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Open-Vessel Microwave-Promoted Suzuki Reactions Using Low Levels of Palladium Catalyst: Optimization and Scale-Up

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Abstract:

Representative Suzuki couplings in water using low catalyst concentrations in conjunction with microwave heating have been transferred from sealed-vessel to open-vessel reaction conditions. They have then been scaled-up to the mole scale using a dedicated multimode microwave apparatus. The reactions are complete within 20 min of heating at reflux.

Introduction

Microwave-promoted synthesis is an area of increasing interest in both academic and industrial laboratories.[1–3] As well as being energy efficient,[4] microwave heating can also enhance the rate of reactions and in many cases improve product yields. An area of increasing research interest is the scale-up of microwave-promoted chemistries. While many reactions have been performed on the small scale using microwave heating, few have been further developed into larger-scale syntheses. This clearly needs to be addressed if the technology is going to impact process chemistry.[5,6] 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.[7–11] The drawback of a continuous flow microwave apparatus is 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, reoptimization of reaction conditions often being required. The other option is to use a batch-type process. This could either involve using one large vessel[12–14] or parallel batch reactors.[15,16] A drawback with performing large-scale reactions in batch mode can be the penetration of microwave irradiation into the reaction mixture as the vessel size is increased. Continuously stirring the reaction mixture offsets this problem to some degree.

Our research in the area of microwave-promoted chemistry recently led to the discovery that it is possible to perform Suzuki couplings in water using ultralow quantities of palladium catalyst.[17–20] Water is an excellent solvent for microwave-promoted synthesis. Although it has a dielectric loss factor which puts it into the category of only a medium absorber, even in the absence of any additives it heats rapidly

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(1) A number of books on microwave-promoted synthesis have been published recently: (a) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinhiem, 2005. (b) Lidström, P., Tierney, J. P., Eds. *Microwave-Assisted Organic Synthesis*; Blackwell: Oxford, 2005. (c) Loupy, A., Ed. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, 2002. (d) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002.

(2) For a recent review see: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.

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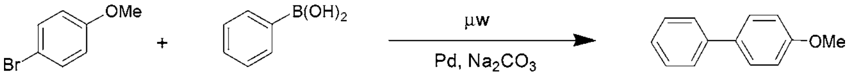
Table 1. **Optimisation of conditions for the open-vessel microwave-promoted Suzuki reactions in water**



entry	reaction conditions[a,b]	product yield (%)
1	18.5 mmol Na_2CO_3, 5 mmol TBAB, 0.045 mol % Pd, 30 mL H_2O, 0 min	68
2	18.5 mmol Na_2CO_3, 5 mmol TBAB, 0.045 mol % Pd, 30 mL H_2O, **20 min**	83
3	18.5 mmol Na_2CO_3, 5 mmol TBAB, **0.00045 mol % Pd**, 30 mL H_2O, **20 min**	86
4	**5 mmol Na_2CO_3**, 5 mmol TBAB, **0.00045 mol % Pd**, 30 mL H_2O, **20 min**	60
5	18.5 mmol Na_2CO_3, **1.2 mmol TBAB**, **0.00045 mol % Pd**, 30 mL H_2O, **20 min**	55
6	18.5 mmol Na_2CO_3, **0.0009 mol % Pd**, **15 mL H_2O, 15 mL EtOH**, **20 min**	70
7	18.5 mmol Na_2CO_3, **0.0045 mol % Pd**, **15 mL H_2O**, **15 mL EtOH**, **20 min**	94

[a] All reactions were performed using 5 mmol bromoanisole and 6 mmol phenylboronic acid. Reaction mixtures were heated from room temperature to reflux using an initial microwave power of 100 W and held at this temperature for the allotted time. [b] For clarity, changes in reaction conditions from entry 1 are noted in bold.

upon microwave irradiation. Water also offers practical advantages over organic solvents. It is cheap, readily available, nontoxic, and nonflammable. Our reactions were performed using a monomode microwave apparatus, working on a 1 mmol scale in a 10-mL sealed glass vessel. The reactions are run using between 50 ppb and 2.5 ppm palladium and are complete in around 5 min. This offers an easy, fast, and efficient route to biaryl-functionalised products. A further operational advantage of the methodology is that lengthy metal extraction steps for product purification may not be required because the catalyst loading is already below the specification limit for many products.[21]

Since Suzuki[22] couplings are used on a regular basis in the chemical industry for the preparation of, for example, pharmaceuticals, natural products, and advanced materials, we were keen to address issues of scale-up to prepare grams instead of miligrams of product. Some approaches to scale-up of Suzuki reactions have been published. Using a flow cell, conditions involving 20 mol % $PdCl_2(PPh_3)_2$ as the catalyst, ethanol as the solvent, and triethylamine as a base have been developed.[10] The Suzuki reaction has also been used to demonstrate the applicability of a microreactor and a flow-capillary reactor, both developed for use in conjunction with microwave heating.[23,24] Our initial approach was to use an automated stop-flow microwave system that combines the advantages of a batch reactor with those of a continuous flow reactor.[20] It is a monomode apparatus with one 80-mL vessel in the microwave cavity. The reaction mixture is pumped in to and out of the vessel by a peristaltic pump; these functions, as well as running the reaction, are controlled with the use of a computer. The reaction mixture can be introduced into the microwave vessel from two separate feed lines. After the reaction is complete, the reaction vessel can be vented to remove an overpressure and then the contents of the reactor pumped into a collection vessel. This allowed us to scale the reaction from the 1 mmol level to batches of 10 mmol. However, we were keen to develop a procedure for the preparation of multigram quantities of biaryls rapidly and efficiently. To do this, we decided to move away from sealed tubes and instead move towards using an open-vessel since, when working on a large scale, atmospheric pressure conditions offer significant safety and operational advantages. To do this we needed to reoptimise our reaction conditions using a monomode microwave apparatus and then test them on larger scales using a multimode microwave. Our results are presented here.

Results and Discussion

Our first objective was to transfer our Suzuki coupling methodology from sealed-vessel to open-vessel operation. To do this we used the same monomode microwave apparatus as employed for the sealed-vessel experiments since it has the capability to run reactions in open round-bottom flasks of capacity up to 125 mL. The apparatus is equipped with 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 and using a 100-mL round-bottom flask as the reaction vessel we screened a range of reaction conditions with 4-bromoanisole and phenylboronic acid as test substrates. Representative data are shown in Table 1. We decided to start by using, as close as possible, a directly scaled version of our sealed-vessel reaction mixture. A 1:1.2 ratio of aryl halide to boronic acid was used, tetrabutylammonium bromide, TBAB, (1 equiv.) employed as a phase transfer agent, and 30 mL of water as the solvent. When working in water, a major problem can be precipitation of palladium from a stock solution, particularly when working with a salt such as palladium acetate. This was avoided by using an acid-stabilised stock solution such as that purchased as an ICP standard for palladium. This can be diluted accordingly to give solutions of the desired concentrations. Starting with a palladium loading of 50 ppm

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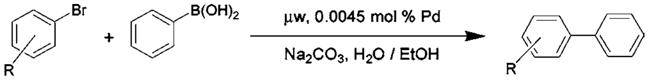
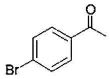
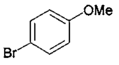
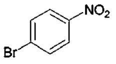
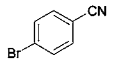
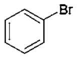
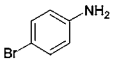
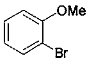
(0.045 mol %) we determined that the optimum reaction time was 20 min at reflux with shorter times leading to lower yields of the desired biaryl product (Table 1, entries 1 and 2). We then turned our attention to the catalyst loading and found that reduction to 500 ppb (0.00045 mol %) did not have a noticeable effect on product yield (Table 1, entry 3). Reduction of the sodium carbonate from 3.7 to 1 equiv or reduction of the TBAB from 1 to 0.25 equiv had a noticeably deleterious effect on product yield (Table 1, entries 4 and 5). Thinking ahead to larger-scale experiments, we were keen to find conditions that would allow us to eradicate the need for addition of TBAB to the reaction mixture for operational reasons. Purification of the product can be troublesome when considerable quantities of TBAB are used. In addition, as the scale is increased, it becomes more and more wasteful to use TBAB as an additive. We screened a water/ethanol mixture as the reaction medium since we knew that this offered an alternative to using neat water as a solvent in conjunction with TBAB.[20] Using a 1:1 water/ethanol mixture as solvent, we found that higher levels of palladium were required to obtain acceptable yields of the desired biaryl product, with catalyst loadings of 1 ppm (0.0009 mol %) and 5 ppm (0.0045 mol %) leading to product yields of 70% and 94%, respectively. This could be due, at least in part, to the fact that the reaction mixture reached reflux at a lower temperature (82 °C) when using the water/ethanol mixture as solvent as opposed to neat water.

We decided that the operational advantages brought by eradicating TBAB from the reaction mixture overcame the disadvantages of having to use a somewhat higher palladium loading. So, with our optimal reaction conditions in hand, we screened a range of aryl bromides in the coupling with phenylboronic acid. The results are shown in Table 2. Comparable yields of product were obtained using the new open-vessel conditions and previously published sealed-vessel conditions.[25] In the case of 2-bromoanisole a lower yield was obtained than when using the para substituted analogue (Table 2, entries 2 and 7). This is also seen when using sealed-vessel conditions and could be attributed, at least in part, to steric effects. Since the reaction is run in water/ethanol as a solvent, isolation of the product can be achieved with a simple aqueous/organic extraction. Since the palladium concentration is low (5 ppm), its removal from the product mixture often is not necessary or, when it is desired, is simple since it stays in the aqueous washings during the product extraction procedure. The reactions could be scaled up further to 10 mmol using the same apparatus, but beyond this the quantity of material became too large for performing the chemistry in a 100-mL reaction vessel.

Table 2. **Open-vessel microwave-promoted Suzuki reactions in water**[a]



entry	aryl bromide	product yield (%)
1		99
2		94
3		92
4		94
5		93
6		91
7		59

[a] Reactions were performed using 5 mmol aryl halide, 6 mmol phenylboronic acid, and 0.0045 mol % Pd as catalyst. Reaction mixtures were heated from room temperature to reflux (80−83 °C) using an initial microwave power of 100 W and held at this temperature for 20 min.

To scale-up the reaction further we moved to a multimode microwave apparatus. Reports in the literature discussing transfer of sealed-vessel chemistry from monomode to multimode apparatus suggest that this can be achieved with little or no modification of reaction conditions. Using a 1-L round-bottom flask, we attempted to scale the reaction of 4-bromoanisole and phenylboronic acid from 5 mmol to 0.25 mol. Our results are shown in Table 3. The multimode microwave apparatus was again equipped with an opening in the top through which a glass tube could be placed, connecting the flask in the microwave cavity with a reflux condenser located outside the microwave apparatus. Working on a large scale, accurate temperature measurement and control is important. This was achieved using a fiber-optic probe inserted into the reaction mixture by means of a glass thermowell. Using reaction conditions identical to those of the 5 mmol reaction, we were able to scale the reaction to 0.25 mol with no significant difference in product yield (Table 3, entry 1). We next moved to the 1 mol scale, working in a 3-L reaction vessel. Again, we obtained a comparable product yield in the coupling of 4-bromoanisole and phenylboronic acid (Table 3, entry 2). Using an initial microwave power of 600 W, the reaction took between 3 and 4 min to reach reflux temperature (82 °C). Since we used a very efficient reflux condenser, we were able to continue putting in close to the maximum allotted microwave power during the course of the reflux. We wanted to reassess the effects of catalyst concentration on the reaction and found that it was possible to reduce the palladium loading from 0.0045 mol % (5 ppm) to 0.0009 mol % (500 ppb) with no decrease in product yield (Table 3, entry 3). We re-ran the reaction but stopped it once it had reached reflux temperature. Analysis of the mixture showed that the reaction had essentially reached completion within this time. However, since we wanted to develop a methodology applicable to a range of substrates, we decided to run the reactions for 20

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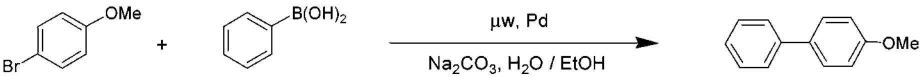
(25) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660.

Table 3. **Optimisation of conditions for the open-vessel multimode microwave-promoted Suzuki reaction in water**



entry	reaction conditions[a]	product conversion (%)[b]
1	0.25 mol 4-bromoanisole, 0.3 mol phenylboronic acid, 0.925 mol Na_2CO_3, 0.0045 mol % Pd, 100 mL H_2O, 100 mL EtOH	99
2	1 mol 4-bromoanisole, 1.2 mol phenylboronic acid, 3.7 mol Na_2CO_3, 0.0045 mol % Pd, 500 mL H_2O, 500 mL EtOH	99
3	1 mol 4-bromoanisole, 1.2 mol phenylboronic acid, 3.7 mol Na_2CO_3, 0.0009 mol % Pd, 500 mL H_2O, 500 mL EtOH	99

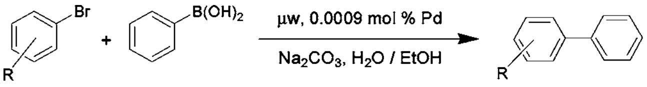
[a] Reaction mixtures were heated from room temperature to reflux (~83 °C) using an initial microwave power of 600 W and held at this temperature for 20 min. [b] Determined using GC−MS analysis.

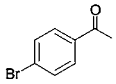
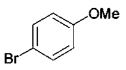
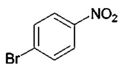
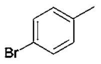
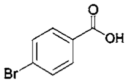
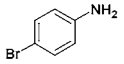
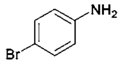
min to ensure complete conversion of the starting materials to the desired biaryl product. The reaction mixture was stirred throughout the reaction by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. However, with the large quantities of material in the flask, better mixing can be obtained using an overhead paddle stirrer. A Teflon paddle attached to a glass shaft can be introduced into the reaction mixture from above the microwave apparatus and an adaptor used for stirring using a conventional stirrer motor while also allowing for efficient reflux.

With our reaction conditions in hand, we screened a range of aryl bromides in the coupling with phenylboronic acid. The results are shown in Table 4. With one exception, comparable yields of product were obtained using the multimode microwave apparatus on the 1 mol scale and the monomode apparatus on the 5 mmol scale but with the added benefit of a lower catalyst loading. When using 4-bromoaniline we find that a higher palladium loading (0.0045 mol %) is required to obtain a good yield of the desired biaryl product. This may be due to the fact that the amine functionality in the 4-bromoaniline could coordinate to the ligandless palladium source used in the reaction.

Although we again tried to reduce the quantity of sodium carbonate used in the reaction, we were unable to do so without compromising reaction yields. From our previous work, we knew that sodium carbonate can sometimes be contaminated with traces of palladium.[18] When performing chemistry on a 1-mole scale, this clearly could be an issue, since it involves adding 392 g of Na_2CO_3 to the reaction mixture. This could make the actual catalyst loading higher than that determined on the basis of the palladium added to the reaction mixture. To determine whether this was a factor, we analysed the sodium carbonate used in the reactions using ICP-MS and found it contained less than 1.5 ppb Pd. We therefore can discount the “indirect” loading of palladium in the reaction mixture and believe our catalyst concentrations to be accurate.

Table 4. **Open-vessel microwave-promoted Suzuki reactions in water on the 1 mol scale[a]**



entry	aryl bromide	product conversion (%)
1		99 (99)[b]
2		99 (96)[b]
3		94
4		87
5		94 (93)[b]
6		50
7[c]		99

[a] Reactions were performed using 1 mol aryl halide, 1.2 mol phenylboronic acid, and 0.0009 mol % Pd as catalyst. Reaction mixtures were heated from room temperature to reflux (80−83 °C) using an initial microwave power of 600 W and held at this temperature for 20 min. [b] Isolated product yield. [c] Using 0.0045 mol % Pd as catalyst.

In summary, we have shown that low catalyst concentration Suzuki couplings can be performed in open reaction vessels using microwave heating. The reaction is scalable from the mmol to the 1 mol scale with no need for reoptimization. The reactions can be performed in air, are run using a mixture of water and ethanol as solvent, and require 1−5 ppm Pd as the catalyst. The catalyst is a cheap, readily available palladium solution, and no ligands are required. Our results compare favourably with those from Suzuki[26] coupling protocols that have been scaled up using conventional heating and reported in the literature. At the low palladium loadings reported here, we find that conventional heating results in much lower product yields and reaction times need to be in the order of hours and not minutes. Rate enhancements over conventional heating methods are attributed to localized superheating of the reaction mixture. It is also possible that at these low catalyst loadings, the microwave heating has an effect in the equilibrium for the agglomeration of the palladium atoms in the direction of very small nanoparticles. Work is currently underway to devise ways to increase the scale of the reaction further as well as to investigate the scope for scale-up of other microwave-promoted methodologies developed in our laboratories.

Experimental Section

General Methods. All materials were obtained from commercial suppliers and used without further purification. The palladium stock solution used was elemental Pd in 5−20% HCl, concentration 1000 mg/mL, J.T. Baker cat. no. 5772−04 or Aldrich cat. no. 207349. All reactions were carried out in air. ^{1}H NMR spectra were recorded at 293 K on a 300 or 400 MHz spectrometer. GC−MS analysis was run using a Perkin-Elmer AutoSystemXL Gas Chromatograph/TurboMass mass spectrometer equipped with a column Elite-5MS (30 m × 0.25 mm × 0.25 μm). All analyses were run using the following temperature gradient: temp 1, 50 °C (1 min); temp 2, 200 °C (2.57 min); rate 31.5 °C/min; temp 3, 250 °C; rate 30.0 °C/min.

Description of the Microwave Apparatus. Small-scale open-vessel microwave reactions were conducted using a commercially available monomode microwave unit (CEM Discover). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. Reactions were performed in a 100-mL round-bottom flask. The temperature of the contents of the vessel was monitored using an IR sensor located underneath the reaction vessel. The contents of the vessel are 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. Temperature, pressure, and power profiles were monitored using commercially available software provided by the microwave manufacturer. For the large-scale reactions a commercially available multimode microwave apparatus was used (CEM MARS). The machine consists of a continuous microwave power delivery system with operator selectable power output from 0 to 1200 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 either 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 or else with the use of an overhead paddle stirrer.

Representative Example of a Suzuki Coupling on a 5 mmol Scale Using the Monomode Microwave Apparatus: Reaction between 4-Bromoanisole and Phenylboronic Acid. In a 100-mL round-bottom flask was placed 4-bromoanisole (0.935 g, 0.625 mL, 5.0 mmol), phenylboronic acid (0.732 g, 6.0 mmol), Na_2CO_3 (1.86 g, 18.5 mmol), palladium stock solution (0.0045 mol % added), ethanol (15 mL), and water (15 mL). The vessel was placed into the microwave cavity. Initial microwave irradiation of 100 W was used, the temperature being ramped from rt to reflux. Once this was reached, taking around 2 min, the reaction mixture was held at this temperature for a further 20 min. After allowing the mixture to cool to room temperature, the contents of the reaction vessel were poured into a separatory funnel. Water (100 mL) and ethyl acetate (100 mL) were added, and the organic material was extracted and removed. After further extraction of the aqueous layer with ethyl acetate, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in vacuo leaving the crude product, which was characterised by comparison of NMR data with that in the literature.

Representative Example of a Suzuki Coupling on a 1 mol Scale Using the Multimode Microwave Apparatus. Reaction between 4-Bromoacetophenone and Phenylboronic Acid. In a 3-L round-bottom flask was placed 4-bromoacetophenone (199 g, 1 mol), phenylboronic acid (146 g, 1.2 mol), Na_2CO_3 (392 g, 3.7 mmol), palladium stock solution (0.0009 mol % added), ethanol (500 mL), and water (500 mL). The vessel was placed into the microwave cavity. Initial microwave irradiation of 600 W was used, the temperature being ramped from rt to reflux. Once this was reached, taking 3−4 min, the reaction mixture was held at this temperature for a further 20 min. After allowing the mixture to cool to room temperature, the contents of the reaction vessel were poured into a separatory funnel. Water (1.5 L) and ethyl acetate (1.5 L) were added, and the organic material was extracted and removed. After further extractions of the aqueous layer with ethyl acetate and combining the organic washings, the ethyl acetate was removed in vacuo leaving the 4-acetylbiphenyl product as a white solid (193 g), which was characterised by comparison of NMR data with that in the literature.

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Supporting Information Available

Images of the open-vessel microwave apparatus used. This material is available free of charge via the Internet at http://pubs.acs.org.

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