We initially passed pure solvent through the reactor while irradiating at full microwave power in order to heat it to the desired reaction temperature of 140 °C. Once this temperature was reached, we transferred the inlet tube to our feedstock reservoir and processed 0.5 mol of phenacyl chloride in 70 min, this corresponding to a flow rate of approximately 34 mL/min. We obtained a quantitative conversion and a 97% isolated yield of the 2-aminothiazole (Scheme 13).

Both the esterification and condensation reactions were simple to process because they were homogeneous solutions and show that, for such reactions, it is possible to move from small-scale sealed-vessel conditions to the continuous-flow apparatus without any modification of reaction conditions or loss in product yield. However, as noted by Moseley in their assessment of the continuous-flow apparatus, processing heterogeneous mixtures could pose an issue. This is because although the bore of the reactor chamber in the microwave cavity is 3.8 cm diameter, there is a narrow bore tube at the inlet of only 2 mm diameter that could easily block with particulate matter. In addition, the exit through the back-pressure regulator is also very narrow and could be prone to blockage. In our 1,4-dihydropyridine synthesis using batch processing we observed that although the reaction mixture was totally homogeneous, as it cooled at the end of the reaction the product precipitated out of solution. Thus, we imagined this would prove a useful test of how readily the exit tube would block in the continuous-flow apparatus. Using a 1:1 mixture of water and ethanol, we heated the reactor

Scheme 14. **Hantzsch synthesis of a 1,4-dihydropyridine using continuous-flow processing**



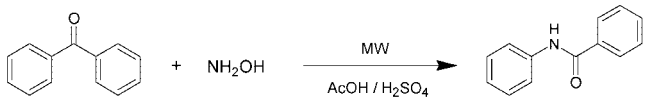
1 : 3.2 : 10 molar ratio of reagents, temperature = 140 °C, 91 % conversion

flow rate = 36 mL / min, residence time = 6 min

to 140 °C in the usual way. We then started to introduce the reaction mixture. We used a 1:3.2:10 molar ratio of benzaldehyde, ethyl acetoacetate, and ammonium hydroxide, respectively, and a water/ethanol mix as solvent. We passed the mixture through the reactor at a rate of 32 mL/min, corresponding to a residence time of approximately 6 min. We found that as we approached the 20 min mark, the flow rate started to decrease, and it was evident that a buildup of the dihydropyridine product in the exit line was responsible for this. In an attempt to mitigate the effects of this, we shut down the flow of coolant passing through the cooler heat exchanger unit. This helped slightly, but after processing a total of approximately 800 mL of feedstock (25 min), we decided to terminate the run. The conversion to product of the material we did process was 91%, indicating that the reaction was taking place very efficiently while the unit was running (Scheme 14). To avoid the blockage, we could either perform the reaction at a higher dilution or reoptimize in an alternative solvent so as to ensure that both starting materials and product remained totally dissolved at room temperature.

In our batch approach to the tandem ketoxime formation between benzophenone and hydroxylamine hydrochloride followed by Beckmann rearrangement to yield *N*-phenylbenzamide, the reaction mixture was heterogeneous due to the poor solubility of hydroxylamine in the acetic acid/sulfuric acid solvent mixture. In moving to continuous-flow processing, we had to find a way to ensure homogeneity of the entire reaction mixture and, more specifically, needed to ensure that the hydroxylamine was fully dissolved. We could achieve this by adding water to the reaction mixture. After preheating the reactor to 160 °C by passing water through while irradiating at full microwave power, we started to introduce the reaction mixture. We used a 1:2 stoichiometric ratio of benzophenone to hydroxylamine hydrochloride and passed the material through the reactor at a flow rate of 66 mL/min, corresponding to a 3 min residence time. Analysis of the product mixture showed an approximate 50% conversion (Scheme 15). We believe that the lower conversion obtained in the continuous-flow approach as compared to the batch processing is due to the presence of water in the reaction mixture. The first step of the reaction, the formation of a ketoxime between benzophenone and hydroxylamine hydrochloride, is an equilibrium process and liberates water itself. The large excess of water required to facilitate the salvation of the hydroxylamine hydrochloride has the effect of limiting the ketoxime formation and thus the subsequent

Scheme 15. **Beckmann rearrangement using continuous-flow processing**



1 : 2 molar ratio of reagents and 500 mL water added, temperature = 160 °C, 50 % conversion

flow rate = 66 mL / min, residence time = 3 min

Beckmann rearrangement step. Again, modifications to maintain homogeneity of the initial reaction mixture while at the same time limiting the water content of the reaction mixture may offer solutions to the problems, but it seems that in the case of both the dihydropyridine synthesis and this ketoxime formation Beckmann rearrangement tandem reaction, batch processing offers operational advantages over the current continuous-flow approach.

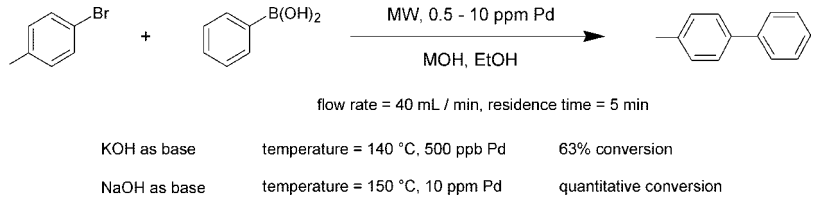
As a final example, we turned to the Suzuki reaction. Again our sealed-vessel work as well as our open-vessel batch approach rely on the fact that heterogeneous mixtures can be processed. In this case, we decided to take time to find reaction conditions that were totally homogeneous and that would allow us to use the continuous-flow apparatus. Traditionally we had performed low-level palladium catalysed couplings either a 1:1 water/ethanol mixture or neat water as solvent, tetrabutylammonium bromide being used as a phase-transfer agent in the case of the latter. We prefer to use the water/ethanol mixture as our solvent because it is cleaner and easier and does not require the use of a costly, hard-to-remove additive. However, whereas the organic substrates readily dissolve in the reaction medium, the sodium carbonate base is only sparingly soluble, and at the end of the reaction, the biaryl product precipitates out of solution even at elevated temperatures. In reaction scouting studies we found that if the base was changed to potassium hydroxide (2 equiv) and the solvent to neat ethanol, then not only were all of the reagents soluble, but the product was also soluble even at moderately low temperatures. Thus, this offered us a way to process the reaction using a continuous-flow approach. In optimization studies performed in a sealed 10 mL tube using 4-bromotoluene and phenylboronic acid as substrates, we found that we could reduce the palladium concentration down to 500 ppb (0.002 mol %) and still obtain a quantitative conversion to the desired 4-methylbiphenyl product. The reaction mixture was heated to 140 °C and held at this temperature for 5 min. It was these conditions that we decided to take on to the continuous-flow apparatus. Using ethanol, we heated the reactor to 140 °C and established a consistent flow rate of 40 mL/min, corresponding to a residence time of approximately 5 min. We then started to introduce the reaction mixture. We processed 0.5 mol of 4-bromotoluene with no issues caused byproduct precipitation, showing that our modified conditions were amenable to the continuous-flow apparatus. Upon work-up we obtained a 63% conversion to the desired product (Scheme 16). We attributed the drop in product conversion to the fact that we were working at the lowest limits of catalyst concentration and reaction time as determined from our small sealed tube experiments. We believed that if the palladium loading was increased, then the product conversion obtained using the continuous-flow apparatus would increase significantly. To test this we reran the reaction on the 0.25 mol scale, quadrupling the palladium loading to 2 ppm (0.008 mol %) and keeping all other variables the same. Although the product conversion improved, towards the end of the run we saw a rise in pressure, this being symptomatic of a solid or precipitate aggregating inside the unit. Further study led us to the conclusion that this was potassium bromide, which is poorly soluble in ethanol. A molar equivalent of potassium bromide is formed during the course of the reaction, originating from the potassium hydroxide base and aryl bromide substrate. While working at the lower palladium loading where the conversion was only moderate, the build-up of potassium bromide was not an issue. However, when increasing the palladium loading and hence the product conversion, problems start to arise. Because sodium bromide is more soluble than potassium bromide in ethanol, we decided to perform a run using sodium hydroxide as base. To aid further the solubility of the salt we used 150 proof as opposed to absolute ethanol. While changing base alleviated the problems from blockage due to salt build-up, we ran into another problem which was that the Suzuki coupling using sodium hydroxide as base is not as efficient as when using potassium hydroxide. Thus it was necessary to modify the reaction conditions slightly. By increasing the temperature to 150 °C and the palladium loading to 10 ppm (0.038 mol%) and using 150 proof ethanol we were able to obtain a quantitative conversion in the coupling of 4-bromotoluene and phenylboronic acid. Upon workup, an overall yield of 83% was obtained.

Our overriding observations from the continuous-flow experiments we performed were that, when the reaction and product mixtures are homogeneous, processing is easy and it is possible to scale up from small sealed tubes to continuous processing with minimal, if any, modification required. However, if either one of the starting materials or the product are particulate, then issues can arise with either pumping material into the reactor or getting it out through the back-pressure regulator at the outlet of the reactor. While in some cases this can be overcome by addition of additional solvent or a cosolvent, this can lead to a drop in product conversion depending on the nature of the reaction, which can be overcome by further modification of reaction parameters.

Summary

Our objective in this study was to assess a range of different processing techniques for the scale-up of microwave-promoted reactions, taking them from the milligram to at least the multigram level. We have looked both at batch and continuous-flow processing. When using batch methodologies, we have shown that working using an open reaction vessel offers operational advantages while still obtaining good yields of desired products. Microwave heating can be used in conjunction with distillation or continuous product removal to facilitate reactions that are equilibria or liberate lower-boiling products, respectively. In cases where open-vessel conditions are not amenable or where particularly volatile or toxic reagents are used, parallel sealed vessels can offer an alternative approach. The same is true when performing reactions involving a gaseous reagent such as carbon monoxide. When processing solvent-

Scheme 16. **Suzuki reaction using continuous-flow processing**



free reaction mixtures comprising solid reagents, it is possible to use a specifically designed open-vessel reactor, either a pot to allow easy access of reagents or, preferably, a tilted glass vessel inside the microwave cavity the rotation of which assures good mixing of even large amounts of solid material.

For continuous-flow processing, homogeneity of the reaction mixture is key. When the mixture is homogeneous, the apparatus works very well and it is possible to move from small-scale sealed-vessel conditions to the continuous-flow apparatus without any modification of reaction conditions or loss in product yield. When either the starting materials or the product mixture contains particulate matter, continuous processing can prove a challenge, but reoptimization of reaction conditions as well as reducing the concentration may allow these difficulties to be overcome.

Together with other reports of scale-up approaches in the literature, our work here shows that microwave heating is not limited to the small-scale discovery chemistry laboratory. While not yet perhaps at the kilogram per day level, multigram synthesis is certainly well within the capability of the commercially available apparatus used in this study. Work is now being initiated in our laboratory to move to the next level of production, this requiring more specialized engineering together with reaction modelling to ensure safety at each step up in scale.

Experimental Section

(a) General Experimental. All reagents were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 293 K on a 300 or 400 MHz spectrometer. For reactions involving the use of low concentrations of palladium, a commercially available palladium ICP standard was used (Aldrich) and diluted accordingly.

(b) Equipment. All equipment used in these studies is commercially available. Reactions performed using a monomode microwave unit were performed in a CEM Discover microwave unit. Open-vessel batch reactions were performed either in a CEM MARS Synthesis unit equipped with an access port in the top of the cavity through which a reflux condenser could be attached or a Milestone SPMR unit. Sealed-vessel chemistry was performed using either a Milestone MicroSynth unit equipped with a 20-position rotor or a Biotage Advancer. Chemistry involving addition of a reactive gas was performed in an Anton-Paar Synthos 3000 equipped with an eight-position rotor and gas-loading bayonet fittings. Continuous-flow reactions were performed in a Milestone FlowSynth, which is the Milestone MicroSynth platform but equipped with a flow-through vessel, pump, back-pressure regulator, tubing, and process control software.

Anton Paar Synthos 3000. The instrument, shown in Figure 2, is equipped with two magnetrons, with combined continuous microwave output power from 0 to 1400 W. Heavy-walled quartz reaction vessels (80 mL capacity, up to 60 mL working volume) were used. These vessels are dedicated for reactions at high pressure (up to 80 bar) and temperatures. The quartz vessels were capped with special seals and a protective PEEK cap and then were placed inside protecting air cooling jackets made of PEEK. The seals comprise a release valve that could be manually operated. The individual vessels were placed in an eight-position rotor and fixed in place by screwing down the upper rotor plate, and the rotor was finally closed with a protective hood. The vessels, once placed and secured in the rotor with the hood attached, were loaded with carbon monoxide using a commercially available gas-loading kit, access being via a bayonet link. They were pressurized directly from a carbon monoxide cylinder to 14 bar (~200 psi). The rotor was then placed into the microwave cavity. The temperature was monitored using an internal gas balloon thermometer placed in one reference vessel and additionally by exterior IR thermography. Pressure was monitored by a simultaneous hydraulic pressure-sensing device for all vessels, with recording of the highest pressure level and pressure increase. Reaction vessels were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. At the end of a reaction, any remaining pressure was vented by releasing the venting screw on each reaction vessel whilst still in the rotor access being via frontal holes in the rotor lid.

Biotage Advancer. The instrument, shown in Figure 3, consists of a continuous microwave power delivery system with power output from 0 to 1200 W. Reactions were performed in a 350 mL capacity Teflon vessel. The temperature of the contents of the vessel was monitored using a fiber-optic probe inserted directly into the reaction mixture by means of a glass

Figure 2

Figure 3

Figure 4

thermowell. The contents of the vessel were stirred by means of a mechanical paddle stirrer. The lid of the reactor also comprises an inlet for nitrogen/air and three extra available entry ports. Pressure is monitored using a load cell. Product mixtures were cooled at the end of a run by using the flash cooling capability, the contents of the Teflon reaction vessel being ejected into a stainless steel holding tank. Using this, the temperature of the mixture is rapidly reduced to the boiling point of the solvent used.

CEM Discover. The instrument, shown in Figure 4, consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. Reactions were performed either in 10 or 80 mL capacity sealed tubes or in a 100 mL capacity round-bottom flask. The temperature of the contents of the vessel was monitored using an IR sensor located underneath the reaction vessel. In the case of sealed-tube experiments, the pressure is controlled by a load cell connected directly to the vessel. The contents of reaction vessel are stirred by means of a rotating magnetic plate located below

Figure 5

Figure 6

the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure and power profiles were monitored using commercially available software provided by the microwave manufacturer.

CEM MARS. The instrument, shown in Figure 5, consists of a continuous microwave power delivery system with operator selectable power output from 0 to 1600 W. Reactions were performed in either a 1 or 3 L round-bottom flask. The temperature of the contents of the vessel was monitored using a fiber-optic probe inserted directly into the reaction mixture by means of a glass thermowell. The contents of the vessel were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

Milestone MicroSynth. The instrument, shown in Figure 6, is equipped with two magnetrons, with combined continuous microwave output power from 0 to 1000 W. In the format used here, twenty quartz reaction vessels (45 mL capacity) were employed. The reagents were placed into the quartz tubes, these in turn being placed into protective sleeves and sealed with a screw-top before being loaded onto a rotor (Q20 rotor). The sleeves, made of a high-temperature resin material and rein-

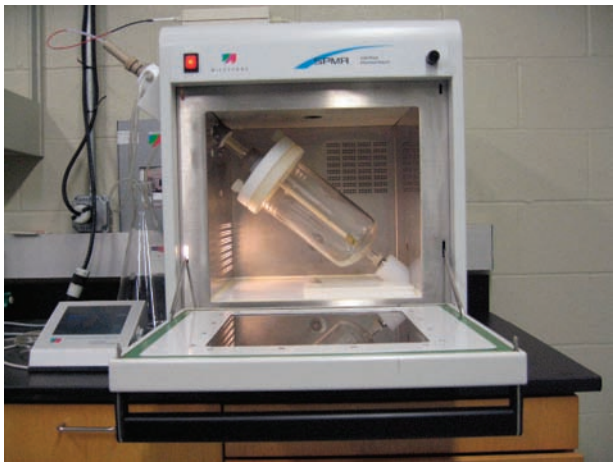


Figure 7

forced with fiberglass, are spring loaded at the bottom such that when the top is screwed down, the spring is compressed, holding the vessel in tight contact with the top. Direct temperature monitoring and control could be achieved via a fiber-optic probe inserted into one reaction vessel. Contact-less IR temperature monitoring and control was possible for all vessels using an infrared sensor located in the cavity floor. While there is no direct pressure measurement, the spring mechanism in the Teflon vessel covers ensures a precalibrated pressure point of 20 bar is not exceeded. In the case of overpressure the system would automatically release the pressure and the vessel would then reseal. Reaction parameters (temperature, microwave power and desired time) were programmed into a controller unit. The software utilized the fiber optic sensor in the control vessel and the continuous stream of data from the contact-less infrared temperature sensor to display individual temperature profiles for the complete collection of vessels.

Milestone SPMR. The instrument, shown in Figure 7, is based on the START multimode platform apparatus. It has one magnetron capable of delivering continuous microwave output power from 0 to 1000 W. It incorporates a tilted glass vessel (2 L capacity in this case) inside the microwave cavity in which the reaction takes place. The rotation of the vessel assured temperature homogeneity of even large amounts of material. Temperature measurement was by both an IR sensor located in the right-hand wall of the microwave unit facing at the bottom of the vessel and by fiber-optic probe inserted directly into the reaction mixture.

Milestone FlowSynth. The instrument, shown in Figure 8 is based on the MicroSynth multimode platform apparatus and is described in detail in the Results and Discussion section. Also, a technical overview of the unit has been published recently.[78]

(c) Experimental Procedures for the Reactions Performed in This Study. *1,4-Dihydropyridine Synthesis Performed in an Open Vessel in a Monomode Microwave Apparatus.* Benzaldehyde (0.51 mL, 5 mmol), ethyl acetoacetate (2.15 mL, 17 mmol), concentrated aqueous ammonium hydroxide (2.8 mL, 4.1 mmol), water (5 mL) and ethanol (5 mL) were combined in a 100 mL round-bottom long neck flask equipped with a stir bar. The flask was placed in the cavity of a CEM Discover microwave unit, an attenuator put in place and a reflux condenser attached to the flask. The solution was

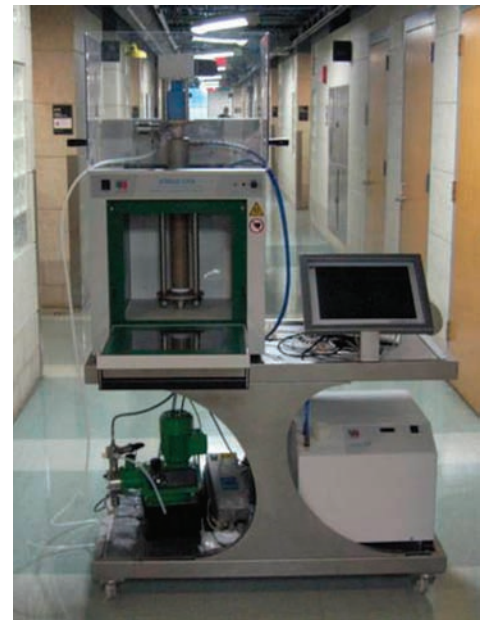


Figure 8

heated to reflux (84 °C) using an initial microwave power of 200 W and then held at this temperature for a further 15 min The contents of the vessel were allowed to cool to 60 °C, and then poured onto ice (30 g). The crude product was filtered, washed with water, redissolved in ethyl acetate (50 mL), and washed with water. The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1.18 g, 72% yield) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 10.7 Hz, 2H), 7.20 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.3 Hz, 2H), 5.59 (bs, 1H), 4.99 (s, 1H), 4.08 (m, 4H), 2.33 (s, 6H), 1.22 (t, J = 7.1 Hz, 6H).

1,4-Dihydropyridine Synthesis Performed in an Open Vessel in a Multimode Microwave Apparatus. Benzaldehyde (100 mL, 1 mol), ethyl acetoacetate (430 mL, 3.4 mol), concentrated aqueous ammonium hydroxide (560 mL, 8.2 mol), and ethanol (500 mL) were combined in a 3 L round-bottom 3-neck flask equipped with a stir bar. The round-bottom flask was placed in a CEM MARS microwave unit and equipped with a reflux condenser and a glass thermal well in order to measure temperature using a fiber-optic probe. The solution was heated to reflux (85 °C) using an initial microwave power of 1600 W and then held at this temperature until a total time of 20 min had elapsed. The solution was allowed to cool to 50 °C and then the flask placed into an ice bath. The precipitate formed was filtered off and collected. The mother liquor was then acidified to pH 3 with acetic acid and allowed to stand overnight whereupon more product crystallized out of solution. This was filtered and combined with the initial product crop to give an overall product yield of 76% (249 g).

1,4-Dihydropyridine Synthesis Performed in a Continuous-Flow Multimode Microwave Apparatus. Benzaldehyde (100 mL, 1 mol), ethyl acetoacetate (430 mL, 3.4 mol), concentrated aqueous ammonium hydroxide (560 mL, 8.2 mol), and ethanol (500 mL) were combined in a 5 L Erlenmeyer flask. A 1:1 water/ethanol mixture was pumped through the reactor inside the microwave unit with the internal stirrer set at 70% of

maximum speed. The water/ethanol mixture was then heated to 140 °C. When the temperature and flow rate had stabilized at 140 °C and 66 mL/min (3 min residence time), respectively, the reactor inlet tube was transferred to the flask with the combined reactants. The reactor outlet tube was placed into an empty Erlenmeyer flask where the product was collected. The apparatus was run until such time that the back-pressure regulator became blocked, this being after processing approximately half of the total reagent solution. The collected product solution was analyzed by ^{1}H NMR to measure the conversion of benzaldehyde to the final 1,4-dihydropyridine product. A 91% conversion was obtained.

Tandem Ketoxime Formation/Beckmann Rearrangement Performed in an 80 mL Sealed Vessel. Hydroxylamine hydrochloride (695 mg, 10.0 mmol) was dissolved in water (1 mL). Concentrated sulfuric acid (1.25 mL) was slowly added, hydrogen chloride gas being evolved. In a separate flask, benzophenone (910 mg, 5.0 mmol) was dissolved in glacial acetic acid (4 mL). The solution containing hydroxylamine was then added to this. A white suspension formed, which was homogenized by adding glacial acetic acid (2 mL). The entire reaction mixture was transferred to an 80 mL thick-walled glass vessel equipped with a stir bar. The vessel was placed into the cavity CEM Discover microwave unit and sealed with a septum with ports for pressure and temperature measurement devices. Using an initial microwave irradiation of 250 W the temperature of the reaction mixture was ramped to 140 °C, this taking approximately 1 min The reaction mixture was then held at this temperature for a further 20 min. The solution was allowed to cool to 60 °C, and then was poured over ice (60 g). The precipitate formed was filtered, washed with water, redissolved in ethyl acetate (50 mL), and washed with saturated sodium bicarbonate (20 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford *N*-phenylbenzamide (730 mg, 74% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.21 (bs, 1H), 7.96 (d, $J = 6.5$ Hz, 2H), 7.78 (d, $J = 7.5$ Hz, 2H), 7.56 (m, 3H), 7.36 (t, $J = 8.0$ Hz, 2H), 7.11 (t, $J = 7.5$ Hz, 1H).

Tandem Ketoxime Formation/Beckmann Rearrangement Performed in an Open Vessel in a Monomode Microwave Apparatus. Hydroxylamine hydrochloride (695 mg, 10.0 mmol), benzophenone (910 mg, 5.0 mmol), and glacial acetic acid (4.0 mL) were combined in a 100 mL round-bottom long neck flask equipped with a stir bar. Concentrated sulfuric acid (1.25 mL) was slowly added, hydrogen chloride gas being evolved. The flask was placed in the cavity of a CEM Discover microwave unit, an attenuator put in place and a reflux condenser attached to the flask. The solution was heated to reflux (120 °C) using an initial microwave power of 250 W and then held at this temperature for a further 5 min The contents of the vessel were allowed to cool to 60 °C, and then poured onto ice (30 g). The crude product was collected and purified using the same procedure as with the sealed-vessel study. *N*-Phenylbenzamide (940 mg, 95% yield) was obtained as a white solid.

Tandem Ketoxime Formation/Beckmann Rearrangement Performed in an Open Vessel in a Multimode Microwave Apparatus. Hydroxylamine hydrochloride (139.0 g, 2.0 mol) was suspended in 200 mL of glacial acetic acid in a 2 L three neck round-bottom flask equipped with a stir bar. Concentrated sulfuric acid (250 mL) was diluted with glacial acetic acid (400 mL) and added at a rate to ensure slow evolution of hydrogen chloride gas. Benzophenone (182.2 g, 1.0 mol) was then dissolved in glacial acetic acid (200 mL) and added to the reaction mixture. The round-bottom flask was placed in a CEM MARS microwave unit and equipped with a reflux condenser and a glass thermal well in order to measure temperature using a fiber-optic probe. The solution was heated to reflux (120 °C) using an initial microwave power of 1600 W, this taking 4 min 40 s, and then held at this temperature for a further 20 min The solution was allowed to cool to 80 °C and then was poured into ice–water (4 L). The precipitate was filtered, washed with water, redissolved in ethyl acetate (4 L), and washed with saturated sodium bicarbonate (2 L). The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford *N*-phenylbenzamide (178 g, 90% yield) as a white solid.

Tandem Ketoxime Formation/Beckmann Rearrangement Performed in a Continuous-Flow Multimode Microwave Apparatus. Benzophenone (500 g, 2.74 mol) was dissolved in glacial acetic acid (3.3 L). In a separate flask, hydroxylamine hydrochloride (381 g, 5.4 mol) was dissolved in water (550 mL), and then concentrated sulfuric acid (685 mL) was added at a rate to ensure slow evolution of hydrogen chloride gas. Glacial acetic acid was pumped through the reactor inside the microwave unit with the internal stirrer set at 70% of maximum speed. The glacial acetic acid was then heated to 180 °C. When the temperature and flow rate had stabilized at 180 °C and 66 mL/min (3 min residence time), respectively, the benzophenone solution and the hydroxylamine solutions were combined into one, and the reactor inlet tube transferred to the resulting solution. The reactor outlet tube was placed into an ice bath where the white precipitate formed was collected. When the last of the reaction mixture had entered the inlet tube, glacial acetic acid (200 mL) was added to the inlet to flush the system. The precipitate collected at the end of the reaction was filtered, washed with water, redissolved in ethyl acetate (6 L), and washed with saturated sodium bicarbonate (4 L). The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford *N*-phenylbenzamide (270 g, 50% yield) as a white solid.

Preparation of 2-Amino-4-phenylthiazole Performed in a 10 mL Sealed Vessel. Phenacyl chloride (77 mg, 0.50 mmol), thiourea (57 mg, 0.75 mmol), and ethanol (2 mL) were combined in a 10 mL capacity microwave tube equipped with a stir bar. The vessel was sealed, placed into the cavity of a CEM Discover microwave unit and the contents heated to 140 °C using an initial microwave power of 300 W, this taking 90 s. The reaction mixture was held at this temperature until a total time of 5 min had elapsed. After being allowed to cool to 50 °C, the contents of the reaction vessel were poured into a separatory funnel containing saturated sodium bicarbonate (20 mL). The aqueous phase was extracted twice with diethyl ether (20 mL). The organic phases were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 2-amino-4-phenylthiazole (71 mg, 80% yield)

as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.40 (m, 2H), 7.32 (m, 1H), 6.75 (s, 1H), 5.04 (bs, 2H).

Preparation of 2-Amino-4-phenylthiazole Performed in an Open Vessel in a Monomode Microwave Apparatus. Phenacyl chloride (1.93 g, 12.5 mmol), thiourea (1.43 g, 18.8 mmol), and ethanol (50 mL) were combined in a 100 mL round-bottom long neck flask equipped with a stir bar. The flask was placed in the cavity of a CEM Discover microwave unit, an attenuator was put in place, and a reflux condenser was attached to the flask. The solution was heated to reflux (79 °C) using an initial microwave power of 200 W and then held at this temperature until a total time of 5 min had elapsed. The product was isolated and purified using the same procedure as with the sealed-vessel study. 2-Amino-4-phenylthiazole (1.56 g, 71% yield) was obtained as a white solid.

Preparation of 2-Amino-4-phenylthiazole Performed in a Continuous-Flow Multimode Microwave Apparatus. Phenacyl chloride (77.25 g, 0.5 mol) and thiourea (57.1 g, 0.5 mol) were dissolved in ethanol (2 L). Ethanol was pumped through the reactor inside the microwave unit with the internal stirrer set at 70% of maximum speed. The ethanol was then heated to 140 °C. When the temperature and flow rate had stabilized at 140 °C and 34 mL/min (6 min residence time) respectively, the reactor inlet tube was transferred to the flask containing the starting materials. The reactor outlet tube was placed into an empty Erlenmeyer flask where the product mixture was collected. When the last of the reaction mixture had entered the inlet tube, ethanol (200 mL) was added to the inlet to flush the system. The collected product solution was concentrated under reduced pressure to 500 mL. The concentrate was poured into diethyl ether (3 L), and the resulting white solid was filtered and then added to a separatory funnel containing saturated sodium bicarbonate (500 mL). The aqueous phase was extracted twice with diethyl ether (500 mL). The organic phases were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 2-amino-4-phenylthiazole (85 g, 97% yield) as a white solid.

Preparation of Methyl N-Phenyl-3-aminopropanoate Performed in a Multimode Microwave Unit Equipped with a 20-Position Rotor. In each of twenty 30 mL quartz tubes was placed 15 mL of a stock solution of aniline (260 mL, 2.85 mol), methyl acrylate (257 mL, 2.85 mol), acetic acid (16 mL, 0.29 mol), and a magnetic stir bar. The vessels were each placed into an individual PEEK vessel cover containing a window in the bottom quadrant, sealed with a screw cap, and placed into a 20-position rotor. The rotor was placed into a Milestone MicroSynth microwave unit. Using an initial microwave power of 1000 W, the contents of the reaction vessels were heated from room temperature to 200 °C as dictated by the IR monitor. The individual temperature profiles of all 20 vessels were recorded simultaneously by means of an infrared sensor reading the temperature of each vessel through the window in the vessel cover. The contents of the vessels took the total allotted reaction time of 20 min to reach 198 °C. Upon completion, the reaction mixtures were allowed to cool to room temperature, the tubes opened and the crude product conversion of a representative selection of the vessels determined by NMR spectroscopy. Then the contents of all vessels were combined and an overall product yield determined (78%). ^{1}H NMR ($CDCl_3$): δ 7.18 (t, $J = 7.5$ Hz, 2H), 6.70 (t, $J = 7.3$ Hz, 1H), 6.62 (d, $J = 7.7$ Hz, 2H), 4.00 (bs, 1H), 3.70 (s, 3H), 3.46 (t, $J = 6.4$ Hz, 2H), 2.63 (t, $J = 6.4$ Hz, 2H).

Preparation of 4′-Methoxycinnamic Acid Performed in a Dedicated Microwave Unit Equipped with a Sealed Vessel. A 2 ppm Pd standard stock solution was prepared by diluting a commercially available 1000 ppm Pd solution (1.0 mL) to 500 mL with deionized water. 4-Bromoanisole (12.5 mL, 100 mmol), methyl acrylate (18 mL, 200 mmol), potassium carbonate (51.2 g, 370 mmol), tetrabutylammonium bromide (32.2 g, 100 mmol), 2 ppm Pd stock solution (100 mL, 1.88 μmol, 0.002 mol %), and water (100 mL) were combined in a 350 mL Teflon vessel. The vessel was heated in a Biotage Advancer microwave unit to 170 °C using a 0.5 °C/s ramp (this taking 5 min) while agitating the reaction mixture by means of a mechanical stirrer. The contents of the vessel were then held at this temperature for 15 min The product mixture was then adiabatically cooled by rapid expansion into a stainless steel collection vessel. The contents of the collection vessel were added into dilute hydrochloric acid (600 mL of a 2 M solution), whereupon a white precipitate formed. The mixture was extracted twice with ethyl acetate (500 mL), and the organic fractions combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The white solid obtained was recrystallized from ethanol (70 mL) to yield 4′-methoxycinnamic acid (16.6 g, 93% yield) as colorless needles. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.0 (bs, 1H), 7.64, 6.97 (AA′XX′ peak, $J_{aa'} = J_{xx'} = 2.5$, $J_{ax} = 8.5$, $J_{ax'} = 0.2$ Hz, 4H), 7.55 (d, $J = 15.9$ Hz, 1H), 6.38 (d, $J = 15.9$ Hz, 1H), 3.80 (s, 3H).

Esterification of Acetic Acid Performed in an Open Vessel in a Multimode Microwave Apparatus. Glacial acetic acid (347 mL, 6 mol), butanol (553 mL, 6 mol), and concentrated sulfuric acid (3 mL, 1 wt %) were placed in a 3 L three neck round-bottom flask equipped with a stir bar. The round-bottom flask was placed in a CEM MARS microwave unit and equipped with a glass extender tube onto which a Dean–Stark trap was attached followed by a reflux condenser. A glass thermal well was placed into one of the necks of the flask in order to measure temperature using a fiber-optic probe. The solution was heated to 103 °C using an initial microwave power of 1000 W and held at this temperature until a total time of 10 min had elapsed, during which water (35 mL) was collected in the Dean–Stark trap. The temperature of the reaction mixture was then raised to 117 °C and held until no further water was collected in the Dean–Stark trap. Upon cooling, an 89% conversion to butyl acetate was determined by NMR spectroscopy.

Esterification of Acetic Acid Performed in a Continuous-Flow Multimode Microwave Apparatus. Glacial acetic acid (2.5 L, 43.8 mol) and butanol (2 L, 21.9 mol) were combined in a 6 L flask. Glacial acetic acid was pumped through the reactor inside the microwave unit with the internal stirrer set at 70% of maximum speed. The ethanol was then heated to 150 °C. When the temperature and flow rate had stabilized at 150 °C and 200 mL/min (1 min residence time), respectively, concentrated sulfuric acid (15 mL, 27 mmol) was added to the flask containing the reagents, and then the reactor inlet tube was transferred to the flask. The reactor outlet tube was placed into

an Erlenmeyer flask containing sodium bicarbonate (1 kg). When the last of the reaction mixture had entered the inlet tube, glacial acetic acid (200 mL) was added to the inlet to flush the system. The resulting solution was washed with water (2 L). The organic fraction was dried over magnesium sulfate and filtered. Analysis by NMR spectroscopy showed the solution composition to be 78% butyl acetate and 20% butanol.

Transesterification of Diethyl Adipate with Butanol Performed in an Open Vessel in a Multimode Microwave Apparatus. Diethyl adipate (200 mL, 1 mol), butanol (182 mL, 2 mol), and concentrated sulfuric acid (1.5 mL, 1 wt %) were placed in a 3 L three neck round-bottom flask equipped with a stir bar. The round-bottom flask was placed in a CEM MARS microwave unit and equipped with a glass extender tube onto which a Dean–Stark trap was attached followed by a reflux condenser. A glass thermal well was placed into one of the necks of the flask in order to measure temperature using a fiber-optic probe. The solution was heated to 105 °C using an initial microwave power of 1600 W and held at this temperature until a total time of 10 min had elapsed. The temperature of the reaction mixture was then raised to 115 °C and held until no further ethanol was collected in the Dean–Stark trap. The temperature of the reaction mixture was then raised to 145 °C and held until no further butanol was collected in the Dean–Stark trap. Upon cooling, a 59% conversion to dibutyl adipate was determined by NMR spectroscopy.

Dehydration of 2-Octanol Performed in an Open Vessel in a Multimode Microwave Apparatus with Continuous Addition. 2-Octanol (160 mL, 1 mol) and concentrated sulfuric acid (6 mL) were placed in a 3 L three neck round-bottom flask equipped with a stir bar. The round-bottom flask was placed in a CEM MARS microwave unit and equipped with a glass extender tube onto which a Dean–Stark trap was attached followed by a reflux condenser. A glass thermal well was placed into one of the necks of the flask in order to measure temperature using a fiber-optic probe. Into the other neck was placed a Teflon tube that passed out of the microwave unit to a peristaltic pump. The reaction mixture was heated to 145 °C using an initial microwave power of 800 W, and once at temperature, 2-octanol was added to the flask at a rate of 15 mL/min. The octene and water formed were collected in the Dean–Stark trap. After processing 300 mL of 2-octanol the process was halted. Upon analysis by NMR spectroscopy the product formed was found to be mainly 2-octene (a mixture of *cis* and *trans*) and <5% 1-octene.

Preparation of Fluorescein in an Open Vessel in a Monomode Microwave Apparatus. Resorcinol (220.2 g, 2.0 mol) and phthalic anhydride (148.1 g, 1.0 mol) were ground together in a mortar and pestle and then transferred to a dedicated 500 mL reaction pot. The pot lid with four ports was secured using a custom-made Teflon collar. The vessel was placed inside a CEM MARS multimode microwave unit. The reaction mixture was stirred by means of an overhead paddle stirrer inserted through the center port in the reaction pot. The other three ports were sealed using rubber septa. Through one septum, a glass thermal well was inserted in order to measure temperature using a fiber-optic probe. The positioning of the thermal well was initially just above the vessel contents, so that the mechanically stirred solids would not break it. Two PTFE tubes (3 mm inner diameter) were threaded through another septum and out of the MARS system to provide an outlet for the water released during the course of the reaction. Initially the reaction mixture was heated for 5 min using a continuous power of 800 W. A temperature of 100 °C was reached as monitored by an external hand-held IR thermometer. At this point, the fiber optic temperature probe was lowered into the reaction contents since they had liquefied. Using an initial microwave power of 1600 W, the contents of the reaction vessel were heated to 220 °C, this taking 5 min, and then held at this temperature for a further 10 min The resulting molten mixture was allowed to cool to 80 °C, before being dissolved in aqueous sodium hydroxide (2 L of a 2 M solution). Crude product was precipitated out of the basic solution as an orange-red powder by the slow addition of hydrochloric acid (700 mL of a 6.0 N solution). The solid was filtered, and transferred to a 5 L round-bottom flask and water (2 L) added. The flask was placed into the cavity of the MARS microwave unit and refluxed for 20 min Upon cooling, the reaction mixture was filtered and allowed to air-dry to afford fluorescein (250 g, 80% yield) as a dark red powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 (bs, 2H), 7.99 (dt, $J = 7.5$, 1.2 Hz, 1H), 7.80 (td, $J = 7.5$, 1.2 Hz, 1H), 7.27 (dt, $J = 7.5$, 1.1 Hz, 1H), 6.69 (m, 2H), 6.57 (m, 2H).

Preparation of Fluorescein in an Open Vessel in a Dedicated Monomode Microwave Apparatus Equipped with a Tilted Glass Vessel. Resorcinol (330.0 g, 3.0 mol) and phthalic anhydride (222.1 g, 1.5 mol) were ground together in a mortar and pestle and then transferred to a dedicated 3 L capacity glass vessel. The vessel was placed inside a Milestone SPMR multimode microwave unit, and a ceramic thermal well containing a fiber-optic probe was inserted into the reaction mixture. The contents of the vessel were agitated by rotation. The reaction mixture was heated to 220 °C over the period of 15 min using variable microwave power so as to ensure a linear temperature ramp. The reaction mixture was then held at 220 °C for a further 15 min The resulting molten mixture was allowed to cool to 80 °C before water (300 mL)was added, then reheated to 80 °C over the period of 2 min, and held at this temperature for 20 min. Upon cooling, the crude product was filtered and then transferred back into the reaction vessel containing clean water (300 mL). The contents were then heated using the microwave unit to 80 °C over the period of 5 min and held at this temperature for 10 min. Upon cooling the product was filtered and allowed to air-dry to afford fluorescein (397 g, 85% yield) as a dark red powder.

Ethoxycarbonylation of Iodobenzene Using a Multimode Microwave Unit Equipped with an Eight-Position Rotor. A stock solution of palladium(II) acetate (22.4 mg, 0.100 mmol) in ethanol (92 mL) was prepared. To each of eight quartz vessels equipped with a stir bar were added iodobenzene (1.40 mL, 12.5 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (2.10 mL, 13.75 mmol), and the ethanol solution (11.5 mL, 0.1 mol % palladium), for a total volume of 15 mL in each vessel. The vessels were loaded onto the rotor and each individually charged with carbon monoxide (250 psi). [CAUTION: When loading vessels with carbon monoxide, extreme care needs to be taken.] The rotor was loaded into an Anton Paar Synthos 3000

microwave and heated to 125 °C using a microwave power of 1200 W. The reaction mixture was held at this temperature until a total reaction time of 30 min had elapsed. The maximum pressure during this process was measured to be 19.5 bar (~283 psi). Upon cooling, the vessels were vented and their contents combined with brine (200 mL) and aqueous hydrochloric acid (10 mL of a 2 M solution). Extraction with diethyl ether (3 × 250 mL) and addition of petroleum ether (400 mL) to the combined organics yielded a biphasic solution. The lower layer (consisting primarily of ethanol) was removed. The remaining organic layer was washed with hydrochloric acid (50 mL of a 2 M solution) then brine (50 mL). The organic layer was concentrated under reduced pressure. Silica gel (200 g) chromatography (hexane to elute the iodobenzene, followed by 10% ethyl acetate in hexane) yielded pure ethyl benzoate (12.17 g, 81% yield).

Preparation of 4-Methylbiphenyl Performed in a Continuous-Flow Multimode Microwave Apparatus Using Potassium Hydroxide as Base. Ethanol was pumped through the Flowsynth with the internal stirrer set at 70%. The ethanol was then heated to 140 °C. When the temperature and flow rate had stabilized at 140 °C and 40 mL/min (5 min residence time) respectively, the reaction solution was prepared. Phenylboronic acid (79.2 g, 0.65 mol), 4-bromotoluene (85.6 g, 0.5 mmol), ethanolic potassium hydroxide (0.5 M, 2 L, 1 mol), and 1000 ppm Pd standard solution (1.0 mL, 9.4 μmol, 0.002 mol %) were thoroughly swirled until all of the starting materials had dissolved. The reactor inlet tube transferred to the flask containing the combined reactants. The reactor outlet tube was placed into an empty Erlenmeyer flask where the product was collected. When the last of the reaction mixture had entered the inlet tube, ethanol (200 mL) was added to the inlet to flush the system. The product solution collected was concentrated under reduced pressure to a total volume of approximately 500 mL and then poured into a separatory funnel containing diethyl ether (2 L) and water (1 L). The aqueous fraction was washed with additional diethyl ether (2 L). The organic fractions were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Analysis by NMR showed a 63% conversion to 4-methylbiphenyl.

Preparation of 4-Methylbiphenyl Performed in a Continuous-Flow Multimode Microwave Apparatus Using Sodium Hydroxide as Base. Ethanol was pumped through the Flowsynth with the internal stirrer set at 70%. The ethanol was then heated to 150 °C. When the temperature and flow rate had stabilized at 150 °C and 40 mL/min (5 min residence time), respectively, the reaction solution was prepared. Phenylboronic acid (39.6 g, 0.325 mol), 4-bromotoluene (42.5 g, 0.25 mmol), sodium hydroxide (2.0 M, 250 mL, 0.5 mol), ethanol (200 proof, 750 mL), and 1000 ppm Pd standard solution (10.0 mL, 94 μmol, 0.038 mol %) were thoroughly swirled until all of the starting materials had dissolved. The reactor inlet tube transferred to the flask containing the combined reactants. The reactor outlet tube was placed into an empty Erlenmeyer flask where the product was collected. When the last of the reaction mixture had entered the inlet tube, ethanol (200 mL) was added to the inlet to flush the system. The product solution collected was concentrated under reduced pressure to a total volume of approximately 500 mL and then poured into a separatory funnel containing diethyl ether (2 L) and water (1 L). The aqueous fraction was washed with additional diethyl ether (2 L). The organic fractions were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure, to afford 4-methylbiphenyl as a white solid (34.8 g, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.52, 7.27 (AA′XX′ peak, $J_{aa'} = J_{xx'} = 2.0$, $J_{ax} = 7.7$, $J_{ax'} = 0.5$ Hz, 4H), 7.45 (m, 2H), 7.34 (m, 2H), 2.42 (s, 3H).

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