

# **High-Speed Heck Reactions in Ionic Liquid** with Controlled Microwave Heating

Karl S. A. Vallin, Per Emilsson, Mats Larhed,\* and Anders Hallberg

Department of Organic Pharmaceutical Chemistry, Uppsala University, BMC, Box-574, SE-751 23 Uppsala, Sweden

mats@orgfarm.uu.se

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Abstract: Palladium-catalyzed Heck arylations in the polar and robust ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF<sub>6</sub>), have for the first time been accomplished under microwave irradiation. The couplings were efficiently performed in sealed tubes within 5-45 min of heating. Without significant reductions in yield, a phosphine-free ionic catalyst phase could be recycled in five successive 20 min reactions at 180 °C. The product was easily removed from the reaction medium by distillation.

The chemical and pharmaceutical industry is under an accelerating pressure to find environmentally friendly organic reaction methodologies. Among a variety of possible "green" solvent alternatives for catalytic reactions,<sup>1-4</sup> nonvolatile room-temperature ionic liquid reaction media continue to be an area of increasing research activity.5-7 Ionic liquids of the dialkylimidazolium class may simplify metal catalyst recycling techniques and, due to their high polarity and special properties, allow for new reaction protocols to be developed. Ionic liquids interact very efficiently with microwaves through conduction and are rapidly heated without any significant pressure increase.<sup>8</sup> Therefore, safety problems arising from over-pressurization of heated sealed reaction vessels can be minimized.

Offsetting the advantages of utilizing ionic liquids as reaction media are some detractions. The long reaction times required with palladium-catalyzed transformation are a significant drawback for high-throughput applications.<sup>9</sup> More generally, all ionic liquid-based methods need to come to grips with the high price of ionic liquids.

We previously reported on very rapid palladiumcatalyzed coupling reactions both in solution and on a solid phase under microwave irradiation.<sup>10-12</sup> This heat-

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 TABLE 1. Heck Arylations in BmimPF<sub>6</sub> with Different
 Palladium Catalysts<sup>a</sup>



<sup>a</sup> Reactions were performed in a 1.0 mmol scale for 45 min at 180 °C with microwave heating. <sup>b</sup> Palladium (0.02 equiv). <sup>c</sup> Monodentate/bidentate phosphine ligand (0.04 equiv). <sup>d</sup> GC yields were determined with 2,3-dimethylnaphthalene as the internal standard. <sup>e</sup> LiCl (0.04 equiv).

ing methodology  $^{13,14}$  offers a potential solution to the reaction rate problem, and we therefore decided to assess this technology for acceleration of a prototypical ionic liquid coupling reaction. In addition, we wanted to investigate catalyst/ionic liquid recycling after microwave treatment. We herein describe a high-temperature stable catalytic system suitable for rapid microwave-assisted Heck arylations<sup>4,15,16</sup> relying on a combination of the ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF<sub>6</sub>), and PdCl<sub>2</sub>. Convenient product isolation and an efficient catalytic recycling protocol are reported.

We selected a standard Heck reaction, with the deactivated aryl halide bromoanisole (1a) and the electronpoor olefin butyl acrylate (2a), as an appropriate first test reaction. The common ionic liquid bmimPF<sub>6</sub> was chosen as the ionic solvent for a number of reasons: (a) it is proven to constitute a suitable reaction medium for palladium(0)-catalyzed coupling reactions,<sup>6,7</sup> (b) it is air, moisture, and temperature stable,<sup>8</sup> and (c) it is virtually insoluble in water and alkanes.<sup>6,9</sup> The catalytic stability and the coupling reactivity were first investigated under air with four different palladium sources and three common phosphine ligands (Table 1). The temperature (180 °C) and the irradiation time (45 min) were selected to allow only very reactive catalytic systems in the ionic liquid to afford full conversion of the sluggish bromoanisole. Unexpectedly, it was found that replacement of the standard Pd(OAc)<sub>2</sub> by the old fashioned PdCl<sub>2</sub> led to a marked increase in the catalytic efficiency, while per-

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TABLE 2. Heck Arylation in  $BmimPF_6$  with DifferentAryl and Heteroaryl Halides<sup>a</sup>



<sup>*a*</sup> Reaction conditions: Reactions were performed in a 1.0 mmol scale with 1.0 equiv of **1a**–**f**, 2.0 equiv of **2a**, 0.04 equiv of PdCl<sub>2</sub>, 0.08 equiv of P(*o*-tol)<sub>3</sub>, 1.5 equiv of Et<sub>3</sub>N, and 0.5 g bmimPF<sub>6</sub>. <sup>*b*</sup> Purity > 95% according to GC/MS. <sup>*c*</sup> Phosphine-free, 0.02 equiv of PdCl<sub>2</sub>. <sup>*d*</sup> Compound **2a** (5.0 equiv) was added to reduce the competing homocoupling.

forming the reaction with a Pd(OAc)<sub>2</sub>/LiCl combination did not result in a similar success (entries 1, 2, and 7). With  $PPh_3$  as the ligand instead of  $P(o-tol)_3$  under otherwise identical conditions, a significant level of aryl migration forming byproduct 3b was encountered (entries 3 and 4). The best catalytic system for the Heck reaction, comprised of P(o-tol)<sub>3</sub> in combination with PdCl<sub>2</sub>, delivered 99% yield and full conversion and gave no trace of products derived from aryl migration or dehalogenation (entry 8). Inferior results were observed with Herrmann's palladacycle (trans-di(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II)) or  $Pd/C^{17}$  as well as with  $Pd(OAc)_2$ in combination with the bidentate ligand 1,3-bis(diphenylphosphino) propane (DPPP) (entries 5, 6, and 9). In general, the investigated catalytic systems were more temperature tolerant in the ionic liquid media than in ordinary solvents. For example, applying the same phosphine-free condition as in entry 1 with DMF as the solvent at 180 °C afforded only small amounts of the product and a massive formation of "palladium black".

The key criterion for the development of flash-heated methodologies is, by definition, the reduction of reaction time. The PdCl<sub>2</sub>/P(o-tol)<sub>3</sub> reaction condition selected from Table 1 was therefore further time-optimized, and the final preparative results with different aryl and heteroaryl halides (1a-f) and the olefin 2a are presented in Table 2. The couplings with any bromides in ionic liquid were best performed in 20 min at 220 °C.18 For instance, the reaction of bromobenzene (1b) produced an isolated yield of 87% 3b (entry 3). The cinnamic acid ester (3b) was also synthesized employing iodobenzene (1f) in a reaction time of only 5 min and consuming only a fraction of the energy that normally is needed for a standard, oil-bath-heated reaction (entry 7). Attempts to further accelerate the phosphine-free PdCl<sub>2</sub>-catalyzed reaction with the deactivated aryl bromide 1a by increas-



**FIGURE 1.** Temperature, power, and pressure profiles for the vinylation of 4-bromoanisol (Table 2, entry 1). The enlarged area shows the initial temperature response (27–220 °C) and the corresponding microwave power during the first 30 s of irradiation.

#### **SCHEME 1**



<sup>a</sup> Isolated yield.

ing the reaction temperature were not successful, and a considerable amount of **1a** remained unreacted, suggesting a collapse of the catalytic system (entry 7, Table 1, and entry 2, Table 2). The bromopyridyl (**1e**) reacted much less efficiently than the other aryl halides despite an increased concentration of butyl acrylate (entry 6). In all reactions, a convenient product separation by distillation from the high-boiling ionic solution was possible. The impressive temperature control and the very low reaction pressure for the arylation of **2a** with **1a** in bmimPF<sub>6</sub> (Table 2, entry 1) are illustrated in Figure 1.<sup>19</sup> An extremely rapid heating ramp demonstrates the high microwave activity of the bmimPF<sub>6</sub>-based reaction system.

The  $\beta$ , $\beta$ -diphenylacrylate (**4**) was successfully synthesized in 45 min by a double-Heck arylation employing an excess of phenyl bromide and with the sterically hindered and stable 1,2,2,6,6-pentamethyl-piperidine (PMP) as the base (Scheme 1).<sup>20</sup> With triethylamine as the base, small quantities of *N*,*N*-diethyl-3,3-diphenylacrylamide were observed as deduced from a GC/MS analysis.<sup>21</sup>

The recyclability of the catalytic ionic system was studied employing iodobenzen (**1f**) as the arylating agent and butyl acrylate (**2a**) as the olefin.  $PdCl_2$  was used as catalyst with no phosphine ligand present. To ensure complete conversion of iodobenzene, the irradiation time for each cycle was prolonged to 20 min and the palladium concentration slightly increased. The results are summarized in Figure 2 and reveal that the ionic catalyst phase is recyclable at least five times.<sup>22</sup> After each cycle, the product was directly isolated in high yield by rapid

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(18) When the temperature was increased to 220 °C, a small amount of **3b** (~8%) was detected due to aryl scrambling (Table 2, entry 1).

<sup>(21)</sup> Less than 10% *N*,*N*-diethyl-3,3-diphenyl-acrylamide was formed. To explain this observation, we believe diethylamine must be generated from triethylamine at the accelerated conditions.



**FIGURE 2.** Recyclability of the ionic catalyst phase. Reactions were performed in a 2.0 mmol scale for 20 min at 180 °C with microwave heating, employing 1.0 equiv of **1f**, 2.0 equiv of **2a**, 0.05 equiv of PdCl<sub>2</sub>, 1.5 equiv of Et<sub>3</sub>N, and 3.0 g of bmimPF<sub>6</sub>.

### **SCHEME 2**



 $^a$  Isolated as the corresponding methyl ketone (6) after acid treatment.

distillation under reduced pressure (170 °C, 1-2 mmHg). For the next reaction cycle, new **2a**, **1f**, and Et<sub>3</sub>N were added to the original PdCl<sub>2</sub>/bmimPF<sub>6</sub> catalyst media. In situ-generated, catalytically active palladium–biscarbene complexes have been suggested to be involved in similar processes.<sup>9,23</sup>

To investigate Heck coupling reactions that proceed not only via neutral intermediates, the bidentate ligandcontrolled internal arylation of butyl vinyl ether (2b) with 1d was examined in bmimPF<sub>6</sub> with microwave heating. The latter reaction is anticipated to involve cationic aryl palladium species most often created from aryl triflates or, alternatively, from aryl halides combined with halide abstractors such as thallium salts.<sup>24,25</sup> Due to the highly polar media, no addition of toxic thallium salts were needed to promote the reaction in the presence of the DPPP ligand.<sup>26</sup> High internal regioselectivity of product 5 and complete conversion was accomplished when the temperature was set to a maximum of 130 °C (terminal/ internal arylation < 1/99) (Scheme 2). Increasing the reaction temperature, excluding the addition of DPPP, or exchanging  $Pd(OAc)_2$  with  $PdCl_2$  caused a loss in regioselectivity. The DPPP requirement for obtaining high internal regioselectivity indicates that the active catalyst is a Pd(0)-DPPP complex and not a potential imidazolylidine-palladium carbeneoid complex.

In summary, it has been demonstrated that Heck reactions can be performed in 5-45 min with controlled microwave heating and that the bmimPF<sub>6</sub>-based ionic catalyst solution can be reused repeatedly. The ionic catalyst systems were found to be stable despite high reaction temperatures (180–220 °C). Further systematic

investigations will be necessary to take full advantage of the huge potential of the ionic liquid/microwave heating combination.

#### **Experimental Section**

**General.** The microwave heating was performed in a single mode cavity, producing controlled irradiation at 2450 MHz. Reaction temperature and pressure were determined using the built-in, on-line IR and pressure sensors. Microwave-mediated reactions were performed in sealed process vials under air with magnetic stirring. Prepacked silica columns were used for flash chromatography. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> at 270 and 67.8 MHz, respectively. Mass spectra were recorded on a GC/MS equipped with an HP-1 (25 m × 0.20 mm) capillary column, utilizing electron impact (EI) at an ionizing energy of 70 eV. The regioisomers were assumed to have the same GC/MS response factor. The isolated cinnamic acid esters (**3a**-e),  $\beta$ , $\beta$ -diphenylacrylate (**4**), and 1-acetyl naphthyl (**6**) have previously been characterized, and the data obtained corresponded satisfactorily with MS and NMR literature data.<sup>27-30</sup>

**Materials.** The acrylate ester **2a**, vinyl ether **2b**, aryl and heteroaryl halides **1a**–**f**, palladium(II)acetate, palladium(II)dichloride, tri-*o*-tolyl phosphine, triphenylphosphine, 1,3-bis-(diphenylphosphino)propane (DPPP), Pd/C, LiCl, 1,2,2,6,6-pentamethyl-piperidine (PMP), and triethylamine were purchased from commercial suppliers and used directly as received. The ionic liquid bmimPF<sub>6</sub> was prepared by a literature procedure.<sup>31,32</sup>

General Procedure for Microwave-Assisted Terminal Heck Reaction with Aryl or Heteroaryl Halides 1a-f(Table 2). The bmimPF<sub>6</sub> (0.50 g, 1.75 mmol), PdCl<sub>2</sub> (7.8 mg, 0.04 mmol), and P(o-tol)<sub>3</sub> (24 mg, 0.08 mmol) were mixed in a process vial (0.5–2.0 mL) equipped with a magnetic stirrer and heated to 80 °C for 5 min in a heating block to form the ionic liquid solution of the catalyst. Butyl acrylate (2a) (0.256 g, 2.0 mmol), triethylamine (0.152 g, 1.5 mmol), and the corresponding aryl halide 1a-f (1.0 mmol) were added, and the reaction mixture was heated to 220 °C for 20 min in a microwave synthesizer. After complete consumption of the starting aryl halide as analyzed by GC/MS, the reaction mixture was distilled with a kugelrohr device at 1–2 mmHg and 170 °C. The clear distillate was separated from the amine salt by extraction with diethyl ether to give the pure product 3 (>95% GC/MS).

Microwave-Assisted Heck Arylations with Different Palladium Catalysts (Table 1). The arylation of 2a with 1a was performed as described under General Procedure for Microwave-Assisted Terminal Heck Reaction with Aryl or Heteroaryl Halides 1a-f, but the amount of palladium was 0.02 mmol and the amounts of phosphine monodentate/bidentate ligands were 0.04 mmol. The reaction mixture was heated to 180 °C for 45 min in a microwave synthesizer. The yields were determined by a GC/MS mean value of two injections from calibration curves made from pure 3a and 2,3-dimethylnaphthalene as internal standards.

**Double Heck Arylation of 2a (Scheme 1).** The  $\text{bmimPF}_6$  (0.50 g, 1.75 mmol),  $\text{PdCl}_2$  (7.8 mg, 0.04 mmol), and  $\text{P}(o\text{-tol})_3$  (24 mg, 0.08 mmol) were mixed in a process vial (0.5–2.0 mL) equipped with a magnetic stirrer and heated to 80 °C for 5 min in a heating block to form the ionic liquid solution of the catalyst. Butyl acrylate (**2a**) (0.256 g, 1.0 mmol), PMP (0.466 g, 3.0 mmol), and the phenyl bromide (0.785 g, 5.0 mmol) were added, and the reaction mixture was heated to 220 °C for 45 min in a

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# JOC Note

microwave synthesizer. After complete consumption of the butyl acrylate (**2a**) as analyzed by GC/MS, the reaction mixture was worked up by a three-phase extraction between the ionic liquid, 0.1 M NaOH (aq), and diethyl ether. Product **4** was purified by column chromatography on a prepacked silica column. Eluent: isohexane/ethyl acetate.

**Recyclability of the Ionic Catalyst Phase (Figure 2).** The bmimPF<sub>6</sub> (3.0 g, 10.5 mmol), PdCl<sub>2</sub> (17.7 mg, 0.05 mmol), butyl acrylate (**2a**) (0.512 g, 4.0 mmol), triethylamine (0.303 g, 3.0 mmol), and phenyl iodide (**1f**) (0.408 g, 2.0 mmol) were mixed in a process vial (2.0–5.0 mL) equipped with a magnetic stirrer. The reaction mixture was heated to 180 °C for 20 min in a microwave synthesizer. Compound **3b** was purified as described for the cinnamic acid esters (**3a**–**e**). For recycling, **2a**, **1f**, and triethylamine were added to the nonvolatile catalytic ionic media in the same original process vial. The reaction system was thereafter irradiated to 180 °C for 20 min.

Internal Arylation of 2b with Bromonaphthalene (1d) (Scheme 2). The  $bmimPF_6$  (2.5 g, 9.0 mmol),  $Pd(OAc)_2$  (9.0 mg,

0.04 mmol), DPPP (25 mg, 0.06 mmol), butyl vinyl ether (**2b**) (0.100 g, 1.0 mmol), triethylamine (0.152 g, 1.5 mmol), and 1-bromonaphthalene (**1d**) (1.035 g, 5.0 mmol) were mixed in a process vial (2.0–5.0 mL) equipped with a magnetic stirrer, and the reaction mixture was heated to 130 °C for 120 min in a microwave synthesizer. After complete conversion of the starting **2b** as analyzed by GC/MS, the vinyl ether (**5**) was hydrolyzed by adding 5 mL of 5% HCl for 60 min. The reaction was worked up and extracted with isohexane. The methyl ketone (**6**) was purified by column chromatography on a prepacked silica column. Eluent: isohexane/dichloromethane.

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