# **One-Pot Halogenation–Heck Coupling Reactions in Ionic Liquids**

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This paper is dedicated to Professor Richard Heck, whose efforts opened a vast new area of fundamental importance to the synthesis of organic products.

**Abstract:** Traditional cross-coupling approaches rely upon two steps – halogenation and coupling – each of which is viewed and conducted independently. In an effort to develop a one-pot approach, we have noted that the halogenation and Heck coupling reactions can both be conducted in a room-temperature ionic liquid without the need to isolate the halogenated intermediate. Application to several systems shows that this approach works well for moderately to highly electron-rich aromatics.

Key words: cross-coupling, Heck coupling, room-temperature ionic liquids

Certainly, transition-metal-mediated cross-coupling reactions, including the Heck coupling, the Stille coupling, and the Suzuki coupling, have revolutionized the way that the organic chemist approaches synthesis.<sup>1</sup> The ready availability of halogenated aromatics and various coupling partners (alkenes, organotins, organoborons, etc.) has made these reactions one of the basic methods for forming carbon–carbon bonds.

At the same time, it is somewhat surprising to note that the two critical parts of these couplings – the preparation of the halogenated aromatic and the coupling itself – remain viewed as completely independent entities. As a result, assuming that the haloaromatic is not commercially available, the common approach is always to halogenate the aromatic ring, work up and purify this product, and then perform the cross-coupling reaction. But, is it really necessary to isolate the halogenated intermediate or can these two steps be performed in a sequential, but one-pot, method?

Part of the driving force behind this question is our longstanding interest in the use of room-temperature ionic liquids (RTILs) in organic synthesis.<sup>2</sup> Numerous groups, including our own, have studied many cross-coupling reactions in RTILs,<sup>3</sup> especially the Heck coupling.<sup>4</sup> RTILs based on imidazole have been demonstrated to be excellent reaction solvents for these reactions, with the solvent often times playing an active role in maintaining, and even enhancing, the reactivity of the palladium catalyst.<sup>5</sup> As a result, the concept of using a RTIL for a cross-coupling reaction is well established.

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More recently, there have been efforts to use RTILs in the halogenation of aromatic substrates. Yadav and co-workers have reported that halogenations using *N*-halosuccinimides are remarkably accelerated using RTILs such as 1-butyl-3-methylimidazolium hexafluorophosphate or tetrafluoroborate ([BMIM]PF<sub>6</sub> or [BMIM]BF<sub>4</sub>).<sup>6</sup> Thus, even the less reactive *N*-iodosuccinimide (NIS) will rapidly iodinate a wide range of moderately to highly electronrich aromatics, providing reliable access to these compounds quickly and in high yield.<sup>7</sup>

Since it is clear that both reactions will work independently in a RTIL, the next question was if such reactions could be carried out sequentially in one pot (Scheme 1). The primary advantage of such an approach would be in avoiding the necessity of working up the reaction and isolating the intermediate product. This could be of particular value in automated and/or parallel synthesis.

ArH 
$$\xrightarrow{\text{NIS}}$$
 Arl  $\xrightarrow{\text{R}}$   $\xrightarrow{\text{Pd}(OAc)_2}$   $\xrightarrow{\text{R}}$  Arl  $\xrightarrow{\text{Pd}(OAc)_2}$  Ar

#### Scheme 1

As an initial test, the iodination of anisole was conducted in [BMIM]BF<sub>4</sub> (Table 1, entry 1). After 2 hours, a Heck coupling with methyl acrylate was performed under conditions used previously in these labs and the reaction was allowed to proceed overnight.<sup>8</sup> Extraction with diethyl ether then afforded the clean Heck coupling product in 99% yield.<sup>9</sup>

Table 1 Halogenation–Heck Coupling of Anisole<sup>a</sup>

Entry	Alkene	Isolated yield (%)
1	Methyl acrylate	99
2	Styrene	78
3	1-Decene	10 <sup>b</sup>
4 <sup>c</sup>	Methyl acrylate	98

<sup>a</sup> Reaction conditions: 0.5 mmol of anisole, 0.5 mmol of NIS, 2 mL of  $[BMIM]BF_4$ . After 2–3 h, 0.75 mmol of alkene, 0.05 mmol of Pd(OAc)<sub>2</sub>, and 1 mmol of Et<sub>3</sub>N at 140 °C for 20 h.

<sup>b</sup> 80% Recovery of *p*-iodoanisole.

<sup>c</sup> 1-Butyl-3-methyl-4-hydroxymethylimidazolium triflimide was used as the solvent.

Anisole was also employed as the starting point for Heck couplings with two other, less-activated alkenes (Table 1, entries 2 and 3). With styrene, the reaction proceeded well to afford the anticipated stilbene in 78% yield. On the other hand, the reaction with less reactive 1-decene afforded only a small amount of the Heck coupling product and mostly recovered *p*-iodoanisole. While the low reactivity of the alkene is clearly part of the problem, another factor could be the relatively limited solubility of 1-decene in [BMIM]BF<sub>4</sub>.

Although it was anticipated that these conditions should be applicable to a wide range of RTILs, it was encouraging to note that this was actually the case (Table 1, entry 4). Thus, the use of our fructose-derived RTIL again afforded the Heck coupling product over these two steps in excellent overall yield.<sup>10</sup> There is a potential additional advantage to the use of a much more hydrophobic RTIL in that the succinimide by-product can be removed at the end of the reaction by extraction with water. As a result, it should be possible to recycle the solvent through several couplings, thereby reducing the cost associated with the use of RTIL solvents in this one-pot approach.

In examining other aromatic substrates, the one-pot sequence again worked well (Table 2). Thus, highly electron-rich aromatics such as dimethylaniline, thiophene, and mesitylene all afforded the desired Heck products in good yield (Table 2, entries 1–3). A problem was encountered when attempting this sequence on less electron-rich aromatics, though. Application of the conditions reported by Yadav for the iodination of naphthalene and *m*-xylene failed completely. Fortunately, this limitation could be overcome by either heating the solution to 80 °C for 6–12 hours or by employing an acid catalyst, as has been reported by Castanet and co-workers in the iodination of aromatics in acetonitrile using N-iodosuccinimide.<sup>11</sup> With this modification, the moderately electron-rich aromatic *m*-xylene afforded good yields of the anticipated Heck product (Table 2, entry 5). Unfortunately, an even less electron-rich aromatic - naphthalene - failed to undergo iodination even with this activation.

 Table 2
 Halogenation–Heck Couplings of Aromatics with Methyl

 Acrylate<sup>a</sup>
 Image: Head of the second second

Entry	Aromatic	Isolated yield (%)
1	Dimethylaniline	99
2	Thiophene	90
3	Mesitylene	96
4 <sup>b</sup>	<i>m</i> -Xylene	89
5°	<i>m</i> -Xylene	90

<sup>a</sup> Reaction conditions: 0.5 mmol of the arene, 0.5 mmol of NIS, 2 mL of [BMIM]BF<sub>4</sub>. After 6–12 h, 0.75 mmol of methyl acrylate, 0.05 mmol of Pd(OAc)<sub>2</sub>, and 1 mmol of Et<sub>3</sub>N at 140 °C for 20 h.

<sup>b</sup> Initial iodination performed at 80 °C.

<sup>c</sup> Iodination performed in the presence of 0.05 mmol of TFA.

Although aryl iodides are the most reactive of the aryl halides in the Heck coupling, they are also the most difficult and expensive to prepare (particularly on less electron-rich aromatic rings). As a result, there is clear interest in examining the potential for using a similar bromination-Heck coupling sequence. Much to our delight, bromination proceeded well in the ionic liquid solvent. The Heck coupling, however, did not proceed as well under the simple palladium acetate conditions. Still, the Heck coupling product with anisole could be isolated in 58% yield over this two-step, one-pot sequence (Table 3, entry 1). The bulk of the remainder of the material was *p*-bromoanisole. Presumably, the lower yield is due to the lower reactivity of aryl bromides in the Heck coupling. As a result, one possible solution to this incomplete conversion would be to employ a more reactive catalyst for the Heck coupling, of which many are available.

 Table 3
 Halogenation–Heck Coupling Using NBS and Methyl

 Acrylate<sup>a</sup>
 Image: Coupling Using NBS and Methyl

Entry	Aromatic	Isolated yield (%) <sup>b</sup>
1	Anisole	58 (30)
2	Mesitylene	21 (78)
3°	Naphthalene	75
4	<i>m</i> -Xylene	82

<sup>a</sup> Reaction conditions: 0.5 mmol of the arene, 0.5 mmol of NIS, 2 mL of [BMIM]BF<sub>4</sub>. After 6–12 h, 0.75 mmol of methyl acrylate, 0.05 mmol of Pd(OAc)<sub>2</sub>, and 1 mmol of Et<sub>3</sub>N at 140 °C for 20 h. <sup>b</sup> The yield in parenthesis is of recovered bromoarene.

<sup>c</sup> Initial bromination performed at 80 °C.

The potential advantage of the bromination conditions can be more readily seen in the reaction with *m*-xylene (Table 3, entry 4). In this case the bromination could be performed at room temperature, instead of the elevated temperature required with NIS. The Heck coupling product was then isolated in 82% yield – a result nearly equivalent to that obtained using the iodination sequence. Even more impressive is the reaction with naphthalene (Table 3, entry 3). The bromination reaction did have to be heated to proceed to completion, but ultimately afforded the Heck coupling product in reasonable yield.

In conclusion, we have developed a one-pot method for the halogenation and Heck coupling of a variety of aromatic substrates. Based upon the observations with the less-polar triflimide RTIL, it should be possible to also recycle the RTIL solvent, thereby rendering this method of even greater use. Already it has promise in automated or parallel synthesis. Further, the same approach should be applicable to a wide range of coupling reactions and be of very general utility.

### **Representative Coupling Procedure**

To 2.0 mL of 1-butyl-3-methylimidazolium tetrafluoroborate was added 58  $\mu$ L (0.50 mmol) of anisole and 112 mg (0.50 mmol) of *N*-iodosuccinimide. The reaction was stirred for 2 h. Then, 140  $\mu$ L (1.5 mmol) of Et<sub>3</sub>N and 12 mg (0.05 mmol) of Pd(OAc)<sub>2</sub> was added and the mixture stirred for 1–2 min before the addition of 68  $\mu$ L (1 mmol) of methyl acrylate. The reaction was heated to 140 °C and stirred overnight. The reaction was then cooled to r.t. and extracted with Et<sub>2</sub>O (4 × 3 mL). The Et<sub>2</sub>O extracts were concentrated in vacuo to afford 95 mg (99%) of the Heck coupling product as a pale yellow solid.

## Acknowledgment

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