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Palladium catalyzed C–P cross-coupling reactions in ionic liquids

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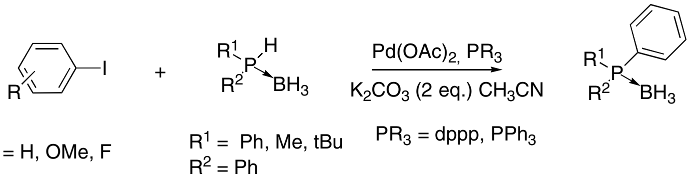
Abstract—C–P cross-coupling reactions between phosphine–borane complexes and aryl iodides are successfully performed in imidazolium based ionic liquids (ILs). To improve the recycling of the catalyst, a monophosphine covalently attached to a pyridinium salt was prepared. Associated to palladium, this catalyst shows a high catalytic activity and stays immobilized in the IL. It was reused at least in six cycles.

Since more than 30 years, the prominence of phosphine ligands in the field of organometallic catalysis is a reality.[1] Thus, intensive efforts have been done to produce phosphines with different steric and electronic properties. Main approaches involve stoichiometric reactions between haloarylphosphines and organometallic species, or phosphide anion and alkyl halides.[2] Given the recent rapid development of a more environment friendly chemistry, it is surprising that only few contributions dealing with a greener approach to phosphines have been reported. A 100% atom efficient method for the preparation of P-alkyl or P-vinyl substituted phosphines is the hydrophosphination reaction[3] of alkenes and alkynes. However, this reaction does not allow the preparation of the widely used arylphosphines. In order to develop a greener access to arylphosphines the metal catalyzed C–P cross-coupling reaction could be a valuable solution. However, this methodology has only been poorly studied[4,5] and its technical use still suffers from some difficulties. The reaction after completion requires an aqueous work up, which damages the catalyst and precludes its recycling. Furthermore, the extraction of the highly oxidable phosphines is tedious. Few years ago, we reported some information on the palladium catalyzed C–P cross-coupling reaction between aryl iodides and secondary phosphine–borane complexes.[6] The reaction was performed under mild conditions due to the activation induced by the borane group[7] (Scheme 1). However, the catalyst could not be recycled.

The high solvating ability and the immiscibility of various ILs[8] with many organic solvents should allow the development of a heterogeneous system in which the reaction is carried out in the IL and the product recovered by simple liquid–liquid extraction.[9] Herein, we report preliminary results dealing with the use of ionic liquids as a medium for the C–P cross-coupling reaction.

In our preliminary investigation, we selected *meta*-iodoanisole **1a** and diphenylphosphine–borane **2** to examine



Scheme 1. C–P cross-coupling reaction in acetonitrile.

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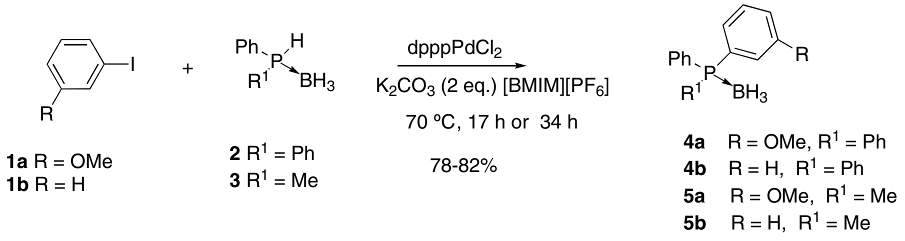


Scheme 2. C–P cross-coupling reaction in [BMIM][PF_6].

the feasibility of the reaction in an ionic liquid. Various imidazolium based ionic liquids ([BMIM][BF_4], [BMIM][Cl] and [BMIM][PF_6]) were tested to evaluate the influence of the hydrophilicity/hydrophobicity of the IL on the catalytic performance and on the separation of the ionic liquid and the product. First sets of C–P cross-coupling experiments were performed under the conditions optimized for the coupling in volatile organic solvent (acetonitrile). Typically, a stoichiometric amount of **2** and **1a** was dissolved in [BMIM][PF_6] (10 equiv), potassium carbonate (2 equiv) and 10 mol % of $dpppPdCl_2$ were added and the heterogeneous mixture was stirred at rt for 24 h leading to the expected product **4a** as determined by ^{31}P [^{1}H] NMR spectroscopy ($\delta = 22.1$ ppm). However, these conditions do not afford good conversion even after extended reaction time (48 h), and the use of a higher loading of catalyst (15 mol %) does not provide significantly enhanced rate or yield. This dramatic decrease of the reaction rate can be ascribed either to the high viscosity of the IL or to a lower level of catalytic activity in the IL. To improve the reaction, the temperature was raised to 70 °C. A complete conversion was obtained after 17 h (monitored by ^{31}P NMR) (Scheme 2).

After cooling to rt, the product was extracted from the reaction mixture with toluene. It turns out that for successful extraction of **4a**, the temperature of the mixture should be lowered to 0 °C to limit the partial solubility of toluene in [BMIM][PF_6]. Thus after five extractions with 0.5 mL of toluene, the crude yield in **4a** amounted to 90%. Purification of **4a** was then easily performed by filtration through a pad of silica in air (82% yield). Under similar conditions, the reaction was also successful on using iodobenzene **1b** and phosphine **2**. With the less reactive methylphenylphosphine–borane **3**, the reaction required 36 h for a complete conversion to **5a** and **5b**.

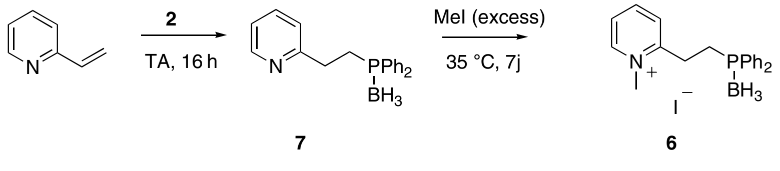
Under similar conditions, two other salts ([BMIM][BF_4] and [BMIM][Cl]) were tested. The reaction proved to be less clean due to a partial decomplexation–oxidation of **4a** leading to $ArPh_2P{=}O$. These results can be ascribed to residual traces of water in [BMIM][Cl] and [BMIM][BF_4], salts which are more hygroscopic than [BMIM][PF_6] (Table 1).

Table 1. Comparative use of various imidazolium based ILs in the synthesis of **4a**

	Conversion[a] (%)	$ArPh_2PBH_3$ (**4a**) (%)	$ArPh_2P$ (%)	$ArPh_2P{=}O$ (%)
[BMIM]-[PF_6]	100	94	1	5
[BMIM]-[Cl]	100	50	10	40
[BMIM]-[BF_4]	100	70	17	23

[a] Determined by ^{31}P NMR.

We then turned our attention to the recovering and the recycling of the palladium catalyst. Thus after extraction of **4a** and outgassing under reduced pressure to eliminate volatiles, the ionic liquid was reused successfully in a second and a third run by adding to the IL a stoichiometric amount of **2**, aryliodide **1a** and potassium carbonate for each cycle. Nevertheless, low conversions were progressively obtained in the next runs due to a partial extraction of the catalyst in the organic phase. To avoid this leaching problem, we decided to increase the affinity of the catalyst for the ionic liquid by alteration of the ligand structure. Precedents of this strategy have already given satisfactory results.[10] Thus to adequately immobilize the catalyst in the IL phase, we prepared a ligand having an inexpensive pyridinium tag. The route to ligand **6** was straightforward as depicted in Scheme 3. Starting from commercially available vinylpyridine, hydrophosphination using **2** under conditions previously defined by some of us[11] (solvent free conditions) afforded phosphine **7** after 16 h at rt. Then alkylation of the pyridine with methyl iodide gave ligand **6** with 57% overall yield. The characteristic phosphine–borane signal for **6** was observed in ^{31}P NMR at $\delta = 16.7$ ppm with a $^{1}J_{PB} = 55.8$ Hz. Compound **6** was



Scheme 3. Diphenylphosphine ligand with pyridinium tag.

Table 2. Comparative recycling of the pyridinium-tagged catalyst derived from **6** and dpppPdCl$_2$

Catalyst	Cycle	1	2	3	4	5	6	7
dpppPdCl$_2$	Conversion[a]	>98	95	97	33	—	—	—
6/Pd(OAc)$_2$	(%)	>98	98	94	95	90	88	42

[a] Determined by ^{31}P NMR spectroscopy with **2** and **1b** as substrates.

fully characterized by ^{1}H, ^{13}C, ^{31}P, ^{11}B NMR and HRMS.[12]

[BMIM][PF$_6$] containing 15% of **6** and 5% of Pd(OAc)$_2$ was stirred at 70 °C for 30 min and then used as a reaction medium for the C–P cross-coupling reaction between **1b** and **2** under the previously defined conditions. We were pleased to see that this cheap and easily prepared new catalyst displayed a high activity comparable to that of the expensive dpppPdCl$_2$ catalyst. The reaction was completed in 17 h at 70 °C. It is noteworthy that deprotection of the phosphine–borane **6** before its use was not required[13] and occurred directly when **6** was mixed with Pd(OAc)$_2$. With this new catalyst, it was possible to recycle both the IL and the catalyst at least six cycles without significant loss in activity (Table 2).

In conclusion, we have shown that the C–P cross-coupling reaction between a phosphine–borane and an aryl iodide can be performed with success in imidazolium based ionic liquids. The best results were obtained in [BMIM][PF$_6$] with an excellent preservation of the phosphine–borane complexes. One of the main advantages of using ILs instead of classical organic solvents is related to the easy separation of the product and the catalyst without any aqueous work-up, which is often detrimental for phosphines. Moreover, in this new medium, the palladium catalyst (dpppPdCl$_2$) can be recycled three times. To improve the recycling, a monophosphine covalently attached to a pyridinium salt was prepared. Associated to palladium, this ligand showed a high catalytic activity for the C–P cross-coupling. The catalyst stayed immobilized in the IL and was reused at least six times without significant loss in activity. Extension of the reaction to more challenging substrate is currently under investigation.

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12. An oven-dried schlenk tube was charged with phosphine–borane **2** (60 mg, 0.3 mmol). After three oil pump vacuum/nitrogen cycles, 2-vinylpyridine (38 μL, 0.36 mmol) was added under nitrogen flow. The mixture was stirred for 16 h at room temperature and directly purified on silica gel chromatography (Et$_2$O–pentane, 1:1). The product was dried under oil pump vacuum, affording 2-(2-(diphenylphosphino)-ethyl)pyridine **7** as a white solid in 76% yield. Then the compound **7** (70 mg, 0.229 mmol) was reacted with 9 equiv of methyliodide and the mixture was stirred for 7 days at 35 °C. The crude precipitate was washed with ether, dried under oil pump vacuum affording the salt **6** in 75% yield. ^{1}H NMR (CD$_3$CN): δ 0.38–1.76 (3H, q, $J = 187$ Hz), 3.08–3.19 (2H, m), 3.42–3.52 (2H, m), 4.52 (3H, s), 7.49–7.52 (6H, m), 7.88–7.96 (4H, m), 8.08 (1H, m), 8.33 (1H, d, $J = 7.2$ Hz), 8.61 (1H, m), 9.14 (1H, d, $J = 6.3$ Hz). ^{13}C NMR (CD$_3$CN): δ 23.5, 27.6, 46.8, 129.9, 130.2, 130.9, 132.4, 133.0, 135.6, 146.4, 149.8, 160.9. ^{31}P NMR (CD$_3$CN): 16.7. ^{11}B NMR (CD$_3$CN): −37.2. HRMS calcd for $C_{20}H_{24}BNP$: 320.1739, found 320.1741.
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