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## Heck Coupling in Ionic Liquids

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Additional information is available at the end of the chapter

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### 1. Introduction

Synthetic and medicinal chemistry intersect at the production of compounds. However there are stark contrasts in approach with synthetic chemistry typically producing complex molecules and developing synthetic approaches. In medicinal chemistry, the focus is on compound access to facilitate compound screening and structure activity data acquisition to enable the synthesis of more active compounds. Medicinal chemistry relies on a small range of highly robust and reliable reactions to gain access to a wide array of potentially bioactive reactions.[1, 2]

This reliance on robust chemistries has been significantly enhanced through the development of efficient C-C coupling protocols, in particular the coupling of aryl halides with  $\alpha,\beta$ -unsaturated building block. The power of these new coupling technologies has been reflected in the recent Nobel prizes in this area to Heck,[3] Suzuki,[4] Grubb and their co-workers.[5]

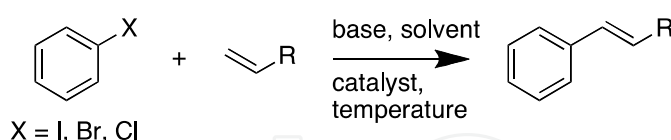
While the development of new methodologies is of paramount importance across all areas of synthetic chemistry, simple developments and increased understanding of reaction conditions and reaction media often enhance these new methodologies. In this latter regard the growth of knowledge in and around room temperature ionic liquids and their ability to moderate reaction outcomes through their tuneable nature and ability to act as solvents for a wide range of chemical compounds has proved, arguably, equally important. Importantly, the combination of developments in C-C coupling technology and RTILs has allowed enhancement in the overall process efficiency. That is, these processes are becoming more environmentally sustainable.

Our group's primary focus requires rapid access to focused compound libraries of bioactive molecules spanning multiple potential therapeutic targets: the inhibition of dynamin GTPase, protein phosphatases 1A and 2A and the development of anti-cancer lead compounds.[6-12]

Where possible we are keen to apply green chemistry principles around reagent, solvent and synthetic pathway choice.[13-16] Within our own research efforts we have routinely tolerated low yields and difficult purifications to gain access to the desired compounds.[17, 18] We have thus invested considerable resources in the examination, and application, of RTILs and other emerging technologies to the synthesis of bioactive focused compound libraries.[19-23] A current program focus within our team is the development of robust flow and microwave approaches to Pd-mediated C-C coupling reactions, especially the Heck-Mizoroki (Heck reaction).

### 1.1. The Heck–Mizoroki reaction (the Heck reaction)

The cross-coupling of organic halides with alkenes in the presence of catalytic quantities of Pd(0) and a base was first reported by Mizoroki and Heck in 1971.[24, 25] Over the next four decades this has become known as “the Heck reaction” and has been the subject of a number of synthetic and mechanistic studies. It is now generally accepted that there are four key requirements / conditions to a successful Heck coupling reaction: 1) *Solvent*: The Heck reaction generally requires a polar solvent such as dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO); 2) *Base*: The Heck reaction bases are usually selected from Et<sub>3</sub>N, NaOAc or aqueous Na<sub>2</sub>CO<sub>3</sub> or NaHCO<sub>3</sub>.[26] 3) *Catalyst*: The Heck reaction uses 1-5 mol% catalytic palladium (0) or palladium (II) complexes. Most commonly in the form of Pd(0)-phosphine complexes such as tetrakis(triphenylphosphine)palladium(0) [Pd(PPh<sub>3</sub>)<sub>4</sub>] or dibenzylidene-acetone complexes of Pd(0) such as Pd<sub>2</sub>(dba)<sub>3</sub>(dba).[27] Simple palladium salts such as PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> in the absence of stabilizing phosphine ligands have also been widely used.[28]-[30] 4) *Halide*: The reactivity of the halide precursor effects the time and temperature required to effect the desired coupling reaction (Figure 1).



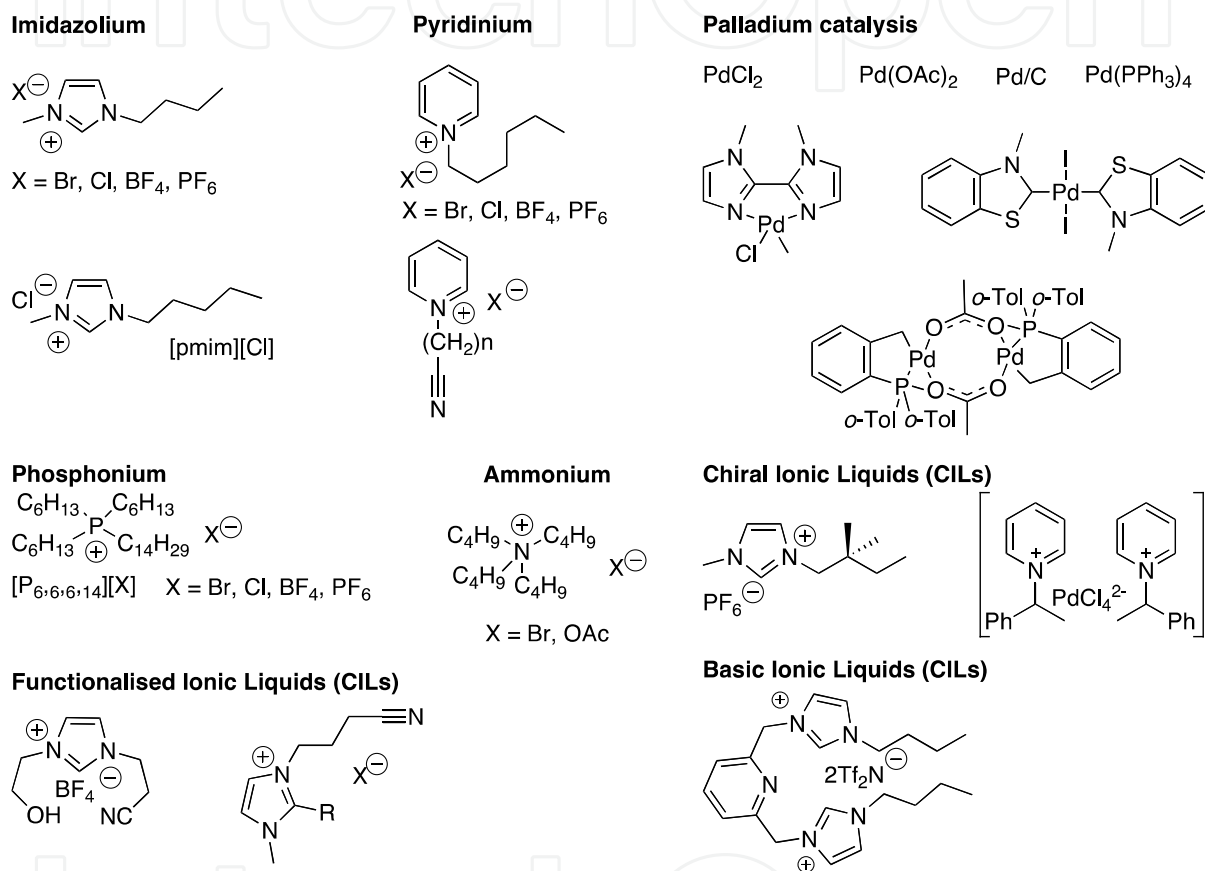
**Figure 1.** General reaction scheme of a Heck cross coupling between an aryl and an olefin indicating the four key variables: base, solvent, catalyst and temperature.

## 2. Heck reaction in Room Temperature Ionic Liquids (RTILs)

The emergence of room temperature ionic liquids (RTILs) has allowed the investigation of the Heck reaction in a wide range of novel and tuneable solvents systems.

These novel solvents cover a wide range of structural moieifs from the now well established methylimidazolium and pyridinium salts through ammonium and phosphonium based systems. RTILs now comprise a wide array of sub classes including protic (PILs), basic (BILs), chiral (CILs), solid supported (SLIPs) and functionalised (FIL).[31, 32] Key examples of these

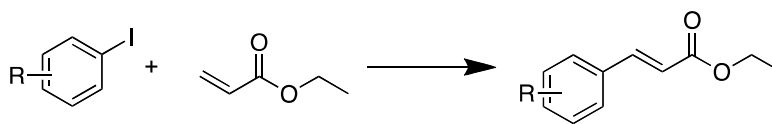
systems are shown in Figure 2. The custom design nature of these RTILs modifies their ability to solubilise materials and affects the outcome of a wide range of chemical transformations. Herein our focus is the Heck reaction. In addition to the variable nature of the RTIL, a number of novel Pd-catalysts have been developed to enhance the Heck coupling outcomes, especially with the use of deactivated aryl halides and olefins. Selected examples of these Pd-catalysts are also shown in Figure 2.



**Figure 2.** Selected examples of ionic liquids and Pd-catalysts used in the Heck reaction.

## 2.1. Imidazolium and pyridinium RTILs

The coupling efficiency of ethyl acrylate with iodobenzene mediated by  $\text{Pd}(\text{OAc})_2$  was examined in the presence of *N*-hexylpyridinium  $[\text{N}-\text{C}_6\text{H}_{13}\text{Py}][\text{X}]$ , where  $\text{X} = \text{Cl}, \text{PF}_6$  and  $\text{BF}_4$ , and with  $[\text{bmim}][\text{PF}_6]$  and 1-pentyl-3-methylimidazolium chloride  $[\text{pmim}]\text{Cl}$  RTILs (Scheme 1). The  $\text{N}-\text{C}_6\text{H}_{13}\text{Py}$  systems afforded higher yields of the coupled product, *E*-ethyl cinnamate, than the equivalent  $[\text{bmim}]\text{Cl}$ . Similarly, a higher coupling yield was obtained with  $[\text{N}-\text{C}_6\text{H}_{13}\text{Py}][\text{BF}_4]$  than  $[\text{N}-\text{C}_6\text{H}_{13}\text{Py}][\text{PF}_6]$ , but required higher reactions temperatures 80 °C and extended reaction durations of 72 h to attain the efficiency of the chloride analogues (Table 1).[33]



**Scheme 1.** Reagents and conditions: 2 mol % Pd(OAc)<sub>2</sub>, a RTIL (see Table 1 for detail), Et<sub>3</sub>N or NaHCO<sub>3</sub>, 40-100 °C, 24-72 h.

RTIL	Base	Temp. °C	Time (h)	Yield %
[N-C <sub>6</sub> H <sub>13</sub> Py]Cl	Et <sub>3</sub> N	40	24	99
[N-C <sub>6</sub> H <sub>13</sub> Py]Cl	NaHCO <sub>3</sub>	40	24	98
[N-C <sub>6</sub> H <sub>13</sub> Py][PF <sub>6</sub> ]	NaHCO <sub>3</sub>	80	72	42
[N-C <sub>6</sub> H <sub>13</sub> Py][BF <sub>4</sub> ]	NaHCO <sub>3</sub>	80	72	99
[N-C <sub>6</sub> H <sub>13</sub> Py]Cl	NaHCO <sub>3</sub>	40	24	82
[N-C <sub>6</sub> H <sub>13</sub> Py]Cl	NaHCO <sub>3</sub>	100	24	99
[pmim]Cl	Et <sub>3</sub> N	80	72	10
[pmim]Cl	NaHCO <sub>3</sub>	100	24	19
[pmim]Cl	NaHCO <sub>3</sub>	40	24	77

**Table 1.** Heck coupling of iodobenzene and ethyl acrylate to give *E*-ethyl cinnamate in *N*-hexylpyridinium and methylimidazolium RTILs and 2 mol% Pd(OAc)<sub>2</sub>.

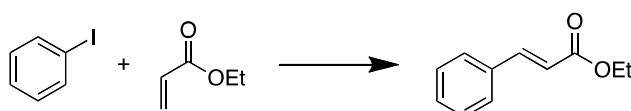
The imidazolium RTILs gave low coupling yield in the absence of phosphine ligands. Addition of Ph<sub>3</sub>P to [bmim][PF<sub>6</sub>] saw a significant rise in *E*-ethyl cinnamate yield to 99%, and this system could be re-used six times with no observable loss in catalyst activity. Pure product was obtained directly via hexane extraction. This approach was also suitable for coupling of the less reactive 4-bromoanisole where the effect of group 15 ligands was also explored and showed enhanced yields relative to the classical approach. The RTILs [N-C<sub>6</sub>H<sub>13</sub>Py][Cl] and [bmim][BF<sub>4</sub>] allowed the facile coupling of benzoic anhydride (as the aryl moiety source) and butyl acrylate giving *trans*-butyl cinnamate in 90-95%. This coupling was conducted at 160 °C with [N-C<sub>6</sub>H<sub>13</sub>Py][Cl] and PdCl<sub>2</sub>, and 200 °C with [bmim][BF<sub>4</sub>] and Pd(OAc)<sub>2</sub> and P(*o*-tol)<sub>3</sub>. [33] Xiao *et al* noted that [bmim][BF<sub>4</sub>] promoted the ionic pathway in the arylation of electron-rich olefins affording high  $\alpha$ -regioselectivity (Table 2). [34]

Yokoyama showed that heating an aryl substrate, olefin and 3 mol% of 10% Pd/C dispersed in [bmim][PF<sub>6</sub>] afforded good yields of the Heck coupling product (Scheme 2). Product isolation was by extraction allowing direct reuse of the RTIL and catalyst without loss of coupling efficiency. [35]

ILs	Aryl halide	Temp. °C	Halide conversion %
[bmim][Br]	iodobenzene <sup>a</sup>	90	94
	4-bromobenzaldehyde <sup>b</sup>	100	71
[bmim][BF <sub>4</sub> ]	iodobenzene <sup>a</sup>	90	35
	4-bromobenzaldehyde <sup>b</sup>	100	3

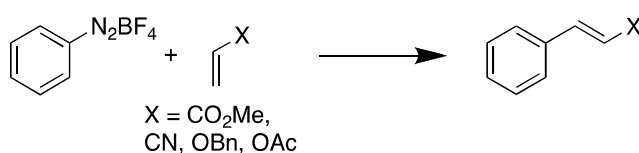
<sup>a</sup> reaction with ethyl acrylate, <sup>b</sup> reaction with butyl acrylate.

**Table 2.** Selected results for Heck reaction between the listed arylhalides and ethyl acrylate or butyl acrylate in [Bmim]Br and [Bmim]BF<sub>4</sub>.



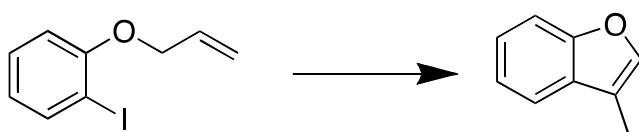
**Scheme 2.** Reagents and conditions: 3 mol % Pd/C (10%) / [bmim][PF<sub>6</sub>], Et<sub>3</sub>N, Δ.

Arene diazonium salts in RTILs have proved to be viable alternatives to aryl bromides and iodides in Pd-mediated couplings.[36, 37] In [bmim][PF<sub>6</sub>], arene diazonium BF<sub>4</sub> salts were readily coupled with acrylonitrile, but vinyl ethers and esters were less reactive requiring more forcing conditions of higher temperature and longer reaction duration (Scheme 3).[38]



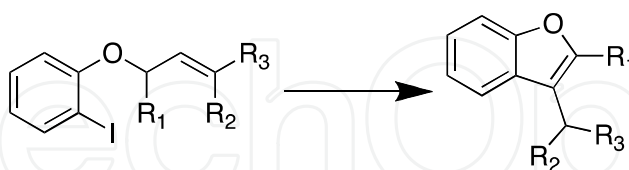
**Scheme 3.** Reagents and conditions: 2 mol % Pd(OAc)<sub>2</sub>, [bmim][PF<sub>6</sub>] at 50 °C, 2-4 h.

The Pd(OAc)<sub>2</sub> mediated intramolecular Heck reaction of *o*-iodoarylallyl ethers present an attractive route to benzofurans, but typically requires extended reaction times in traditional solvents (80 °C, 2 days).[39] However, in [bmim][BF<sub>4</sub>] treatment of *o*-iodobenzyl allyl ether with 5 mol % PdCl<sub>2</sub>, 1.5 eq. (n-Bu)<sub>3</sub>N and 1 eq. NH<sub>4</sub>OOCH at 60 °C for 24 h gave 3-methyl-benzofuran in a 71% yield (Scheme 4).[40]



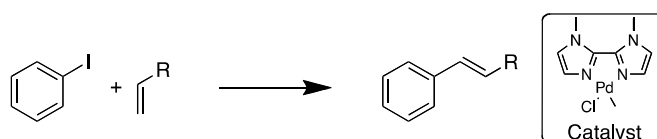
**Scheme 4.** Reagents and conditions: 5% PdCl<sub>2</sub>, (n-Bu)<sub>3</sub>N, [bmim][BF<sub>4</sub>], 60 °C, 24 h.

The use of more substituted *o*-iodoaryl allyl ethers using the above approach allowed rapid access to 3-substituted benzofurans (Scheme 5). The isolated yields varied from modest to good.[40]



**Scheme 5.** Reagents and conditions: 5% PdCl<sub>2</sub>, (n-Bu)<sub>3</sub>N, [bmim][BF<sub>4</sub>], 60 °C, 24 h.

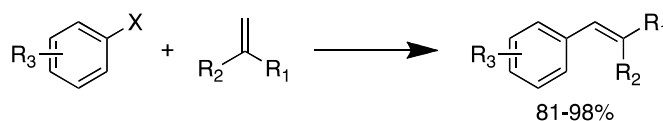
Specialty highly recyclable Pd-complexes, such as Alper's Pd(II)-bisimidazole (Scheme 6), have proved effective recyclable (five cycles with no loss of activity) Heck coupling catalysts. [4][1][4][5]



**Scheme 6.** Reagents and conditions: 2 mol % Pd-catalyst, [BMIM]BF<sub>4</sub>, 60 °C, 24 h.

## 2.2. Phosphonium RTILs

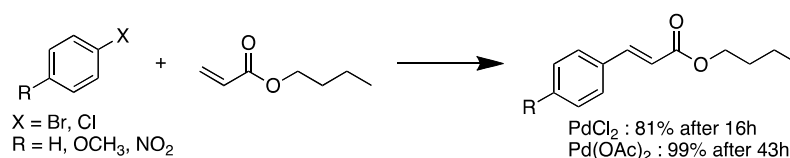
A wide range of phosphonium based RTILs have been explored for use in the Heck reaction. [46] Of particular note was the use of salts such as [P<sub>6,6,6,14</sub>][Cl] in the Heck coupling of deactivated and sterically demanding aryl halides (Scheme 7).[47-50] Even with deactivated aryl halides these reactions required mild conditions and short reaction duration (50 °C and 2 h). The reaction requires only 50 °C within 2 h. The solvent and catalyst could be reused. Furthermore, the phosphonium RTIL anion influenced reaction outcome chloride and decanoate anions giving superior outcomes than with BF<sub>4</sub> and PF<sub>6</sub>. [47]



**Scheme 7.** Reagents and conditions: [P<sub>6,6,6,14</sub>][Cl], Pd(OAc)<sub>2</sub>, 100 °C, 18-24 h.

The phosphine free Pd(OAc)<sub>2</sub> / or PdCl<sub>2</sub> mediated Heck coupling has been conducted in [P<sub>6,6,6,14</sub>][Br], which also represented the first report of a Pd-coupling reaction in a RTIL (Scheme 8).[46]



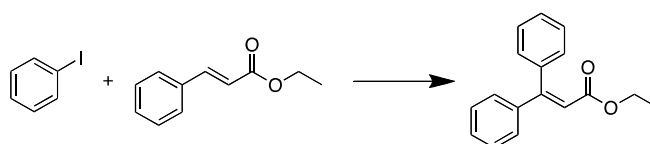


**Scheme 8.** Reagents and conditions:  $[\text{P}_{6/6/6/14}][\text{Br}]$ ,  $\text{Pd(OAc)}_2$ , 100 °C, 124 h.

It was noted with  $\text{Pd(OAc)}_2$  that the addition of 1.5 eq. of  $\text{NaOAc}$ , improved the coupling rate, but decreased selectivity with 5% of the (Z)-isomer detected under these conditions. Also of note with this reaction sequence was the slow precipitation of Pd-clusters on use of  $\text{PdCl}_2$ , but not with  $\text{Pd(OAc)}_2$ . With  $\text{Pd(OAc)}_2$  the catalyst remained soluble and viable, able to catalyse subsequent couplings on removal of the product from the previous catalytic cycle. It was proposed that the RTIL phosphonium salt stabilised the Pd(0) species obtained by *in situ* reduction of the Pd(II) catalyst precursors. This ligand free approach has attracted considerable interest and has purification benefits on reaction scale up.[51]

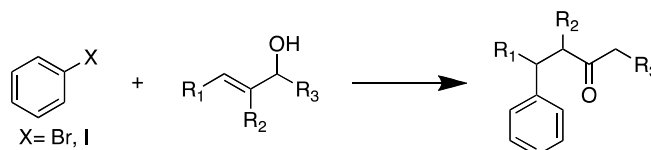
### 2.3. Ammonium RTILs

Tetraammonium salts are the archetypal ammonium based RTILs used in the Heck coupling, with the simplest being the tetrabutylammonium salts ( $[\text{Bu}_4\text{N}][\text{X}]$ ). Coupling of iodobenzene with arylacrylates gave an expedient synthesis of 3,3-diarylacrylates. This coupling was accomplished in good yield and regioselectivity in molten  $n\text{-Bu}_4\text{NOAc}/n\text{-Bu}_4\text{NBr}$  with  $\text{Pd(OAc)}_2$  (Scheme 9).[52]



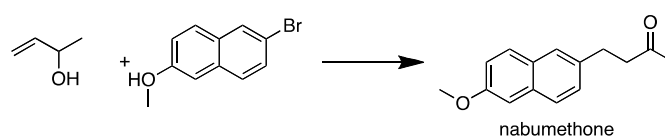
**Scheme 9.** Reagents and conditions:  $\text{Pd(OAc)}_2$ ,  $n\text{-Bu}_4\text{NOAc}/n\text{-Bu}_4\text{NBr}$ , 100 °C.

Others have noted the increased stability of the Pd-catalytic species in RTILs and have exploited this in the  $\text{PdCl}_2$  mediated synthesis of  $\beta$ -arylcarbonyl compounds from allylic alcohols in  $[\text{Bu}_4\text{N}]\text{Br}$ , affording (Scheme 10).[53] Extension of this simple procedure afforded a one-step synthesis of the nonsteroidal antiinflammatory drug (nabumethone), (Scheme 11) and allowed catalyst reuse.[53]



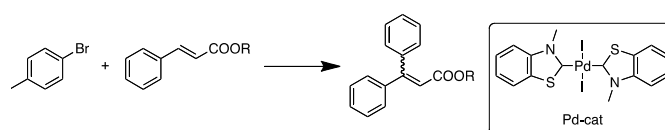
**Scheme 10.** Reagents and conditions:  $\text{PdCl}_2$ ,  $\text{NaHCO}_3$ ,  $\text{Bu}_4\text{NBr}$ , 120 °C, 24 h.





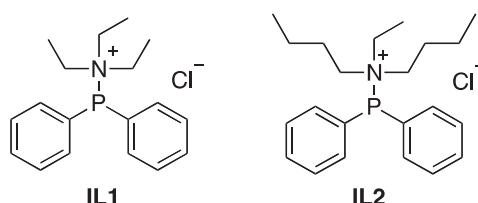
**Scheme 11.** Reagents and conditions:  $\text{PdCl}_2$ ,  $\text{NaHCO}_3$  (1.2 equiv.),  $\text{Bu}_4\text{NBr}$ ,  $120^\circ\text{C}$ , 24 h.

The Pd-benzothiazole carbene complex has been successfully used as the Pd-source (1.5 mol %), and easily recycled, in the coupling of both electron rich and electron deficient *trans*-cinnamates in  $[\text{Bu}_4\text{N}][\text{Br}]$  at  $130^\circ\text{C}$  with added sodium formate and  $\text{NaHCO}_3$  (Scheme 12).[54, 55] The best yields were observed with  $\text{NaOH}$  and DBU and in these instances the reactions were complete in  $< 30$  min.



**Scheme 12.** Reagents and conditions:  $[\text{Bu}_4\text{N}]\text{Br}$ ,  $\text{NaOAc}$ ,  $\text{NaHCO}_3$ ,  $130^\circ\text{C}$ , Pd-cat.

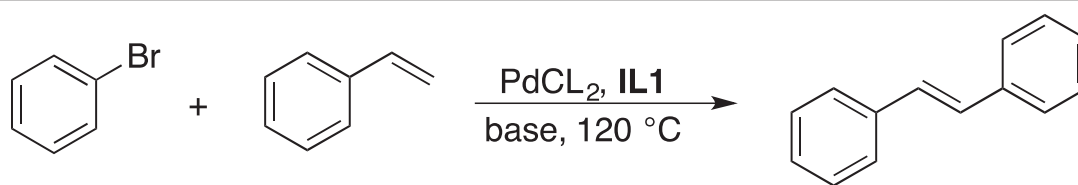
Motevalli's *N*-(diphenylphosphino)triethylammonium chloride (**IL1**) and *N*-(diphenylphosphino)tributylammonium chloride (**IL2**), have been used successfully in Heck couplings of iodobenzene and styrene (Figure 3 and Table 3).[56]



**Figure 3.** Structures of *N*-(diphenylphosphino)triethylammonium chloride (**IL1**) and *N*-(diphenylphosphino)tributylammonium chloride (**IL2**).

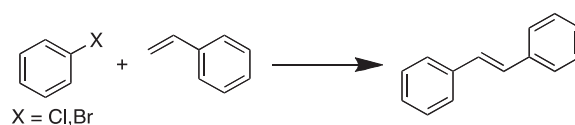
## 2.4. Studies using imidazolium, pyridinium, phosphonium and ammonium RTILs

The coupling of electron poor chloroarenes with mono and di-substituted olefins across a range of RTILs and Pd-sources has been examined.[57] The model system, resulting in the synthesis of stilbene from chlorobenzene and styrene was best conducted with simple, e.g.  $\text{PdCl}_2$ , phospho-based Pd-sources (Scheme 13). RTILs examined included: imidazolium, ammonium and phosphonium salts. The tetraalkylammonium salts, in particular  $[\text{Bu}_4\text{N}][\text{Br}]$ , were superior permitting the coupling of chloroarenes in the presence of less active catalysts such as  $\text{PdCl}_2$  and  $\text{Pd}(\text{Ph}_3\text{P})_4$ . Regardless of the conditions used, all imidazolium based RTILs gave poor results, e.g. 22 % for  $[\text{bmim}][\text{BF}_4]$  and 13 % for  $[\text{bmim}][\text{Br}]$  whereas TBAB gave 72 % of the desired stilbene. With  $[\text{bmim}][\text{BF}_4]$  there was clear evidence of the formation of Pd black.[57]



Entry	Base	Time (h)	Yield %
1	Na <sub>2</sub> CO <sub>3</sub>	24	-
2	CaCO <sub>3</sub>	24	-
3	DBU	25 min	90
4	NaOH	8 min	93
5	Et <sub>3</sub> N	24	60
6	Bu <sub>3</sub> N	24	50

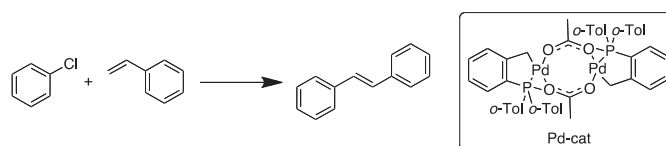
**Table 3.** Effect of different bases on Heck reaction of bromobenzene and styrene in *N*-(diphenylphosphino)triethylammonium chloride (**IL1**).



**Scheme 13.** Reagents and conditions: PdCl<sub>2</sub> or Pd(Ph<sub>3</sub>P)<sub>4</sub>, 150 °C, [bmim][BF<sub>4</sub>] or [bmim]Br or Bu<sub>4</sub>NBr reaction of mono and di-substituted olefins in a diversity of RTILs.

Heck couplings have also been conducted in the thermally and chemically stable [P<sub>6,6,6,14</sub>][X] quaternary phosphonium salts, where X=Br<sup>-</sup>, Cl<sup>-</sup>, I<sup>-</sup>, BF<sub>4</sub><sup>-</sup> and CH<sub>2</sub>(CH<sub>2</sub>)<sub>8</sub>CO<sub>2</sub><sup>-</sup> and the resulting FILs used in the coupling of iodobenzene with methylacrylate.[58] The effect of anion on the coupling outcome was determined by screening using Pd<sub>2</sub>dba<sub>3</sub>.CHCl<sub>3</sub> and each of the phosphonium FILs in turn. High coupling efficiency was observed [P<sub>6,6,6,14</sub>][CH<sub>2</sub>(CH<sub>2</sub>)<sub>8</sub>CO<sub>2</sub>] (75%) and [P<sub>6,6,6,14</sub>][Cl] (78%), with [P<sub>6,6,6,14</sub>][Cl] also providing a simpler work up.

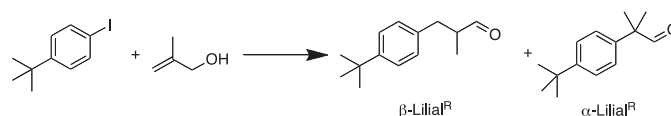
The coupling of bromobenzene and butyl acrylate was examined in a range of what were designated, non-aqueous ionic liquids (NAILs), with *trans*-di(μ-acetato)-bis[o-(di-*o*-tolylphosphino)benzyl] dipalladium(II) as catalyst (Scheme 14).[59, 60] These NAILs were drawn from Bu<sub>4</sub>NBr, Bu<sub>4</sub>NOAc, 1-methyl-3-propylimidazolium bromide ([MPIM]Br), tri-*n*-butyl-*n*-hexadecylphosphonium bromide (TBHDP), triphenylmethylphosphonium chloride (TPMPC) and triphenylmethylphosphonium bromide (TPMPB), all of which gave homogeneous reaction media and permitted facile catalyst recycling.



**Scheme 14.** Reagents and conditions: 0.5% Pd-cat, NAIL.

### 3. Functionalized Ionic Liquids (FILs)

Functionalised (FILs) or, as they are sometimes known, task specific ionic liquids, incorporate additional functional moieties within the cation or anion.[61] FILs can be discrete liquids or be supported reagents and have applications as reagents and catalysts.[62]–[66] FILs have been examined as novel media for the  $\text{Pd}(\text{OAc})_2$  mediated Heck reaction of 2-methylprop-2-en-1-ol and 4-*tert*-butyliodobenzene in  $[\text{iPr}_2\text{N}(\text{CH}_2)_2\text{mim}][\text{NTf}_2]$  and  $[\text{iPr}_2\text{N}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{N}_{112}][\text{NTf}_2]$ . In  $[\text{Pr}_2\text{N}(\text{CH}_2)_2\text{mim}][\text{NTf}_2]$  only 32 % of 3-(4-*tert*-butylphenyl)-2-methylpropanal ( $\beta$ -Lilial<sup>®</sup>) was present after 10 h; this increased to 84% on using  $[\text{iPr}_2\text{N}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{N}_{112}][\text{NTf}_2]$ . These outcomes correlate well with the relative basicity of these two FILs. The equivalent coupling in neat Hünig's base showed a conversion of 39%, supporting a catalytic role for the PILs.[67] The selectivity between 3-(4-*tert*-butylphenyl)-2-methylpropanal and 2-(4-*tert*-butylphenyl)-3-methylpropanal was found to be >95% respect to  $\beta$ -Lilial<sup>®</sup> and independent of the PIL basicity (Scheme 15).



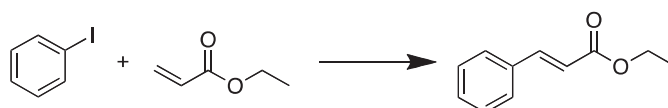
**Scheme 15.** Reagents and conditions:  $\text{Pd}(\text{OAc})_2$ , 95 °C, time, base tethered-RTIL.

RTILs based on dialkylimidazolium salts have attracted particular attention, as they are easy to prepare and handle, having good solubility for many substrates and molecular catalyst and are readily synthesised through a variety of green chemistry approaches.[68]–[70] 1-Octyl-3-methylimidazolium nonafluorobutanesulfonate [omim][FNBS] represents a novel dialkylimidazolium based hydrophobic ionic liquid which is effective in ligand-free Heck couplings with electron deficient olefins (Scheme 16).[71]



**Scheme 16.** Reagents and conditions:  $\text{Pd}(\text{OAc})_2$ ,  $\text{Et}_3\text{N}$ , [omim][FNBS], 100 °C, 3–12 h.

Nitrile modified imidazolium and pyridinium salts have been used in Pd-catalysed cross-coupling reactions (Scheme 17).[72, 73] These FILs are highly effective solvents for the Heck reaction with excellent yields observed (Table 4).[74]

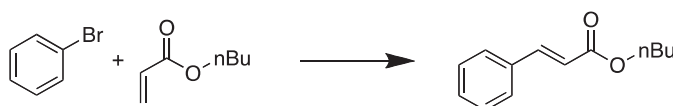


**Scheme 17.** Reagents and conditions: 5 mol % Pd,  $[\text{C}_3\text{CNmim}][\text{Tf}_2\text{N}]$ , 80 °C, 12 h.

No.	Cat.	Base	Time (h)	Additive	Yield %
1	PdCl <sub>2</sub>	[cholinium][OAc]	12	HCOONH <sub>4</sub>	99
2	(C <sub>3</sub> CNdmim) <sub>2</sub> [PdC <sub>14</sub> ]	[cholinium][OAc]	12	HCOONH <sub>4</sub>	96

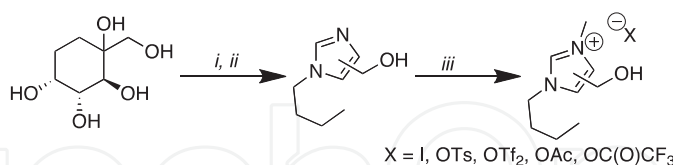
**Table 4.** Selected examples of the Heck Coupling of Iodobenzene with ethyl acrylate in [C<sub>3</sub>CNmim][Tf<sub>2</sub>N] at 80 °C.

Numerous studies have highlighted the deprotonation of imidazolium RTILs to yield an imidazol-2-ylidene *N*-heterocyclic carbene (NHC) as a crucial step in subsequent reactions complex generated by deprotonation of the ionic liquid cation.[75-78] Many transition-metal carbene complexes have been prepared and their catalytic applications described.[79, 80] This has led to the evaluation of novel RTILs as catalysts in Pd-coupling reactions.[81, 82] Metal-NHC complexes have been generated and examined in RTILs, with the metal-NHC complex reactivity examined for Heck coupling efficacy in DMF and [bmim][NTf<sub>2</sub>] based of an NHC located from an ionic liquid cation and investigate the catalytic activity in both molecular and ionic liquid solvents in the Heck coupling of butyl acrylate and bromobenzene (Scheme 18). [83-86]



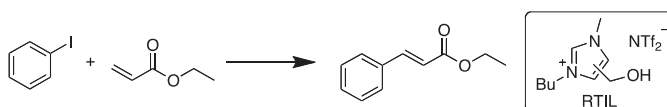
**Scheme 18.** Reagents and conditions: 5 mol% Pd-cat, Cs<sub>2</sub>CO<sub>3</sub>, [Bmim][NTf<sub>2</sub>], 150 °C, 18 h.

Fructose has been used as a renewable resource in the synthesis of novel hydroxymethylimidazolium based protic ionic liquids (PILs) (Scheme 19).[86-91]



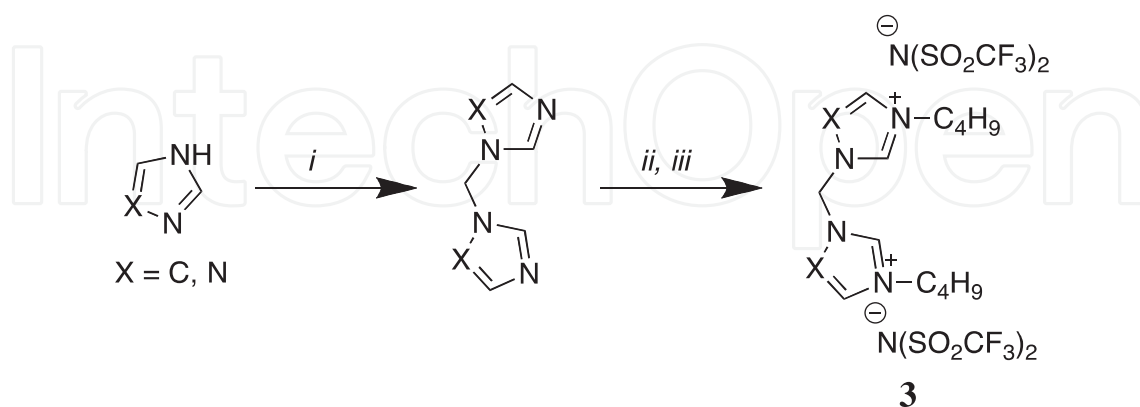
**Scheme 19.** Reagents and conditions: (i) NH<sub>2</sub>, CH<sub>2</sub>O, CuCO<sub>3</sub>; (ii) BuBr, KOtBu, EtOH; (iii) MeI, CH<sub>2</sub>Cl<sub>2</sub>; Metal-X.

Use of these fructose derived PILs in the Pd(OAc)<sub>2</sub> mediated Heck coupling of methyl acrylate with iodobenzene afforded rapid conversion (1 h) to methyl cinnamate in > 95% yield at 100 °C (Scheme 20). Both the PIL and catalyst were readily recycled with no loss of activity.



**Scheme 20.** Reagents and conditions: 2 mol % Pd(OAc)<sub>2</sub>, Et<sub>3</sub>N, RTIL, 100 °C.

Shreev, *et al*, synthesized the new RTIL, shown in (Scheme 21), which contain the dication 1,1'-methylene-3,3'-dialkylbis(imidazolium) or 1,1'-methylene-4,4'-dialkylbis(1,2,4-triazolium) with NTf<sub>2</sub> as the anion, and evaluated its efficacy in the Heck reaction (Table 5).[92]



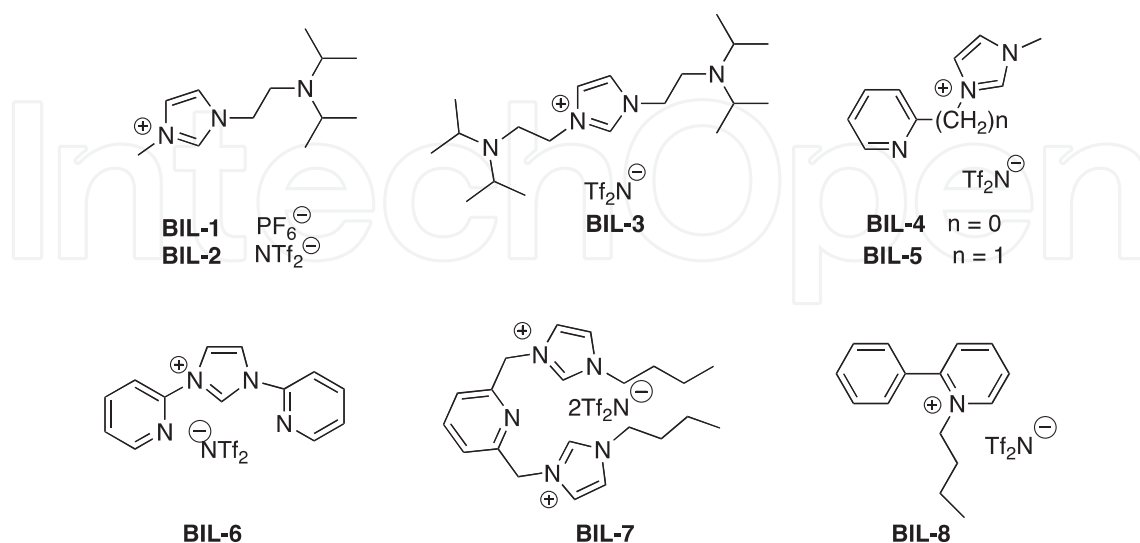
**Scheme 21.** Reagents and conditions: (i) CH<sub>2</sub>Cl<sub>2</sub> or CH<sub>2</sub>Br<sub>2</sub>, KOH, Bu<sub>4</sub>NBr; (ii) RI, 110-130 °C, 20; (iii) LiN(SO<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>, CH<sub>3</sub>OH/H<sub>2</sub>O (10:1), RT, 2 h.

Entry	Pd source	R	X	Time (h)	Yield %
1	PdCl <sub>2</sub>	H	I	6	92
2	PdCl <sub>2</sub>	H	Br	18	71
3	PdCl <sub>2</sub>	H	Cl	24	3
4	PdCl <sub>2</sub>	NO <sub>2</sub>	Br	18	69
5	PdCl <sub>2</sub>	CF <sub>3</sub>	Br	18	57
6	PdCl <sub>2</sub>	CH <sub>3</sub>	Br	12	76

**Table 5.** Heck cross-coupling reactions in the ionic liquid-**3** and different anions (X) with selected aryl halides and butyl acrylate.

In a related study Shreeve *et al*, also examined the use of a range basic RTILs as both the base and solvent for the Heck coupling of iodobenzene and butyl acrylate (see Figure 3 for chemical structures of the BILs). With BILs, **BIL-1**, **BIL-2** and **BIL-3** quantitative conversion and regioselectivity was observed. All other BILs (**BIL-4-BIL-8**) displayed low to no reactivity

under the conditions examined (Table 6). In this study, these results suggest that RTILs with pendant aliphatic tertiary amines are superior to the pyridinium salts.[93]



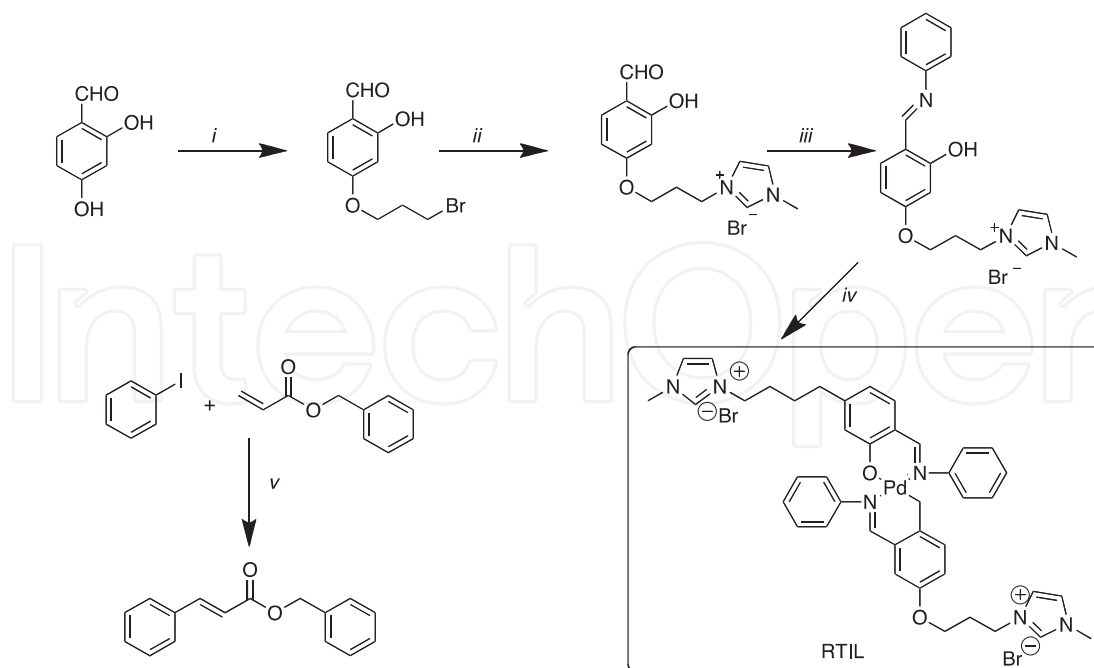
**Figure 4.** Chemical structures of Basic ionic liquid cations.

ILs	BIL-1	BIL-2	BIL-3	BIL-4	BIL-5	BIL-6	BIL-7	BIL-8
Conv.[%]	100	100	100	0	41	0	5	0

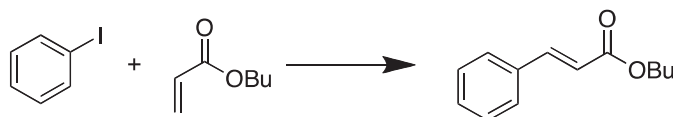
**Table 6.** Heck reactions between butyl acrylate and iodobenzene in the presence of basic ionic liquid (**BIL1-BIL8**) (Fig. 3).

The novel imidazolium RTIL tagged Pd-Schiff base complex was active in both Heck and Suzuki couplings in aqueous media. Relative to other Pd-catalyzed reactions in aqueous media, this catalyst was effective in the coupling of water insoluble aryl halides without the aid of a phase transfer catalyst or organic solvents (Scheme 22).[94] Optimised Heck coupling conditions required the use of 1 mol % catalyst,  $K_2CO_3$  and with iodobenzene and cyclohexyl acrylate gave benzyl cinnamate in 96% yield, (Scheme 23).

Chitosan supported  $Pd(OAc)_2$  nanoparticles (Pd-NP) in TBAB with added tetrabutyl ammonium acetate (TBAA) gave rise to very rapid Heck couplings of aryl bromides, iodides and activated chlorides (Scheme 23).[95] The supported catalyst was amenable to multiple recycles, whereas the free nano particles rapidly lost activity.

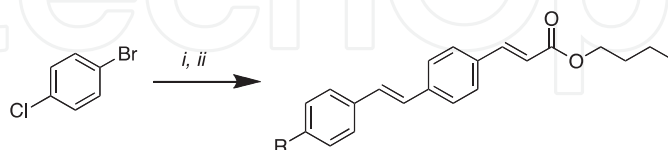


**Scheme 22.** Reagents and conditions: (i)  $\text{BrCH}_2\text{CH}_2\text{CH}_2\text{Br}$ , acetone,  $\text{NaHCO}_3$ ,  $60^\circ\text{C}$ , 60 h; *N*-methylimidazole,  $80^\circ\text{C}$ , 48 h; (iii) aniline, EtOH, reflux, 4 h;  $\text{Pd}(\text{OAc})_2$ ; (iv)  $\text{H}_2\text{O}$ , imidazolium ILs,  $80^\circ\text{C}$  and 4 h; (v) RTIL,  $80^\circ\text{C}$ ,  $\text{K}_2\text{CO}_3$ .



**Scheme 23.** Reagents and conditions: Pd-NP /chitosan,  $[\text{Bu}_4\text{N}][\text{Br}]/[\text{Bu}_4\text{N}][\text{OAc}]$ , 15 min to 1.5 h,  $130^\circ\text{C}$ .

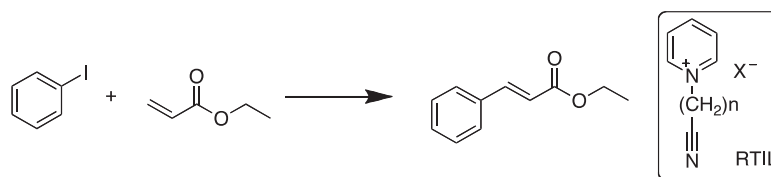
With Pd-NP in a mixture of  $[\text{Bu}_4\text{N}][\text{Br}]/[\text{Bu}_4\text{N}][\text{OAc}]$  it was possible to couple 1-bromo-4-chlorobenzene with two different olefins in a one-pot sequential manner by activating the C-Br and C-Cl bonds on the aromatic ring at two different temperatures of  $100$  and  $120^\circ\text{C}$  (Scheme 24).[96]



**Scheme 24.** Reagents and conditions: (i) butyl acrylate, Pd-NP,  $[\text{Bu}_4\text{N}][\text{Br}]/[\text{Bu}_4\text{N}][\text{OAc}]$ ,  $100^\circ\text{C}$ , 30 min; (ii) styrene, Pd-NP,  $[\text{Bu}_4\text{N}][\text{Br}]/[\text{Bu}_4\text{N}][\text{OAc}]$ ,  $120^\circ\text{C}$ , 30 min.

There have been multiple reports on the use of nitrile-functionalized RTILs, such as the imidazolium and pyridinium based systems, in Pd-catalysed reactions, including the Heck reaction. Heck coupling in these FILs typically afforded a 90% isolated yield of the desired product (Scheme 25).[97, 98]

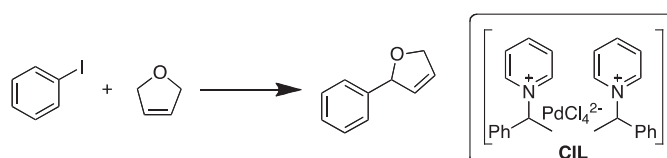




**Scheme 25.** Reagents and Conditions: 5 mol % Pd-cat; IL, 80 °C, 12 h.

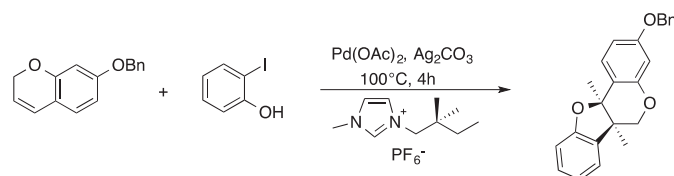
### 3.1. Chiral Ionic Liquids (CIL)

To date the use of chiral RTILs (CILs) in Heck couplings has met with limited success. The arylation of 2,3-dihydrofuran with iodobenzene catalysed by a chiral pyridinium ILs with  $[\text{PdCl}_4]^{2-}$  (Figure 4), (used as a co-solvent with  $[\text{bmim}][\text{PF}_6]$ ), (Scheme 26).[99]



**Scheme 26.** Reagents and conditions: 2,3-dihydrofuran with iodobenzene catalysed by CILs with  $[\text{PdCl}_4]^{2-}$ , Et<sub>3</sub>N,  $[\text{bmim}][\text{PF}_6]$ , 100 °C.

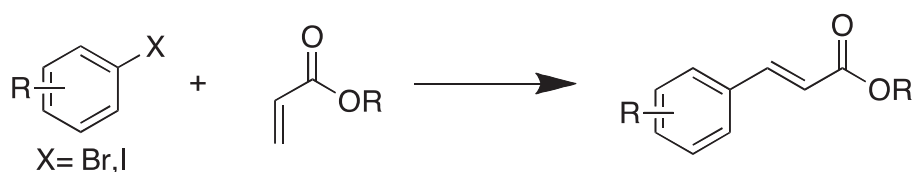
However, the use of the chiral  $[\text{bmim}][\text{PF}_6]$ , did give rise to the desired 7-benzyloxy-2H-chromene in good yield and modest e.e. (15%) (Scheme 27).[100]



**Scheme 27.** Reagents and conditions: The oxyarylation of 7-benzyloxy-2H-chromene in CILs,  $\text{Pd}(\text{OAc})_2$ ,  $\text{Ag}_2\text{CO}_3$ , 100 °C and 4 h.

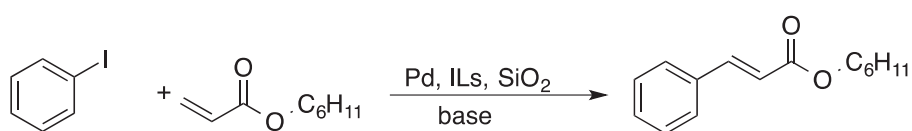
### 3.2. Supported ionic liquid phase (SILP) catalyst system

Immobilisation of the Pd-catalyst and the RTIL onto high surface area porous solids such as silica yields a supported ionic liquid phase (SILP) catalyst system. SLIPs are considered, while being solids, to contain the active species comprise solubilized in the IL phase behaving as a homogeneous catalyst, and as such offer the potential for novel reactivity. Suzuki has examined this reactivity with a range of  $\text{Pd}(\text{OAc})_2$ /silica based SLIP catalyst systems. The SLIPs were air and thermally stable, provided simple storage conditions, easily recyclable and highly effective in the Heck coupling of substituted arylhalides with vinyl esters (Scheme 28).[101, 102]



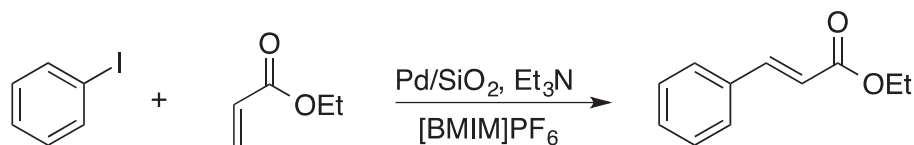
**Scheme 28.** Reagents and conditions:  $\text{Pd}(\text{OAc})_2$ , SILP,  $\text{Na}[(\text{Ph})_2\text{P}(m\text{-PhSO}_3)]$ ,  $150^\circ\text{C}$ , 7-17 h.

In a related study,  $\text{Pd}(\text{OAc})_2$  and  $[\text{bmim}][\text{PF}_6]$  were immobilized on reversed phase silica gels such as aminopropylated or *N,N*-diethylaminopropylated silica.[103] The Heck reaction between iodobenzene and cyclohexyl acrylate was carried out as shown in (Scheme 29). The catalyst was reused five times with no loss of catalytic activity.



**Scheme 29.** Reagents and conditions:  $\text{Pd}(\text{OAc})_2$ ,  $[\text{bmim}][\text{PF}_6]\text{-SiO}_2$ ,  $30^\circ\text{C}$ , 1.5-3 h.

Yokoyama *et al.*, has been reported the use of a  $\text{SiO}_2$  supported  $\text{Pd}(\text{II})/[\text{bmim}][\text{PF}_6]$  as a highly active and reusable SLIP for the phosphine free Heck reaction of iodobenzene and ethyl acrylate (Scheme 30).[104] The addition of low levels of  $\text{Et}_3\text{N}$  increased the  $[\text{bmim}][\text{PF}_6]$  decomposition temperature in this system from  $130$  to  $160^\circ\text{C}$ .



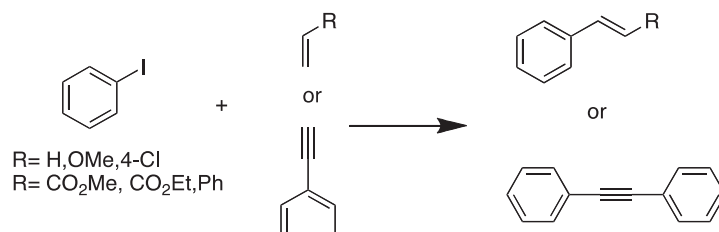
**Scheme 30.** Reagents and conditions:  $\text{Pd}(\text{II})\text{-SiO}/[\text{bmim}][\text{PF}_6]$ ,  $\text{Pd/SiO}_2$ ,  $\text{Et}_3\text{N}$ ,  $[\text{bmim}][\text{PF}_6]$ ,  $130\text{-}160^\circ\text{C}$ , 24 h.

### 3.3. Ultrasonic synthesis approaches

In the RTILs, 1,3-di-*n*-butylimidazolium bromide  $[\text{bbim}][\text{Br}]$  and 1,3-di-*n*-butylimidazolium tetrafluoroborate  $[\text{bbim}][\text{BF}_4]$ , under ultrasonic irradiation significant rate enhancements were noted for the  $\text{NaOAc} / \text{PdCl}_2$  mediated coupling of substituted iodobenzenes with alkenes/alkynes at  $120^\circ\text{C}$  (Scheme 31).[105] Isolated yields were good to excellent (up to 87%) with only the *trans* product obtained. These couplings only required 1.5-3 h.

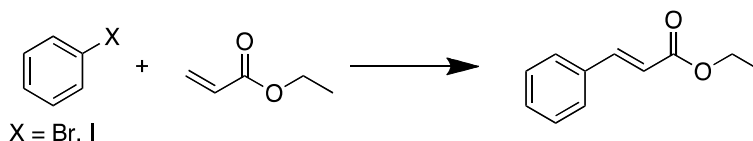
### 3.4. Microwave synthesis approaches

Microwave heating has been applied to the Heck reaction in RTILs significantly reducing the time required to effect coupling, and influencing product yield and the extent of by-product generation.[106, 110] Generally microwave approaches have focused on the use of aryl iodides



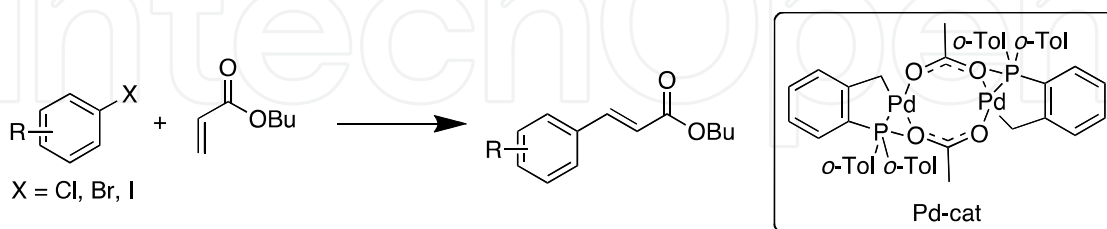
**Scheme 31.** Reagents and conditions: (i) 2 mol%  $\text{PdCl}_2$ , [bbim][Br] or [bbim][BF<sub>4</sub>], 120 °C, 1.5-3 h.

and active aryl bromide, such as those reported by Larhed *et al* in [bmim][PF<sub>6</sub>] (Scheme 32). [111] Using 4 mol %  $\text{PdCl}_2$  (4 mol %),  $\text{P}(o\text{-tolyl})_3$  as the added Pd-ligand, reactions were complete after 5-45 min, at 180 – 220 °C. The catalyst system and RTIL were and the time 20 minutes and 45 minutes for trans formations without the phosphine ligand. This system was recyclable at least five times, and the volatile product was directly isolated in high yield by rapid distillation under reduced pressure.[111]



**Scheme 32.** Reagents and conditions:  $\text{PdCl}_2$ ,  $\text{P}(o\text{-tolyl})_3$ ,  $\text{Et}_3\text{N}$ , [bmim][PF<sub>6</sub>],  $\mu\text{W}$ , 180-220 °C, 5-45 min.

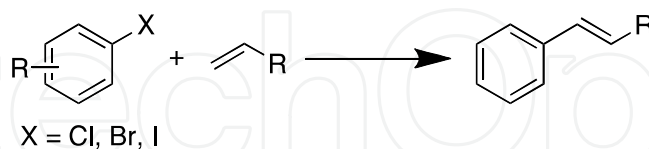
More complex Pd-catalysis such as Herman's palladacycle, *trans*-di( $\mu$ -acetato)bis[*o*-di-*o*-tolylphosphanyl)-benzyl]dipalladium, have been developed in efforts to enhance Pd-coupling outcomes with unreactive aryl chlorides.[112] Using this Pd-catalyst (1.5 – 10 mol %), Heck coupling in [bmim][PF<sub>6</sub>] / dioxane mixtures with aryl chlorides and butyl acrylate gave the desired cinnamic esters.[113] High levels of phosphine ligand (3-20 %) were required dependent on the reactivity of the aryl chloride. Under microwave irradiation the yields were moderate to excellent (Scheme 33).[114]



**Scheme 33.** Reagents and conditions: Herrmann's palladacycle, [(*t*-Bu)<sub>3</sub>PH][BF<sub>4</sub>], Cy<sub>2</sub>NMe, [bmim][PF<sub>6</sub>]/dioxane,  $\mu\text{W}$ , 180 °C, 30-60 min.

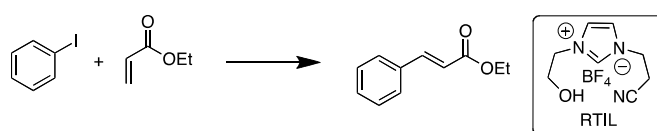
Microwave irradiation of [omim][BF<sub>4</sub>] with 3-5 mol % Pd/C proved effective in the phosphine free Heck coupling of aryl iodides and aryl bromides with butyl acrylate. The reactions were typically complete in 1.5 min affording 33-89% yield of the *trans*-butyl cinnamates. This

microwave based Pd-coupling approach was effective across a range of olefinic substrates including styrene, 2-methylbutyl acrylate and methyl cinnamate with iodobenzene. The steric bulk of the olefin affected reaction outcome with yields ranging from 27 – 86 % (Scheme 34). [115]



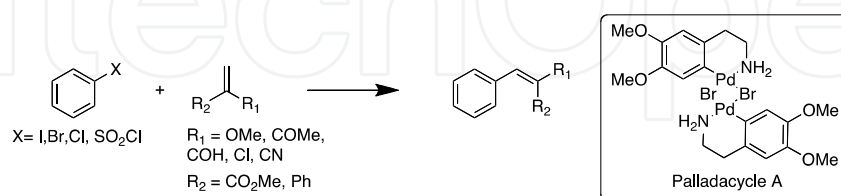
**Scheme 34.** Reagents and conditions: Pd/C, (n-Bu)<sub>3</sub>N, [omim][BF<sub>4</sub>], μW, 1.5 min at 375W.

Under conventional heating for 24 h, the Heck coupling of iodobenzene with ethyl acrylate in 1-(2-cyanoethyl)-3-(2-hydroxyethyl)-1*H*-imidazol-3-ium tetrafluoroborate, afforded a modest 25% yield of ethyl cinnamate with PdCl<sub>2</sub>. Using microwave irradiation (200 W, 120 °C), the same reaction system gave 88% yields of ethyl cinnamate in 5 min (Scheme 35). The system showed good stability and maintained the efficiency after six consecutive runs without significant loss of activity.[116]



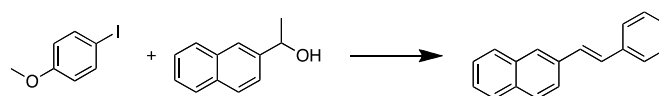
**Scheme 35.** Reagents and conditions: PdCl<sub>2</sub>, RTIL, μW, 120 °C, 5-20 min.

Under microwave irradiation in TBAB, the {Pd[C<sub>6</sub>H<sub>2</sub>(CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>)-(OMe)<sub>2,3,4</sub>](μ-Br)}<sub>2</sub> (palladacycle A) mediated Heck coupling of aryl bromides, aryl iodides, aryl chlorides and arene sulfonyl chlorides increased dramatically with reaction times reducing from hours to minutes (Scheme 36).[117]



**Scheme 36.** Reagents and conditions: palladacycle A, [Bu<sub>4</sub>N][Br], μW, 130 °C, 1-20 min.

The scope of the Heck olefin precursor has been extended through the use of microwave approached to 2° alcohols in a dehydrative Heck coupling approach. The combination of [hmim][Br], [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] along with LiCl and the combination of HCO<sub>2</sub>Na and piperidine and microwave irradiation reduced reaction times to 15 min (Scheme 37).[118]

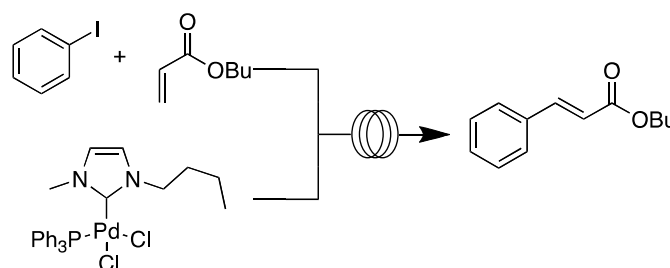


**Scheme 37.** Reagents and conditions: [hmim][Br],  $\text{HCO}_2\text{Na}$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ ,  $\mu\text{W}$ ,  $150^\circ\text{C}$  at 15–40 min.

### 3.5. Flow chemistry approaches

Micro reactor technology has had a significant impact on the chemical synthesis and production. This technology has many advantages including: 1) highly efficient material mixing; 2) high volume to area ratio; 3) efficient heat transfers ability; 4) the avoidance of “hot spots” by effective temperature control and mixing; and 5) high operational safety.[119] The transition metal catalysed reactions have been reported by using a micro flow system, such as hydrogenation[120] and oxidation,[121] and the Heck reaction.[122]

RTILs present a challenge for flow chemistry approaches due to their often-high viscosity. Ryu has examined the use of a low viscosity RTIL, [bmim]NTf<sub>2</sub> as well as a high viscosity RTIL, [bmim][PF<sub>6</sub>].[122] The Heck coupling of iodobenzene with butyl acrylate was sluggish in [bmim][PF<sub>6</sub>], but the use of [bmim][NTf<sub>2</sub>] in a CPC CYTOS lab system gave 10 g.h<sup>-1</sup> of, and in a single run with catalyst recycling, 115.3g of butyl cinnamate (Scheme 38).[123]



**Scheme 38.** Reagents and conditions: 0.1–0.5 mL.h<sup>-1</sup>, [BMIM]NTf<sub>2</sub>,  $130\text{--}150^\circ\text{C}$ , 10–50 min residence time.

## 4. Conclusions

In the last twenty years has shown an increasing interest in applying ionic liquids as green solvents in organic synthesis. This approach has been extended to the palladium-catalysed Heck reactions as a key synthetic protocol for C–C bond formation. Factors affecting this approach including the type of ionic liquid used, the base and the catalyst have been investigated by many research groups. In addition, limited number of microwave-based and flow chemistry based Heck reactions have been reported. Despite these efforts, only simple aryl halides and olefines were used in the reported investigations. Active research in this area is still required to increase the scope of Heck reaction in ILs to involve more complicated substrates and larger scale.

## Author details

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