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# A novel hydrophobic fluorous ionic liquid for ligand-free Mizoroki–Heck reaction

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### ABSTRACT

Mizoroki–Heck reaction is carried out in a novel hydrophobic fluorous ionic liquid which was catalyzed by Pd-nanoparticles formed in situ from  $Pd(OAc)_2$  used in the reaction. This reaction is operable under mild, aerobic, and ligand-free conditions in excellent yields. Aryl iodides, bromides as well as chlorides can be used showing its versatility. The key feature of the system is that catalyst along with ionic liquid can be reused at least five times with superior activity.

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The recent Nobel Prize in Chemistry for the year 2010 dedicated to Heck, Suzuki, and Negishi highlights the importance of C-C bond forming reactions. Pd-catalyzed coupling reactions constitute the important tool to generate carbon-carbon and carbon-hetero atom bonds<sup>1</sup> and find applications in pharmaceuticals,<sup>1</sup> agrochemicals,<sup>1</sup> natural products,<sup>2</sup> etc. Due to these multifarious applications, many efforts have been devoted to the development of new combination of Pd-catalysts and solvent (either homogeneous or heterogeneous phase)<sup>3</sup> which could be operated under mild conditions and a simple operating process. Ionic liquid [IL] in combination with palladium catalyst has been used in nearly all cross coupling reactions with replacement of organic solvents by ILs as green alternatives.<sup>4,5</sup> Ionic liquids have gained increasing attention as green, multi-use reaction media, and solvents for a variety of applications due to the fact that they posses negligibly small vapor pressure, high thermal as well as chemical and electrochemical stability with widely tunable properties with regard to polarity, hydrophobicity, solvent miscibility, etc.<sup>6</sup> These outstanding properties attract the attention of synthetic chemists to synthesize new ILs and apply them in coupling reactions.<sup>7</sup>

Among the various coupling reactions, the Mizoroki–Heck reaction is one of the most powerful method for C–C bond formation and generally carried out in polar solvents such as DMF, *N*,*N*-DMAC, and CH<sub>3</sub>CN, etc. In this reaction for less reactive bromides and chlorides, phosphine ligands<sup>8</sup> are normally required to stabilize catalytically active palladium species. This can also be achieved by employing salt additives such as ammonium and phosphonium chlorides and bromides, probably via formation of zero valent palladium halide species and accelerates the olefination reaction.<sup>9</sup> Therefore, to overcome these drawbacks and in view of industrial and pharmaceutical needs, reports of ligand-free heck arylations are clearly on the rise. Continuous efforts are being taken by scientists working in this field.<sup>10</sup> In light of this, developing a new green solvent system operable under ligand-free condition for the Heck reaction is highly desirable.

We have been interested in the development of synthetic methodologies employing principles of 'Green Chemistry'.<sup>11</sup> In continuation of our interest, in the present manuscript, we report a simple, efficient, and green approach for the ligand-free Heck reaction.

Seddon et al.<sup>12</sup> explored the hydrophobic ionic liquid viz. 1butyl-3-methylimidazolium hexafluorophosphate [bmim]PF<sub>6</sub> first time for Heck reaction of aryl halides with alkenes using homogeneous palladium complex catalysts along with phosphine ligand. The hydrophobic ionic liquid attracted the attention of synthetic chemists, as they can be separated from the products by simple decantation of the organic solvent and water, respectively.

Initial attempts were directed toward the synthesis of novel hydrophobic ionic liquid for ligand-free Heck reaction. ILs 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.<sup>4,5,13</sup>

The synthesis of hydrophobic IL viz. 1-octyl-3-methylimidazolium nonafluorobutanesulfonate was achieved by following reaction sequence as shown in Scheme 1. The reaction of 1-methyl-



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Scheme 2. Mizoroki-Heck reaction of electron deficient olefins.

#### Table 1

Sr. no.	Base	Yield (%)
1	_	20
2	Na <sub>2</sub> CO <sub>3</sub>	40
3	NaOAc	45
4	K <sub>3</sub> PO <sub>4</sub>	60
5	Triethyl amine	92

Reaction conditions: bromobenzene (**6a**, 1 mmol), styrene (**7a**, 1.1 mmol), Pd(OAc)<sub>2</sub> (2 mol %), base (2 mmol), IL **5** (2 mL), temp: 100 °C.

imidazole (**1**) with 1-bromooctane (**2**) in toluene at 80 °C has afforded 1-octyl-3-methylimidazolium bromide (**3**). Subsequent reaction of **3** with potassium 1,1,2,2,3,3,4,4,-nonafluorobutane-1-sulfonate (**4**) in acetone at room temperature for 48 h afforded

Table 2	
Effect of different palladium catalysts on Mizoroki-Heck reactio	n

Sr. no.	Palladium source	Cat. mol %	Yield (%)
1	Pd/C	2	20
2	$Pd_2(dba)_3$	2	35
3	Pd(PPh) <sub>4</sub>	2	55
4	PdCl <sub>2</sub>	2	80
5	$Pd(OAc)_2$	2	92
6	$Pd(OAc)_2$	2.5	92
7	$Pd(OAc)_2$	1.5	83
8	$Pd(OAc)_2$	1	69

Reaction conditions: bromobenzene (**6a**, 1 mmol), styrene (**7a**, 1.1 mmol), catalyst (2 mol %), base (2 mmol), IL **5** (2 mL), temp:100  $^{\circ}$ C.



Figure 2. UV-vis spectra of reaction mixture.



Figure 3. TEM images of in situ formed Pd-NPs.

## Table 3 Effect of substrates on ligand-free Mizoroki-Heck reaction

Entry no.	Aryl halide (6)	Olefin (7)	Product ( <b>8</b> / <b>9</b> )	Time (h)	Yield <sup>*</sup> (%)
a	Br			3	92
b	O →→Br			5	85
c	NC		NC	4	85
d	H <sub>2</sub> N		H <sub>2</sub> N	5	75
e	0 <sub>2</sub> N1		O <sub>2</sub> N	5	80
f	NCBr		NC	4	85
g	°→−√¯→−Br			5	82
h	O <sub>2</sub> N		O <sub>2</sub> N O	5	77
i	° CI		off	12	60
j	CI		Co-	12	62
k	0-	0 0		4	86

Table 3	(continued)
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Entry no.	Aryl halide ( <b>6</b> )	Olefin ( <b>7</b> )	Product ( <b>8</b> / <b>9</b> )	Time (h)	Yield <sup>*</sup> (%)
1		° ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	° °	5	85
m	°→−CI	≪CN	O CN	12	58
n	CI-CI	≪~CN	CN	12	64
0	OBr	$\sim$	og Conton	5	78
р		°, •,		5	82
q	NCBr		NC	4	77
r		$\sim$	Conton	3	87
S	O- Br			3	79
t		<b>≫</b> 0 <i>√</i>		4	86ª
u		≫0,√		4	83 <sup>a</sup>

<sup>a</sup> Reaction conditions: aryl halide (1 mmol), styrene/acrylate/acrylonitrile (1.1 mmol), Pd(OAc)<sub>2</sub> (2 mol %), triethyl amine (2 mmol), IL **5** (2 mL), temp: 100 °C. <sup>a</sup> 100% regioselectivity (isolated yields).

 ${\bf 5}.^{16}$  The structure of  ${\bf 5}$  was confirmed by  $^1$  H,  $^{13}$  C,  $^{19}$  F NMR, and MS(E-SI) spectroscopy.  $^{17}$ 

In <sup>19</sup>FNMR (Fig. 1) (400 MHz, DMSO- $d_6$ ) four signals at  $\delta$  –81.04 (s, CF<sub>3</sub>), –115.13 (s, CF<sub>2</sub>), –121.69 (s, CF<sub>2</sub>), –126.14 (s, CF<sub>2</sub>) confirmed the formation of **5**.

In an initial study, we have carried out a screening of base first for a standard Mizoroki–Heck reaction of bromobenzene (**6a**), styrene (**7a**) (Scheme 2), employing the conditions mentioned in Table 1. In the course of this study, it was found that triethyl amine is the most effective base in terms of the yield (92%) of **8a**. Compared with an organic base, the yield of **8a** decreased with the use of an inorganic base viz.  $K_3PO_4$ , NaOAc, and Na<sub>2</sub>CO<sub>3</sub> in 60%, 45%, and 40%, respectively (Table 1). The acid formed in the reaction gets neutralized with triethyl amine forming a highly hydrophobic quaternary salt and this step is essential for breaking the activated complex, leading to product formation which generates again the catalytic species for fresh reactant.

We next investigated, the effect of palladium source on the Heck reaction (Table 2) and found that simple palladium inorganic salts viz.  $Pd(OAc)_2$  and  $PdCl_2$  proved to be the best choice (92% and 80% yields, respectively) while Pd/C,  $Pd_2(dba)_3$ ,  $Pd(PPh_3)_4$  were found to be inferior.

Among the several variations tested to optimize the condition, the condition involving  $Pd(OAc)_2$  (2 mol %) with triethylamine (2 mmol) was found to be the best and yielded product **8a** in 92%.

After the completion of reaction, we have extracted the reaction mixture by ethylacetate–petether [3:97] which have been analyzed

by recording UV–vis spectrum in ethanol medium and compared the same with that of  $Pd(OAc)_2$  and ionic liquid (Fig. 2). The absorption at 405 nm due to  $Pd(OAc)_2$  disappeared from the reaction mixture due to the formation of Pd–nanoparticles. These Pd–nanoparticles with variable size in the range of 20–100 nm are confirmed by TEM analysis (Fig. 3). Pd nanoparticles with high catalytic activity are efficiently stabilized by the IL used for the reaction.

With the optimized conditions in hand, we evaluated the scope of Pd-NPs/IL(5) system for coupling of a variety of olefins possessing electron withdrawing substituents with aryl halides.<sup>14</sup> It is clear from Table 3 that aryl bromides and iodides containing electron donating, electron withdrawing, or electron neutral substituents are coupled in excellent yields (Table 3, entries a–h, k, l, o–s). However, aryl chloride coupled with olefins in moderate yields (Table 3, entries i, j, m, n).

We then focused our attention on Heck arylation of ethyl vinyl ether with aryl halides and carried out reactions (Table 3, entries t, u) under optimized reaction conditions (Scheme 3).<sup>15</sup> After hydrolysis we observed the formation of corresponding arylmethylke-tones with 100%  $\alpha$ -regioselectivity.

Reusability of Pd-nanoparticles along with ionic liquid was investigated by carrying out reaction of **6a** with **7a** under optimized reaction conditions. The product formed was isolated by extraction with 3% ethyl acetate. The solvent was evaporated under vacuum and Pd-nanoparticles along with ionic liquid were reused for subsequent runs, at least for five times resulted 92%, 91%, 89%, 88%, and 85% yields, respectively (Fig. 4).



Scheme 3. Heck arylation of ethylvinylether with aryl halides.



Figure 4. Recycle study of the Pd-NPs/IL 5 for the Heck reaction.

In summary, we have developed an ecofriendly cost-effective method for Heck reaction catalyzed by in situ formed Pd-nanoparticles in hydrophobic IL under ligand-free conditions. The reaction of olefins with iodoarenes, bromoarenes, and chloroarenes generated the corresponding coupling product in good to excellent yields.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.027.

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- 14. *Typical procedure:* Aryl halide (1 mmol), olefin (1.1 mmol), Et<sub>3</sub>N (2 mmol), Pd(OAc)<sub>2</sub> (2 mol %), and IL 5 (2 mL) were added in a 25 mL round bottomed flask. The mixture was stirred vigorously at 100 °C for the time mentioned in Table 3. After cooling to room temperature, the desired product was isolated from IL by extracting with 3% ethyl acetate in petroleum ether (7 mL × 5). The product obtained after evaporation of the solvent was purified by column chromatography (silica mesh size 60–120).
- 15. Heck arylation of ethyl vinyl ether: 4-Methoxy/methyl iodobenzene (1 mmol), ethyl vinyl ether (5 mmol),  $Et_3N$  (2 mmol),  $Pd(OAc)_2$  (2 mol %) and IL 5 (2 mL) were added in a 25 mL round bottomed flask. The mixture was stirred vigorously at 100 °C for 4 h. After cooling to room temperature, aqueous HCI (5%, 5 mL) was added and the mixture was stirred for 0.5 h, the desired product was isolated by extracting with ethyl acetate and water. The product obtained after evaporation of the solvent was purified by column chromatography (silica mesh size 60–120).
- 16 Preparation of ionic liquid (1-octyl-3-methylimidazolium nonafluorobutane sulfonate): To a vigorously stirred solution of 1-methylimidazole (50 mmol) in toluene (25 mL), 1-bromo octane (55 mmol) was slowly added at  $0 \,^{\circ}$ C. The quaternisation reaction was carried out at 80 °C for 24 h, after which it was placed in a freezer at 0 °C for 4 h. Toluene was decanted and the remaining viscous oil was repeatedly washed with ethyl acetate to yield yellow oil, which was dried in vacuum to give [OMIM]Br in approximately 90% yield. [OMIM]Br was dissolved in acetone and followed by addition of potassium 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate and stirred it for 48 h at room temperature. The suspension was filtered to remove the precipitated bromide salt and the solvent was evaporated under reduced pressure. Again it was dissolved in dichloromethane washed repeatedly with small volumes of water (30 mL) until no precipitation of AgBr occurred in the aqueous phase on addition of a AgNO3 solution. The organic phase was then washed two times with water to ensure complete removal of the bromide salt. The solvent was removed in vacuum until no visible signs of solvents and water, resulting into
- corresponding ionic liquid in 92%.
  17. Spectral data for IL (5): <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz): δ 0.81 (s, 3H), 1.22 (s, 10H), 1.75 (s, 2H), 3.82 (s, 3H), 4.12 (t, 2H), 7.66–7.72 (d, 2H), 9.05 (s, 1H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 75 MHz): 13.22, 22.08, 25.75, 28.59, 28.67, 29.72, 31.34, 35.78, 49.28, 122.64, 123.97, 136.89 [due to presence of 9F atoms in anion the <sup>13</sup>C NMR became complicated and appears signals in 104.98–119.86]; <sup>19</sup>FNMR (400 MHz, DMSO-d<sub>6</sub>); δ −81.04 (s, CF<sub>3</sub>), −115.13 (s, CF<sub>2</sub>), −12.69 (s, CF<sub>2</sub>), −126.14 (s, CF<sub>2</sub>); MS (ESI): *m/z* 195.2 (+ve mode), 298.9 (−ve mode).