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# Suzuki cross-coupling reactions of aryl halides in phosphonium salt ionic liquid under mild conditions

**James McNulty,*[a] Alfredo Capretta,[a] Jeff Wilson,[a] Jeff Dyck,[a] George Adjabeng[a] and Al Robertson[b]**

[a] *Institute of Molecular Catalysis, Department of Chemistry, Brock University, St. Catharines, Ontario L2S 3A1, Canada. E-mail: jmcnulty@chemiris.labs.brocku.ca; Fax: +1 905 682 9020; Tel: +1 905 688 5550 ext. 3405*

[b] *Cytec Canada Inc, PO Box 240, Niagara Falls, Ontario L2E 6T4, Canada. E-mail: Al_Robertson@WE.cytec.com; Fax: +1 905 374 5879; Tel: +1 905 356 9000*

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**The Suzuki cross-coupling of aryl boronic acids with aryl halides, including aryl chlorides, proceeds in the phosphonium salt ionic liquid tetradecyltrihexylphosphonium chloride under mild conditions.**

The Suzuki[1] cross-coupling reaction has become a standard method for carbon–carbon bond formation between an sp$^2$ or non-β-hydride containing electrophile and a boronic acid derivative. Recent application of the reaction to aliphatic electrophiles[2] has expanded its scope considerably. Much recent effort has gone into devising new ligands for this palladium mediated process and various electron rich alkyl phosphines[3] and mixed aryl/alkyl phosphine ligands[4] have been described. Systems allowing for couplings of aryl chlorides are especially sought after due, in part, to the lower cost and ready availability of these substrates and a number of catalysts have recently been developed which promote their Suzuki coupling with boronic acid nucleophiles.[5,6]

Catalyst expense coupled with the non-recyclability of the expended catalyst have been shown to be major drawbacks of these palladium-mediated processes. One solution involves the application of ionic liquids as solvent. Ionic liquids based on alkylimidazolium and other quaternary ammonium/pyridinium salts have emerged as valuable, alternative “green” solvents for catalytic processes over the last few years.[7–10] Using ionic liquids, it is often possible to recycle the active palladium catalyst subsequent to extraction of the organic product and inorganic salts from the ionic liquid, which form a tri-phasic system with water and a non-polar organic solvent. This process has been applied efficiently to the palladium mediated Heck coupling reaction in quaternary nitrogen ionic liquids[11] and can be conducted at room temperature with the application of ultrasound.[12] The Suzuki reaction has also been carried out successfully in imidazolium ionic liquids both thermally[13] and with sonication.[14] Quaternary phosphonium salts are another class of readily available ionic liquid which have received scant attention in the literature. In one case, hexadecyltributylphosphonium bromide was used to effect Heck coupling of aryl halides with acrylic esters,[15] although the reaction was not efficient with aryl chlorides. We report herein on the use of the room temperature ionic liquid tetradecyltrihexylphosphonium chloride (THPC) containing small amounts of water and toluene (single phase) as an efficient reusable media for the palladium catalyzed Suzuki cross-coupling reaction.

The cross-coupling reactions were found to proceed in THPC using various bases ($Et_3N$, $^iPr_2NEt$, *etc*) but most efficiently when potassium phosphate and water (added for salt solubility) were employed. In order to maintain complete solubility of both the boronic acid and aryl halide in the ionic liquid, a small amount of toluene was added also. All of the reactions reported in Table 1 were therefore performed in an identical media (THPC, aryl halide, aryl boronic acid, $Pd_2(dba)_3$ (1%), $K_3PO_4$, $H_2O$, toluene) with the addition of triphenylphosphine in certain cases as noted.† In many instances, the product biaryl crystallizes from the reaction media as the cross-coupling proceeds.

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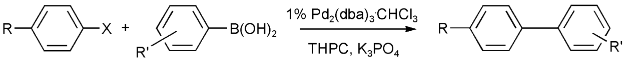
As can be seen from Table 1 (entries 1–9), the cross-coupling reaction of variously substituted iodobenzenes including electron rich derivatives (Table 1, entry 7) with a variety of arylboronic acids proceeded efficiently in THPC and were all complete within 1 h at 50 °C. The reaction was chemoselective in the case of the mixed halide 4-chloroiodobenzene (Table 1, entry 9). The corresponding aryl bromides (Table 1, entries 11–13) also reacted under these conditions but proved to be somewhat more sluggish. We found that the addition of a catalytic amount of triphenylphosphine allowed for complete conversion and high isolated yields even for the electron rich substrates such as 4-methoxybromobenzene (Table 1, entries 12 and 13). As expected, reactions involving aryl chlorides were considerably slower, however addition of triphenylphosphine and heating at 70 °C allowed high conversion of 4-chloroacetophenone (Table 1, entries 14 and 15). The electron rich 4-methoxychlorobenzene was still slow to react under these conditions (Table 1, entry 16).

Addition of water and hexane to the reaction products in the phosphonium salt ionic liquid results in the formation of a triphasic system that differs from that reported for the imidazolium salts.[11] In the case of imidazolium salts, the ionic liquid is more dense than water and forms the bottom phase with an aqueous central phase and organic layer on top. In the case of THPC, the palladium catalyst remains fully dissolved in the central phosphonium salt layer while the product biaryls are extracted into the top hexane phase and inorganic salts (phosphates/borates) into the lower aqueous phase.

The reaction of phenylboronic acid with iodobenzene has been investigated extensively under our conditions in THPC. The yield obtained from hexane extraction and silica-gel

**Table 1** Pd mediated Suzuki cross-coupling of aryl halides and boronic acids in THPC



| Entry | X | R | R′ | Ligand | Temp./ °C | Time/h | Isolated yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | I | H | H | None | 50 | 1 | 95 |
| 2 | I | Ac | H | None | 50 | 1 | 100 |
| 3 | I | Ac | 2-Me | None | 50 | 1 | 97 |
| 4 | I | Ac | 2-Napthyl | None | 50 | 1 | 97 |
| 5 | I | Ac | 2-OMe | None | 50 | 1 | 100 |
| 6 | I | Ac | 4-OMe | None | 50 | 1 | 99 |
| 7 | I | OMe | 4-OMe | None | 50 | 1 | 86 |
| 8 | I | Me | 4-OMe | None | 50 | 1 | 92 |
| 9 | I | Cl | 4-OMe | None | 50 | 1 | 90 |
| 10 | Br | Ac | H | $PPh_3$ | 50 | 1 | 99 |
| 11 | Br | Ac | 4-OMe | $PPh_3$ | 50 | 1 | 98 |
| 12 | Br | OMe | H | $PPh_3$ | 50 | 3 | 99 |
| 13 | Br | OMe | 4-OMe | $PPh_3$ | 50 | 3 | 95 |
| 14 | Cl | Ac | H | $PPh_3$ | 70 | 30 | 84 |
| 15 | Cl | Ac | 4-OMe | $PPh_3$ | 70 | 30 | 76 |
| 16 | Cl | OMe | 4-OMe | $PPh_3$ | 70 | 30 | 17 |

chromatography of the hexane solubles ranged from 82–97% over several runs. On the other hand, direct filtration of the ionic liquid through a short silica-gel column gave slightly higher isolated yields, 95–97%. These results indicate that residual biaryls are still slightly soluble in THPC. The former procedure was more applicable towards the development of a catalyst recycling protocol since chromatography or filtration through silica would make re-use of the catalyst difficult. Thus, following Method A,† when further quantities of iodobenzene, phenylboronic acid and $K_3PO_4$, *but no further catalyst*, was added to the isolated central ionic liquid, heating again at 50 °C resulted in complete turnover of iodobenzene. Repetition of the work-up Method A gave biphenyl in 82–97% yield (repeated five times) for both the initial and recycled reaction sequences. Thus it is clear that a competent palladium catalyst remains fully dissolved in the phosphonium salt allowing its efficient re-use.

The Suzuki cross-coupling reaction recently reported in imidazolium based ionic liquids requires ultrasonic irradiation to proceed at 30 °C.[14] In addition, inactive Pd black is deposited during the reaction resulting in lower conversions (82–92%) with aryl iodides and bromides and particularly so in the case of electron deficient aryl chlorides (42–65%). Even when preformed Pd–biscarbene catalyst is used in this system, conversion of electron deficient aryl chlorides is low to moderate (39–66%).[14] The thermal Suzuki coupling reaction in these imidazolium based ionic liquids does not proceed with aryl chlorides, even at 110 °C.[13] In contrast to these results, complete conversion of aryl iodides and bromides and high conversions with electron deficient chlorides can be achieved in the THPC ionic liquid without the use of a preformed catalyst at 50–70 °C. The rapid coupling of aryl iodides and bromides and high conversions obtained with the aryl chlorides indicate that a very active catalyst is produced in the THPC system. In addition, the higher conversions and recyclability of this Pd THPC–catalyst system indicate the relatively high stability of the active Pd catalyst involved in the Suzuki coupling. Lastly, no homo-coupled products have been observed using the THPC catalyst system reported here.

The phosphonium salt ionic liquid THPC is available in litre quantities and holds a great deal of potential as an economical, recyclable media for metal promoted reactions and process chemistry in general and as we have shown here the Suzuki cross-coupling reaction in particular. Further analysis of the active Pd-catalytic species formed by dissolution of $Pd_2(dba)_3$ in the phosphonium salt ionic liquid and applications of the process to other coupling partners are currently under investigation in our laboratories.

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## Notes and references

† Samples of THPC (trade name Cyphos 3653) can be obtained by contacting Cytec at the address given. A representative procedure for the Suzuki cross-coupling is as follows. THPC (1.0 mL) was degassed in a dry round bottom flask by pumping under reduced pressure (0.5 mm Hg) for 10 min and then filled with argon. Iodobenzene (0.5 mmol, 1.0 equiv.) and $Pd_2(dba)_3 \cdot CHCl_3$ (0.005 mmol, 0.01 equiv.) were added and the mixture heated briefly using a heat gun to effect an orange solution. After cooling to room temperature $K_3PO_4$ (1.65 mmol, 3.3 equiv.), phenylboronic acid (0.55 mmol, 1.1 equiv.) distilled water (0.2 mL) and toluene (0.1 mL) were added. When triphenylphosphine (0.01 mmol, 0.02 equiv.) was used (see Table 1) it was added as a solution in the added toluene. The solution so obtained was heated under argon at the temperature and for the duration indicated in Table 1. The product biaryls can be isolated by using either of two methods. Method A : Addition of water (5.0 mL) and hexane (15 mL) followed by vigorous shaking and settling for 0.5–1 h. The top hexanes layer was removed and concentrated followed by purification of the biaryl on silica gel. The bottom aqueous phase was removed and discarded leaving the central ionic liquid-catalyst. Use of this method allowed for most efficient catalyst recyclability. The ionic liquid was recharged with phenylboronic acid, iodobenzene and $K_3PO_4$ and reheated as indicated in Table 1. Isolated yields ranged from 82–97% for both reactions with no difference being noted in the subsequent reaction. In contrast to the above procedure, exhaustive or continuous extraction (24 h) of the ionic liquid with hexanes results in removal of the catalyst and ionic liquid indicating that both active catalyst and THPC are slightly soluble in hexane.

Method B: In order to determine the isolated yield of the biaryls reported in Table 1 after one run only, the ionic liquid crude reaction mixture was filtered through a silica gel plug, washed with hexanes/ethylacetate followed by silica gel chromatography of the filtrate. Yields reported in Table 1 are based on isolated mass of the pure biaryls so obtained.

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