# Solvent-Free, Open-Vessel Microwave-Promoted Heck Couplings: From the mmol to the mol Scale

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**Abstract:** The rapid, microwave-promoted Heck coupling of aryl iodides in open reaction vessels is presented and scale-up of the reactions to the mol scale demonstrated. Reactions are performed using 0.1 mol% palladium acetate as the catalyst, sodium carbonate and tributylamine as bases and tetrabutylammonium bromide as an additive.

Key words: palladium, Heck reaction, catalysis, solvent-free, microwave

The palladium-catalyzed C–C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base is well known now as the Heck reaction.<sup>1,2</sup> There have been a number of recent reviews of the scope and versatility of the reaction.<sup>3–7</sup> Its popularity started to grow in the mid 1980's when synthetic chemists found that they were able to control the reaction and use it to make disubstituted olefins. More recently, the intramolecular Heck reaction has also been well-established as a powerful synthetic tool.<sup>8,9</sup> It can be used for the construction of complex polycyclic ring systems in the context of natural product synthesis.<sup>10</sup>

Microwave heating is an area of increasing interest in both academic and industrial laboratories because it can enhance the rate of reactions and in many cases improve product yields.<sup>11–13</sup> Microwave heating has been used as a tool in Heck coupling reactions with considerable success.<sup>14,15</sup> Microwave heating has also been used for oxidative Heck couplings.<sup>16</sup> Considerable attention has been focused on the use of microwave heating in conjunction with water<sup>17</sup> or ionic liquids<sup>18,19</sup> as solvents for the reaction but other media, such as fluorous solvents, can also be used.<sup>20</sup>

While many reactions have been performed on the small scale using microwave heating, relatively few have been further developed into larger-scale syntheses. This clearly needs to be addressed if the technology is going to impact process chemistry.<sup>21,22</sup> 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.<sup>23–27</sup> 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; 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<sup>28-30</sup> or parallel batch reactors. The latter has recently been applied successfully by Kappe and coworkers to the scale-up of reactions such as the Biginelli dihydropyrimidine synthesis, the Diels-Alder cycloaddition as well as a Heck coupling.<sup>31</sup> The Heck chemistry was performed using four sealed reaction vessels, each containing 20 mmol of substrate. More recently, Alcázar and co-workers have used a similar parallel scale-up methodology to perform alkylation reactions.<sup>32</sup> In both reports, translation of reaction conditions developed on commercially available single-mode to a multimode reactor for the scale-up proved not to be a problem.

In our laboratories, we have investigated the scale-up of microwave-promoted Suzuki and Heck reactions in water as a solvent. One approach we have taken is to use an automated stop-flow apparatus, this bringing together some of the advantages of a batch reactor with those of a continuous flow reactor. This allowed us to scale the reactions from the 1-mmol level to batches of 10 mmol.<sup>33</sup> However, we were keen to develop a procedure for the preparation of multigram quantities of product in one run. To do this, we decided to move away from sealed tubes and instead investigate the possibility of using an open vessel since, when working on a large scale, atmospheric pressure conditions offer significant safety and operational advantages.

The microwave-promoted Heck reaction has been performed using open-vessel conditions before. Varma and co-workers have used palladium chloride and a tetraphenylphosphonium bromide intercalated clay as a catalyst mixture for the reaction, using DMF as a solvent and heating the reaction for 1–36 hours.<sup>34</sup> Ritter and coworkers have used the Heck reaction in their microwavepromoted synthesis of organic polymers.<sup>35</sup> They perform their reactions on a 1-mmol scale at reflux in organic solvents such as dioxane.

We wanted to perform the open-vessel Heck reaction solvent-free since this could have further operational advantages as well as being a topic that has received considerable attention in conjunction with conventional

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Table 1 Optimization of Conditions for the Heck Reaction



<sup>a</sup> Reactions were run in a 50 mL round-bottomed flask with a reflux condenser attached. The reaction mixture was stirred throughout the microwave heating.

<sup>b</sup> For clarity, changes in reaction conditions from entry 1 are noted in bold.

heating.36-42 Our starting point was to use reaction conditions similar to those developed for the conventional solvent-free Heck coupling; namely using ligandless palladium sources as catalysts, a suitable base and tetrabutylammonium bromide (TBAB) as an additive. As substrates for the reaction, we used 4-bromoacetophenone as the halide component and methyl acrylate as the olefin in a 1:2 stoichiometric ratio. We performed screenings on a 5-mmol scale. Initially, 1 mol% Pd(OAc)<sub>2</sub> was used as the catalyst<sup>43</sup> and sodium carbonate (3.7 equiv) as base. A monomode microwave apparatus was used. The reaction mixture was heated to 120 °C using a microwave power of 150 W, this taking around 45 seconds, and held at this temperature for 20 minutes giving a 43% yield of the desired product (Table 1, entry 1). We decided to add an organic amine to the reaction mixture since this is known to have beneficial effects on the Heck coupling since it potentially can act as a base, a ligand for the palladium catalyst and a sequestrating agent for the HBr generated in the reaction. Keeping all other parameters the same, addition of tributylamine to the reaction mixture resulted in a significant increase in product yield (Table 1, entry 2). A gray colloidal palladium species was clearly observable at the end of the reaction. No product was obtained if the reaction is run in the absence of TBAB (Table 1, entry 3). The catalyst loading could be reduced to 0.1 mol% with no effect on product yield (Table 1, entry 4). The quantity of sodium carbonate could be reduced to 2 equivalents with no effect on product yield (Table 1, entry 5) The time for which the reaction is held at 120 °C could be reduced to 10 minutes with no significant effect on product yield (Table 1, entry 6). The time could be dramatically reduced if the reaction was run at 150 °C. At this temperature, the reaction reaches completion within a total reaction time of 90 seconds. The mixture was heated to 150 °C using a microwave power of 150 W, this taking approximately 1 minute, and then held at this temperature until a total reaction time of 90 seconds had elapsed. There is a slight sacrifice in product yield; the yield under these conditions being 78% (Table 1, entry 7).

We decided to screen a range of aryl halide substrates in the Heck coupling with methyl- and *n*-butyl acrylate using our 90 seconds reaction time conditions (Table 1, entry 7). The results are shown in Table 2. In the coupling with methyl acrylate, aryl iodides (Table 2 entries 1–6) couple better than bromides (Table 2 entries 7–11) using this methodology. This is not unexpected in the light of literature to date. In couplings with representative aryl iodides, comparable or slightly better yields are obtained with *n*butyl acrylate and methyl acrylate (Table 2, entries 12– 14). Reduction of the stoichiometric ratio of aryl iodide to butyl acrylate from 1:2 to 1:1 has a deleterious effect on the product yield; the yield dropping in the coupling with 4-iodoanisole from 90% to 81% (Table 2, entries 12 and 15).

 Table 2
 Heck Coupling of Aryl Halides<sup>a</sup>







<sup>a</sup> Reactions were run in a 50-mL round-bottomed flask with a reflux condenser attached using 5 mmol aryl halide, 10 mmol alkene, 10 mmol Na<sub>2</sub>CO<sub>3</sub>, 5 mmol Bu<sub>3</sub>N and 5 mmol TBAB. An initial microwave irradiation power of 150 W was used, the temperature being ramped from r.t. to 150 °C and held until a total reaction time of 90 s had elapsed. The reaction mixture was stirred throughout the microwave heating.

Our next objective was to scale-up the reaction from 5 mmol to 1 mol. Our results are shown in Table 3. We decided to do this in increments using the coupling of iodobenzene and butyl acrylate as our test reaction. Moving from 5 mmol to 10 mmol required moving from a 50-mL to a 100-mL reaction vessel. This could still be accommodated in the monomode microwave apparatus and, using identical reaction conditions, a 97% yield of the desired product was obtained (Table 3, entry 1).

To scale-up the chemistry further, we needed to move from a monomode to a multimode microwave apparatus. Using a 3-L round-bottomed flask, we attempted to scale the reaction of iodobenzene and butyl acrylate from 10 mmol to 0.5 mol. 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. Since calculations suggest that the Heck reaction is somewhat exothermic, we wanted to be cautious when irradiating large quantities of reagents with microwaves in our solvent-free protocol.44 We performed the reaction using an initial microwave power of 600 W.6 The reaction mixture was heated to 150 °C over a 3 minutes time period but, even after the microwave irradiation was stopped, the contents of the vessel continued to heat to 180 °C demonstrating the exothermic nature of the reaction once initiated. A quantitative conversion to the desired product was obtained. We repeated the reaction on the 0.5-mol scale but heating to 100 °C and holding at this temperature for 10 minutes. In this case, the heating profile of the reaction was more controllable and again a quantitative conversion to the desired product was obtained. We then scaled the reaction to 1 mol and performed the reaction using the same reaction conditions; namely using 600 W microwave irradiation, heating to 100 °C and holding for 10 minutes. The reaction was performed in a 5-L reaction vessel. Although the temperature continued to rise after microwave irradiation was stopped, the heating profile of the reaction was controllable. A quantitative conversion of the desired product was obtained, this corresponding to a 96% isolated yield after work-up. The work-up procedure involved dilution of the reaction mixture with ethyl acetate (500 mL) followed by a hot filtration, washing the solid (sodium carbonate) remaining on the filter with ethyl acetate and then allowing the filtrate to cool. This resulted in the precipitation of the TBAB out of solution. The product, unreacted butyl acrylate, tributylamine and tributylamine hydroiodide remained in solution. The recovered TBAB was very pure and could be recycled in further reactions.

In summary, we have presented here a methodology for fast, solvent-free, open-vessel microwave-promoted Heck couplings of aryl iodides. We show that, with proper precautions, the reaction can readily be scaled from the mmol to the mol level.

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Table 3 Scale-Up of the Heck Reaction<sup>a</sup>

	-IOBu +OBu	MW, 0.1 mol% Pd(OAc) <sub>2</sub> 2 equiv Na <sub>2</sub> CO <sub>3</sub> , 1 equiv Bu <sub>3</sub> N, 1 equiv TBAB	OBu	
Entry	Reaction conditions			Conversion (%)
1	5-mmol scale, 50-mL vessel, monomode microwave apparatus, 150 W microwave power; temperature ramped from r.t. to 150 °C and held until a total reaction time of 90 s had elapsed			97
2	0.5-mol scale, 3-L vessel, multimode apparatus, 600 W microwave power; temperature ramped from r.t. to 150 $^{\circ}\text{C}$ over a 3 min period			100
3	0.5-mol scale, 3-L vessel, multimode apparatus, 600 W microwave power; temperature ramped from r.t. to 100 $^{\circ}$ C and held for 10 min			100

4 1.0-mol scale, 5-L vessel, multimode apparatus, 600 W microwave power; temperature ramped from r.t. to 100 °C 100 and held for 10 min 96<sup>b</sup>

<sup>a</sup> Reactions were run in a round-bottomed flask with a reflux condenser attached. The reaction mixture was stirred throughout the microwave heating.

<sup>b</sup> Isolated yield after work-up.

### **Description of the Microwave Apparatus**

Commercially available microwave apparatus was used for the reactions. Monomode: small-scale open-vessel microwave reactions were conducted using a commercially available monomode microwave unit. The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0-300 W. Reactions were performed in 50-mL or 100-mL round-bottomed flasks. The apparatus is equipped with an opening in the top (attenuator) through which a glass tube can be placed connecting the flask in the microwave cavity with a reflux condenser located outside the microwave. 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 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 Synthesis). The machine consists of a continuous microwave power delivery system with operator selectable power output from 0-1200 W. Reactions were performed in either a 3-L or 5-L round-bottomed flask. The apparatus is equipped with an opening in the top (attenuator) through which a glass tube can be placed connecting the flask in the microwave cavity with a reflux condenser located outside the microwave. The temperature of the contents of the vessel was monitored using a fiberoptic 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.

#### Typical Procedure (5-mmol Scale): The Coupling of 4-Iodoanisole and Methyl Acrylate

In a 50-mL round-bottomed flask containing a stir bar was placed 4-iodoanisole (1.17 g, 5.0 mmol), methyl acrylate (861 mg, 0.90 mL, 10 mmol), Na<sub>2</sub>CO<sub>3</sub> (1.06 g, 10 mmol), TBAB (1.61 g, 5 mmol), Bu<sub>3</sub>N (925 mg, 1.19 mL, 5 mmol) and Pd(OAc)<sub>2</sub> (1.20 mg, 0.005 mmol, 0.1 mol%). The reaction vessel was placed into the microwave cavity, the attenuator locked in place and a reflux condenser attached to the open neck of the flask. The reaction mixture was subjected to a maximum of 150 W microwave power in a ramp to 150 °C and then held at this temperature until a total reaction time

of 90 s had elapsed. The reaction mixture was stirred continuously. Upon completion, the reaction vessel was allowed to cool to 50 °C. Then,  $H_2O$  (10 mL) and EtOAc (10 mL) were added to the reaction flask and the entire contents poured into a separatory funnel. Afterwards,  $H_2O$  (100 mL) and EtOAc (100 mL) were added and the organic material extracted and removed. After further extraction of the aqueous layer with EtOAc, combining the organic washings and drying them over MgSO<sub>4</sub>, and EtOAc was removed on a rotary evaporator leaving the crude product, which was purified by crystallization and characterized by comparison of NMR data with that in the literature.

## Typical Procedure (1-mol Scale): The Coupling of Iodobenzene and Butyl Acrylate

In a 5-L two-neck round-bottomed flask containing a stir bar was placed iodobenzene (204 g, 112 mL, 1.0 mol), butyl acrylate (256 g, 288 mL, 2 mol), Na<sub>2</sub>CO<sub>3</sub> (210 g, 2 mol), TBAB (322 g, 1 mol), Bu<sub>3</sub>N (185 g, 238 mL, 1 mol) and Pd(OAc)<sub>2</sub> (224 mg, 1.0 mmol, 0.1 mol%). The reaction vessel was placed into the microwave cavity and the glass connector tube attached, this connecting the flask in the microwave cavity with a reflux condenser located outside the microwave. The reaction mixture was subjected to a maximum of 600 W microwave power in a ramp to 100 °C and then microwave power modulated to hold at this temperature for 10 min. During this time, the vessel contents reached 152 °C due to the exothermic nature of the reaction once initiated. The reaction mixture was stirred continuously. Upon completion, the reaction vessel was allowed to cool to 65 °C. Then, EtOAc (500 mL) was added to the reaction flask and the entire contents poured into a large Büchner funnel. The solid remaining after an initial filtration was washed with EtOAc, this separating the organic material from the Na<sub>2</sub>CO<sub>3</sub>. The filtrate was then allowed to cool at which point the TBAB precipitated out of solution. A second filtration to recover the solid TBAB followed by washing the TBAB with Et<sub>2</sub>O left product, unreacted butyl acrylate, Bu<sub>3</sub>N and tributylamine hydroiodide in the filtrate. The filtrate was poured into a separatory funnel, H<sub>2</sub>O (1 L) and EtOAc (1 L) were added and the organic material extracted and removed. After further extraction of the aqueous layer with EtOAc, combining the organic washings and drying them over MgSO4, and Et2O and EtOAc were removed on a rotary evaporator followed by placing on a vacuum line. This left the product, which was characterized by comparison of NMR data with that in the literature.

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- (43) It is more appropriate to call the Pd(OAc)<sub>2</sub> a precatalyst since a colloidal palladium species is most likely the catalytically active species.
- (44) (a) It is important that a suitably sized reaction vessel is used for scale-up reactions in the absence of solvent. It is advised that the contents should occupy no more than 10% of the vessel volume. In addition, microwave power should be

carefully modulated. A power no greater than 600 W is advised. (b) At a first glance it may seem that this would be putting in much more microwave power than in the case of the monomode experiments. However, the relative size of the cavity needs to be considered. Multimode microwaves have large cavities and so power is dissipated over a large area. Monomode equipment has a much smaller cavity and the energy density is up to some 30–40 times higher than the multimode apparatus.