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Ionic liquids: Valuable solvents for palladium catalysed C-P cross-coupling reactions

H Vallette[a], S Pican[b], C Boudou[b], J Levillain[b], J C Plaquevent[a] & A C Gaumont[b] *

[a]UMR-CNRS 6014 de l'IRCOF, Université de Rouen, rue Tesnière, F-76821 Mont-Saint Aignan-Cedex, France
[b]UMR-CNRS 6507 LCMT, ENSICAEN-ISMRA, Université de Caen, 6 bd du Maréchal Juin, F-14050 Caen, France
E-mail: gaumont@ensicaen.fr

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Room temperature ionic liquids have been used successfully for the preparation of phosphine derivatives via a palladium catalysed C-P cross-coupling. The use of a pyridinium-modified phosphine ligand combined to palladium acetate afforded a catalyst having a high level of activity and recyclability.

Keywords: C-P cross coupling reactions, ionic liquids, phosphine, palladium catalyst recycling, green chemistry

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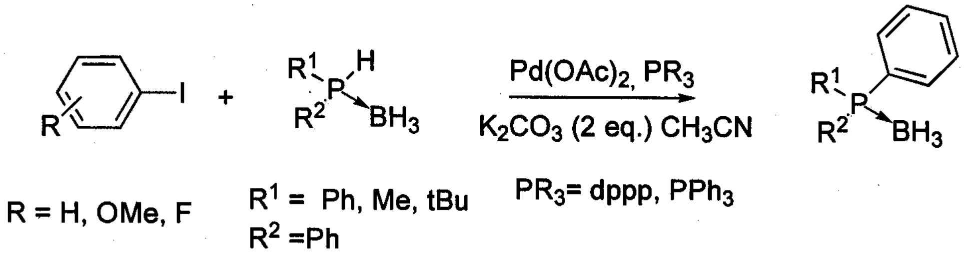
As one of the basic principles in green chemistry[1] is related to the development of catalytic reactions, there is a continuous interest in the development of new catalysts that combine high rates, selectivity and long lifetimes. The efficiency of the catalyst is dependent on both the nature of the metal and the structure of the ligand. Among the latter, phosphines have proven to be the best for a large variety of reactions[2]. Thus, numerous efforts have been done to prepare phosphines having various steric and electronic properties. The main syntheses are the stoichiometric reactions between haloarylphosphines and alkyl-magnesium or lithium derivatives, and the nucleophilic substitution reactions of alkyl halides[3]. These reactions are often troubled by a large number of by-products and require extreme care to avoid oxidation of the desired phosphine. Given the prominence of phosphines in catalysis, it is surprising that so few contributions dealing with a greener approach to phosphines have been reported. An atom efficient and simple method for the preparation of P-alkyl substituted phosphines is the hydrophosphination of inexpensive alkenes[4]. Recently we developed an environmentally benign process, which allows adding a secondary phosphine-borane to an alkene in the absence of solvent under microwave irradiations[5]. The reaction does not require a catalyst, and the activation is induced by the borane group and is completed in 30 to 50 min. Moreover, the troublesome oxidation of the phosphines is avoided by the complexation with the borane, which allows the reaction to occur in air without special protection or equipment[6]. However, the widely used arylphosphines cannot be prepared by this approach. To develop a general access to this class of phosphines, we focused on the catalytic C-P cross coupling reaction. This methodology was, first reported by Stille at the end of the 80’s using stannyl- or a silyl-phosphines[7]. Then a few reports on the C-P cross coupling reactions using free phosphines appeared in the literature[8]. Regardless of the applicability of the C-P cross coupling reaction, its technical use still suffers from some difficulties. The reaction is homogeneously catalysed which means that after completion of the reaction, the catalyst is damaged by the aqueous work-up and cannot be recycled. Furthermore, the extraction of the product is tedious due to the high oxidability of phosphines. Hence, there is a demand for processes, which allow the recovering and the recycling of the catalyst and limit the possible stress for the product. To the best of our knowledge, no such process is available for the C-P cross coupling reaction.

In the last few years, ionic liquids have been used as valuable solvents for catalytic reactions mainly because of the peculiar properties (high solubility, low vapour pressure, high chemical and thermal stability)[9]. Their good ability to solvate polar and apolar species and their immiscibility with many organic solvents should allow to develop an heterogeneous system in which the reaction is carried out in the ionic liquid and the products recovered by liquid liquid extraction using an immiscible solvent[10]. This report describes recent advances in the use of ionic liquids as media for the C-P cross-coupling reactions.

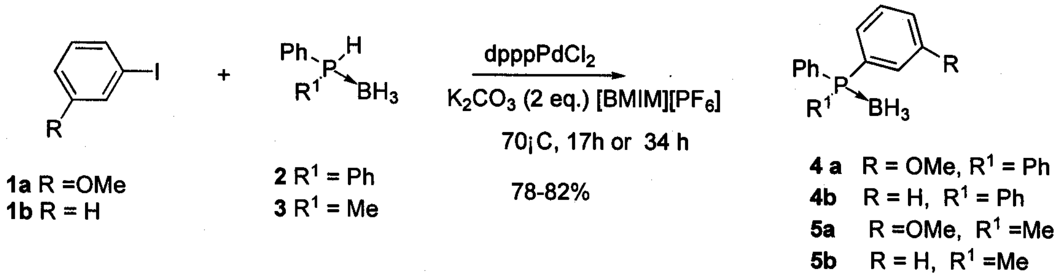
A few years ago, some information on the palladium catalysed C-P cross-coupling reaction between aryl iodides and secondary phosphine-borane complexes were reported[11]. The reaction was performed under mild conditions (temperature between 20 to 50°C) in a polar solvent (acetonitrile) using a weak base (K_2CO_3) and a palladium bisphosphine complex (dpppPdCl_2) or tetrakistriphenylphosphine. The mild conditions used in this coupling reaction can be ascribed to the strong activation induced by the borane (**Scheme I**).

To examine the feasibility of the C-P cross-coupling reaction in an ionic liquid, diphenylphosphine-borane **2** was reacted with phenyl iodide **1b**. 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 ionic liquid. A first set of C-P cross-coupling experiments was performed under the conditions developed in acetonitrile. A stoichiometric amount of diphenylphosphine-borane **2** and iodobenzene **1b** was dissolved in 10 equivalents of [BMIM][PF_6]. Potassium carbonate (2 equiv) dpppPdCl_2 (10 mol%) were added and the heterogeneous mixture was stirred. After 24 hr at rt the expected product was obtained as determined by ^{31}P [^1H] NMR spectroscopy (22.1 ppm). However, under these conditions a low conversion was obtained even after extended reaction time (48hr) and higher catalyst loading (15 mol%). Raising the temperature to 70°C allowed to obtain a complete conversion in 17 hr presumably because of a better solubility of the precursors in the ionic liquid at higher temperature. After completion, the reaction mixture was cooled down to rt and the product was removed from the reaction mixture by extraction with toluene. After 5 extractions with 0.5 mL of toluene, the crude yield in product amounted 87%. With gram scale reaction, the recovery of the product was simply performed by decantation. The tertiary phosphine-borane was purified by filtration through a pad of silica in air. The reaction was also successful with *m*-iodoanisole and with the less reactive methylphenylphosphine-borane **3**, however, in the latter case a complete conversion was obtained only after 36 hr (**Scheme II**).

Performing the reaction in other imidazolium salts ([BMIM][BF_4] and [BMIM][Cl] gave less clean reactions than in ([BMIM][PF_6] due to a partial decomplexation-oxidation of the diphenylphosphine - borane (**Table I**). Furthermore, the extraction was less efficient. These problems can be ascribed to the more hydrophilic character of these ionic liquids compared to [BMIM][PF_6].



Scheme I



Scheme II

Table I — Comparative use of various imidazolium based ILs in the synthesis of **4a**

Conversion [a]	$ArPh_2PBH_3$ (**4a**)	$ArPh_2P$
[BMIM] [PF_6]	94	1
[BMIM] [Cl]	50	10
[BMIM][BF_4]	70	17

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

A chiral thiazolinium ionic liquid (**Figure 1**) was also tested as a reaction medium for the C-P cross-coupling reaction. This original ionic liquid was prepared in our group a few years ago from a dithioester and an enantiopure alaninol[12]. With this salt, our questioning was twice: i) can this new salt be an adequate media for the C-P cross-coupling reaction and ii) can the well-organised chiral ionic liquid transfer chirality to the product?

The reaction between meta-iodoanisole **1a** and methylphenylphosphine-borane **3** was performed in [DTHIA] [PF_6] IL, under the conditions previously defined for [BMIM] [PF_6]. After 24 hr at 70°C, a conversion of 64% was measured by ^{31}P NMR spectroscopy indicating a lower rate of reaction in this salt compared to [BMIM] [PF_6]. Enantiomeric excess in *m*-anisylmethylphenylphosphine-borane was measured by HPLC. However, **5a** was obtained in racemic form indicating that no chiralilty transfer from the IL to the product has occurred.

We then turned our attention to the recycling of the palladium catalyst. The non destructive recovering of the product should allow a recycling of the catalyst if it is not extracted with the product. Thus, after extraction of the desired product and outgassing under reduced pressure to eliminate volatiles, the ionic liquid was reused in a second run by simply adding to the ionic liquid a stoechiometric amount of phosphine, aryliodide and potassium carbonate. A conversion higher than 98% was obtained. A third cycle was then performed with success under the same conditions. Nevertheless, low conversions were progressively obtained presumably because of a partial extraction of the catalyst in the organic phase. To avoid this leaching problem, we modified the structure of the ligand to increase the affinity of the catalyst for the ionic liquid, precedents of this strategy having already given satisfactory results[13]. The route to the new ligand having a pyridinium tag was straightforward (**Scheme III**). Starting from commercially available vinylpyridine, hydrophosphination using diphenylphosphineborane under microwave irradiation and solvent free conditions followed by alkylation of the pyridine with methyl iodide afforded the new ligand with an overall yield of 57%. This compound was characterized by ^{1}H, ^{13}C, ^{31}P, ^{11}B NMR and HRMS.

[DTHIA][PF_6]

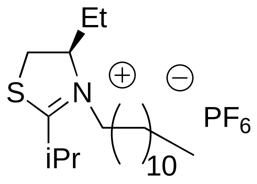
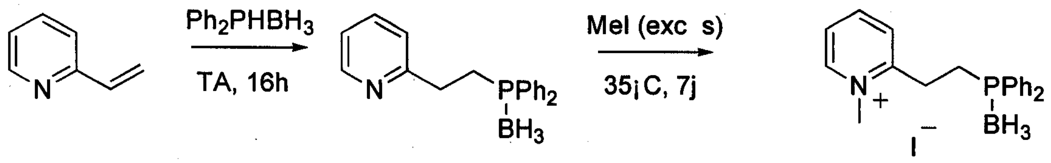


Figure 1

The new ligand is insoluble in apolar solvents (hexane, ether) but is miscible in [BMIM] [PF_6] ionic liquid. This salt containing 15% of the new ligand and 5% of $Pd(OAc)_2$ was used as a reaction medium for the C-P cross coupling reaction under the previously defined conditions. The new catalytic system successfully catalysed the C-P cross coupling reaction. Deprotection of the phosphine-borane before use was not required, deprotection occurring directly in the medium. With this new catalyst, it was possible to recycle both the ionic liquid and the catalyst six cycles with no significant loss in activity.

In conclusion, it is shown that the C-P cross coupling reaction between a phosphine-borane and an aryl iodide can be performed in [BMIM][PF_6] with an excellent preservation of the phosphine-borane complexes. In this new media, the classical palladium catalyst ($dpppPdCl_2$) can be recycled at least 3 times. To improve the recycling, a monophosphine covalently attached to a pyridium salt was prepared. Associated to palladium, this ligand showed a high catalytic activity for the C-P cross coupling and stays immobilised in the ionic liquid. The catalyst was reused at least 6 times (**Table II** and **Figure 2**).



Scheme III

Table II — 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	-	-	-
Pyridine tagged ligand/ $Pd(OAc)_2$	(%)	> 98	98	94	95	90	88	42

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

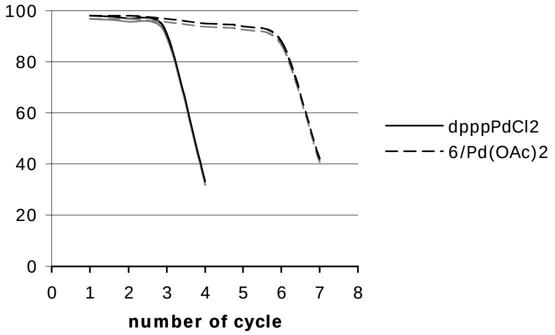


Figure 2 — Comparative recycling of the pyridinium-tagged catalyst derived from **6** and $dpppPdCl_2$

Experimental Section

Synthesis of pyridinium tagged ligand: An oven-dried schlenk tube was charged with phosphine borane **2** (60 mg, 0.3 mmole). After three cycles of oil pump vacuum/nitrogen cycle, 2-vinylpyridine (38 μL, 0.36 mmole) was added under nitrogen flow. The mixture was stirred for 16 hr at room temperature and directly purified on silica gel chromatography (Et_2O-pentane, 1:1). The product was dried under vacuum, affording 2-(2-(diphenylphosphino)-ethyl)pyridine as a white solid in 76% yield. Then, the new compound (70 mg, 0.229 mmole) was treated neat with 9 eq. of methyliodide and the mixture was stirred for 7 days at 35°C. The crude precipitate was washed with ether, dried under vacuum affording the expected salt in 75% yield.

^1H NMR (CD_3CN): 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_3CN): 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_3CN): 16.7. ^{11}B NMR (CD_3CN): -37.2. HRMS Calcd. or $C_{20}H_{24}BNP$: 320.1739, Found 320.1741.

General procedure for recycling: An oven-dried schlenk tube was charged with phosphine borane **2** (60 mg, 0.3 mmole), 1 mL of ionic liquid. After three cycles of oil pump vacuum/nitrogen cycle, 2 equiv of K_2CO_3, 15% mole of the new ligand and 5% mole of palladium catalyst were added. After completion, the product was extracted with 5 × 0.5mL of toluene. The toluene phase was concentrated and the crude product was analysed by ^{31}P NMR. The ionic liquid layer containing the catalyst was outgassing under reduced pressure. After adding 1 equiv of base and one equiv of each reactants, the reaction was run as previously.

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