PALLADIUM CATALYZED SUZUKI CROSS-COUPLING REACTIONS IN AMBIENT-TEMPERATURE IONIC LIQUIDS

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ABSTRACT

Palladium catalyzed Suzuki cross-coupling reactions have been investigated in the ambient temperature ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) and have been found to exhibit unprecedented reactivities in addition to easy product isolation and catalyst recycling. Furthermore, the in situ formation of the mixed phosphine imidazolylidene palladium complex, [(PPh₃)₂Pd(bmim)y][BF₄] (where: bmimy = 1-butyl-3-methylimidazolylidene, X = Cl or Br), from [bmim][BF₄] has been detected under conditions similar to many ionic liquid mediated palladium catalyzed coupling reactions. Ionic liquid solutions of the independently prepared complex give rise to an extremely potent catalytic system.

INTRODUCTION

Ionic liquids are liquids that are composed of ions. Certain combinations of cations and anions result in ionic liquids, which are low melting (< 100 °C) and in some cases liquid at or below ambient temperature (1). A typical ambient temperature ionic liquid consists of a large sterically bulky organic cation associated with an inorganic or organic anion (Figure 1). By careful selection of different ions a wide range of ionic liquids can be afforded with different properties. This allows optimal design for a particular process (‘designer solvents’).

Imidazolium based ionic liquids have recently received a great deal of attention as environmentally more benign solvents due to their distinct physical and chemical properties, including their; negligible vapour pressure; wide liquid and thermal stability range; polar non-coordinating environment and ability to solubilize a broad range of inorganic, organic and polymeric material while being immiscible with many common organic solvents.

The Suzuki cross-coupling reaction is an extremely versatile methodology for the generation of new carbon–carbon bonds and is employed most successfully in the synthesis of biaryls (2). Biaryls and their homologues are fundamental building blocks in the synthesis of numerous pharmaceutically active compounds, herbicides as well as in advanced materials such as liquid crystals and organic electric wires. Other common palladium catalyzed coupling reactions that have been conducted in ionic liquids include
the Stille (3), Heck (4) and allylic alkylation (5) reactions. These all have similar mechanisms, differing in the nature of the nucleophile. The traditionally accepted Suzuki mechanism initially involves the oxidative addition of the arylhalide (electrophile) to the zero-valent co-ordinately unsaturated Pd°L₂ complex, A. Transmetallation then occurs between the nucleophilic carbon of the organoborane and the RPd°L₂X intermediate, B. Finally, reductive elimination affords the cross-coupled product with regeneration of the catalytically active species, Pd°L₂, C, as shown in Figure 2.

![Figure 2. The traditional Suzuki mechanism.](image_url)

**Figure 1.** Commonly used cations and anions for ionic liquids.

![Figure 1. Commonly used cations and anions for ionic liquids.](image_url)
The Suzuki reaction does, however, suffer from a number of drawbacks such as catalyst loss into the product, catalyst decomposition and poor reagent solubilities. We postulated that these problems might be circumvented by the use of ionic liquids.

**RESULTS AND DISCUSSION**

**Ionic Liquid Mediated Suzuki Reactions**

Initially the Suzuki reaction of 4-bromotoluene with phenylboronic acid was investigated in [bmim][BF$_4$]. Our preliminary results were disappointing. Only a 30% yield of 4-methylbiphenyl was afforded after 6 h with extensive catalyst decomposition. Further investigation revealed that modifying the original conditions significantly boosted yields of the desired products, enhanced reaction rates at reduced catalyst concentration and prevented catalyst decomposition (6). The new conditions involved heating the catalyst with the arylhalide and a halide ion source in the ionic liquid at 110 °C until complete solution occurred (Figure 3) (7).

![Figure 3. Ionic liquid mediated Suzuki cross-coupling reaction.](image)

While the addition of 1.2 mol% of halide (1 equivalent to the Pd(PPh$_3$)$_4$) significantly increased the yield of 4-methylbiphenyl, only concentrations of ≥ 4.8 mol % (4 equivalents) prevented catalyst decomposition (Graph 1). The average yield, however, remained constant. A similar pattern was observed with NaCl, [bmim]Cl, NaBr or [bmim]Br as the halide source and with other arylhalides. For this and practical reasons 12 mol% of halide was used. Without the initial formation of the catalytic solution only a 30 % yield was afforded with extensive catalyst decomposition, even in the presence of halide (12 mol %). Once the catalytic solution had been generated the reaction could also be conducted under air with a 65 % yield and no catalyst decomposition.
The scope of the reaction in [bmim][BF₄] was investigated with electron-rich and electron-deficient arylhalides (Table I). The reaction of bromobenzene with phenylboronic acid under the original Suzuki conditions affords biphenyl with an 88% yield in 6 h (5 TON h⁻¹), while in the [bmim][BF₄] a 93% yield was achieved in 10 min (465 TON h⁻¹, Table I, entry 2). Furthermore, 4-methoxybiphenyl was afforded in an 81% yield in 10 min (401 TON h⁻¹, Table I, entry 10.1), cf 40% in 6h with the original conditions. Additionally, the whole catalytic ionic liquid solution can be recycled several times without any significant loss in activity (Table I, entries 10.1–10.4). The effect of the arylboronic acid partner on the ionic liquid mediated Suzuki reaction was also studied and found to parallel the results obtained for the same functional groups on the arylhalide (Table II).

Graph 1. Yield and catalyst decomposition dependence on concentration of halide.
Table I. Variation of the arylhalide in the [bmim][BF_4] mediated Suzuki reaction

![Chemical structures](image)

| Entry | X   | R     | Yield (%)<sup>a</sup> | TON | TON h<sup>-1</sup> |
|-------|-----|-------|------------------------|-----|------------------|
| 1     | I   | H     | 86 (95)                | 72  | 430              |
| 2     | Br  | H     | 93 (95)                | 78  | 465              |
| 3     | Cl  | H     | 1 (1)                  | 1   | 5                |
| 4     | Br  | Cl    | 17                     | 14  | 85               |
| 5     | Br  | COCH<sub>3</sub> | 67 (97)         | 56  | 335              |
| 6     | Br  | CH<sub>3</sub> | 30<sup>b</sup>     | 10  | 2                |
| 7     | Br  | CH<sub>3</sub> | 69 (92)                | 58  | 345              |
| 8     | Br  | CH<sub>3</sub> | 72<sup>d</sup>     | 240 | 240              |
| 9     | Br  | CH<sub>3</sub> | 68<sup>c</sup>     | 57  | 340              |
| 10.1  | Br  | OCH<sub>3</sub> | 81 (92)         | 67  | 401              |
| 10.2  | Br  | OCH<sub>3</sub> | 89                     | 73  | 441              |
| 10.3  | Br  | OCH<sub>3</sub> | 77                     | 64  | 381              |
| 10.4  | Br  | OCH<sub>3</sub> | 82                     | 68  | 406              |

<sup>a</sup> Isolated yields of corresponding cross-coupled product based on arylhalide. Purity confirmed by GC, GC-MS and <sup>1</sup>H NMR. Isolated yields after 3 h in parenthesis. <sup>b</sup> Suzuki reaction without prior activation of catalyst. Original catalyst concentration employed, Pd(PPh<sub>3</sub>)<sub>4</sub> (3 mol%). Catalyst decomposition observed. Reaction time 6 h. <sup>c</sup> Reaction performed under air. <sup>d</sup> Lower catalyst concentration, Pd(PPh<sub>3</sub>)<sub>4</sub> (0.3 mol%). Reaction time 1 h.

Interestingly, the rate of reaction for functionalised electron-rich arylhalides is considerably faster than the electron-deficient arylhalides during the initial 10 min. This is illustrated by the TON h<sup>-1</sup> for the 10 min reactions of functionalised arylhalides; −OCH<sub>3</sub> > −CH<sub>3</sub> > −C(O)CH<sub>3</sub>. This is the reverse order of reactivity generally observed in Suzuki reactions, where the most electron-deficient arylhalides are the most reactive.
Table II. Variation of the arylboronic acid in the [bmim][BF₄] mediated Suzuki reaction

![Diagram of the Suzuki reaction]

| Entry | R²     | Product | Yield (%) | TON | TON h⁻¹ |
|-------|--------|---------|-----------|-----|---------|
| 1     | 4-CH₃  | ![4-CH₃ product](attachment)  | 68 | 57 | 340    |
| 2     | 2-CH₃  | ![2-CH₃ product](attachment)  | 68 | 57 | 340    |
| 3     | 4-OMe  | ![4-OMe product](attachment)  | 81 | 68 | 405    |
| 4     | 4-COCH₃| ![4-COCH₃ product](attachment) | 45 | 38 | 225    |

* Isolated yields of corresponding cross-coupled product based on arylhalide. Purity confirmed by GC-MS and ¹H NMR.

Alternative palladium/phosphine catalytic systems were also capable of catalysing the Suzuki reaction in [bmim][BF₄] (Table III). The catalytic solution was prepared as for Pd(PPh₃)₄, affording similar yields without catalyst decomposition. In the absence of PPh₃, decomposition occurred with only a negligible amount of cross-coupled product formation. Irrespective of the palladium source, isolation of the biaryl products from the [bmim][BF₄] reaction mixture could be achieved by extraction with diethyl ether, sublimation or precipitation by the addition of water, all without any apparent leaching of palladium species into the product. The catalytic solution can be recovered at the end of a reaction by washing with water until the mixture no longer becomes biphasic, indicating that all the Na⁺ salt by-products have been removed.
Table III. Alternative palladium sources in the [bmim][BF₄] mediated Suzuki reaction

![Chemical structure](image)

| Entry | Palladium source | PPh₃ / mol% | Yield (%) | TON | TON h⁻¹ |
|-------|------------------|-------------|-----------|-----|---------|
| 1     | PdCl₂            | 4.8         | 70        | 58  | 348     |
| 2     | 2nd Run          | -           | 67        | 56  | 336     |
| 3     | 3rd Run          | -           | 69        | 58  | 348     |
| 4     | PdCl₂            | None        | <1        | -   | -       |
| 5     | Pd(OAc)₂         | 4.8         | 69        | 58  | 348     |
| 6     | Pd(OAc)₂         | None        | <1        | -   | -       |
| 7     | Cl₂Pd(PPh₃)₂     | 2.4         | 70        | 58  | 348     |
| 8     | Pd₂(dba)₃        | 4.8         | 67        | 56  | 336     |

Identification of Palladium Containing Species in [bmim][BF₄]

The results presented above suggested that the catalytic species operating in [bmim][BF₄] were not those that conventionally originate from Pd(PPh₃)₄. Using Pd(PPh₃)₄ as the palladium source and NaCl as the halide source in [bmim][BF₄] in the presence of bromobenzene, under conditions similar to those used in the catalytic runs, ESI-MS revealed the presence of [(PPh₃)₂Pd(bmimy)X]⁺ (where: bmimy = 1-butyl-3-methylimidazolylidene, X = Cl (3a) or Br (3b)) and ³¹P NMR spectroscopy showed new signals at 22.9 and 21.8 ppm respectively (8). The assignments of these spectra were achieved by comparison to ionic liquid solutions of independently prepared samples. When the reagents were added sequentially, the addition of the aryl bromide to the Pd(PPh₃)₄/NaCl/[bmim][BF₄] mixture initially formed the oxidative addition product, 1, which on vigorous stirring for 1 h afforded a clear orange solution (catalytic solution, Figure 4). At this point the ³¹P signal corresponding to the oxidative addition product was no longer observed. Other unidentified ³¹P signals at 27.8 and 26.3 ppm were detected in addition to signals at 23.2 and -5.5ppm, corresponding to [PPh₄] and free PPh₃ respectively. Subsequent addition of the aqueous solution of Na₂CO₃ afforded a mixture of 3a and 3b as a colourless solution. When independently prepared samples of 1 were used as the palladium source, 3 was also detected. In the absence of an aryl bromide under otherwise similar conditions, 3a was detected only in trace amounts. A mixture of 3a and 3b was also detected with the aryl bromide and NaCl using 2 as the source of palladium, either added directly or prepared in situ from Pd(OAc)₂, or PdCl₂, both with additional PPh₃. Employing these sources of palladium in the absence of the aryl bromide afforded only 3a. Hence, the formation of 3b in the ionic liquid is the result of the
presence of bromide ions originating from the oxidative addition product. Similarly, only 3b was afforded with NaBr without the aryl bromide. Under our conditions no PdX₂(bmimy)₂ (where X = Cl or Br) was observed. Attempts to produce these complexes by removing PPh₃ from the reaction mixture met with no success. In one case, however, when Pd(OAc)₂ was used in the absence of PPh₃ with NaBr instead of NaCl, PdBr₂(bmimy)₂ was observed.

In contrast to other palladium sources the independently prepared complexes 3a and 3b are readily soluble in the [bmim][BF₄] and are catalytically comparable without any initiation period (68% 4-methylbiphenyl; 10 min; 110 °C, cf. Table III). Once generated in situ or added as independently prepared samples, complexes 3a and 3b cannot be isolated from the ionic liquid (by any extraction techniques tested thus far).

Figure 4. Identification of Palladium species in [bmim][BF₄].

| X | ESI-MS | ³¹P |
|---|--------|-----|
| Cl (3a) | 803 | 22.9 ppm |
| Br (3b) | 849 | 21.8 ppm |

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CONCLUSIONS

It has been demonstrated that the Suzuki cross-coupling reaction can be successfully conducted in the ambient temperature ionic liquid, [bmim][BF₄], with a number of advantages. Notably, inexpensive air stable catalyst precursors that exhibit enhanced reactivity with long-term catalyst stability can be employed. The cross-coupled products can also be readily isolated from the catalytic solution, which can then be recycled without loss of catalytic activity.

Furthermore, the in situ formation of mixed phosphine imidazolylidene palladium complexes, 3, have been detected in [bmim][BF₄] under conditions similar to many ionic liquid mediated palladium catalyzed coupling reactions. It has been demonstrated that the ionic liquid solutions of these independently prepared complexes are extremely effective in the Suzuki reaction.

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7. Typical Suzuki reaction: The arylhalide (0.75 mmol) was added to a suspension of Pd(PPh₃)₄ (10.4 mg, 1.2 mol%) and NaCl (5.22 mg, 12 mol%) in degassed [bmim][BF₄] (1.5 cm³) under N₂. The mixture was slowly heated to 110 °C with vigorous stirring affording a yellow–orange solution. The solution was cooled and the aryloboric acid (0.825 mmol) and a solution of Na₂CO₃ (159 mg, 1.5 mmol) in water (0.75 ml) was added. The mixture was reheated at 110 °C with vigorous stirring for a further 10 min, then cooled and extracted with diethyl ether (3 × 15 cm³). The combined extracts were washed first with brine (2 × 10 cm³) then water (2 × 10 cm³) and dried (MgSO₄).
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