

Heck reactions of aryl halides in phosphonium salt ionic liquids: library screening and applications

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Received 27 July 2004; revised 16 August 2004; accepted 17 August 2004

Abstract—The Heck cross-coupling of aryl iodides and bromides with olefins proceeds in the phosphonium salt ionic liquid trihexyl(tetradecyl)phosphonium chloride (THP-Cl) in excellent yields. Furthermore, it is shown that the counter anion matched to the phosphonium cation exerts a measurable effect on the overall yield.

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The Heck cross-coupling reaction has now become a common procedure for carbon–carbon bond formation between alkenes and organic halides or triflates lacking sp^3 -hybridized β -hydrogens.¹ Given the power and popularity of the reaction, a great deal of recent interest has been expressed in the development of Heck reactions carried out in ionic liquid media.² Non-volatile, room temperature ionic liquids (IL) based on alkylimidazolium and other quaternary ammonium/pyridinium salts have emerged as valuable, alternative ‘green’ solvents for catalytic processes over the last few years offering a number of advantages to traditional solvent based systems. Using ionic liquids, it is often possible to recycle the active (and often expensive) catalyst subsequent to extraction of the organic product and inorganic salt by-products. A number of Heck reactions have been performed in ionic liquids; however, these invariably involve nitrogen-based salts and require elevated temperatures (greater than 120 °C in many instances),³ microwave heating⁴ or sonication⁵ for reasonable conversions.

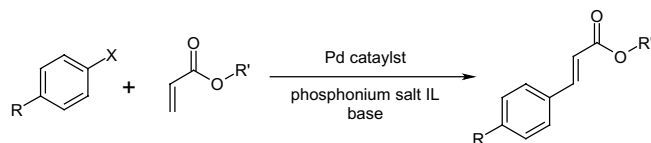
Another class of readily available, often overlooked ionic liquid are those based on quaternary phosphonium salts.⁶ Generally displaying increased stability towards thermal and chemical degradation compared to their ammonium counterparts, quaternary phosphonium salts have been used to good effect in hydroformylation⁷ and the Suzuki reaction.⁸ Furthermore, Kaufmann has

successfully carried out Heck reactions in tributyl(hexadecyl)phosphonium bromide at 100 °C.⁹ Our interest in these methodologies stems from initial exploratory experiments carried out in our laboratories wherein we found that the counter anion matched to the phosphonium cation exerted a measurable effect on the overall yields obtained. This is in keeping with the recent observations of Handy and Okello¹⁰ who have demonstrated that certain halides can have an accelerating effect on the Heck reaction in nitrogen-based ionic liquids. The present paper describes the results of parallel screening to determine a set of general conditions suitable for the Heck coupling of a variety of aryl halides in phosphonium salt ionic liquids.

Our initial efforts focussed on the Heck couplings of aryl iodides. Table 1 shows the results of the phosphonium salt ionic liquid library screen in the coupling of iodo-benzene and methyl acrylate using $Pd_2dba_3 \cdot CHCl_3$ as the catalyst and triethylamine as the base. Entries 1–8 show that the counter anion to the trihexyl(tetradecyl)-phosphonium (THP) cation plays a significant role in the outcome of the reaction. The best ionic liquids were shown to be THP-Cl (entry 2) and THP-decanoate (entry 5) allowing for conversions of 78% and 75%, respectively. While the results for the two ionic liquids are comparable, THP-Cl demonstrated itself to be much easier to work with in the purification stage. Addition of hexane and brine to the reaction mixture containing THP-Cl allowed for the separation of three distinct phases with the palladium remaining in the middle ionic liquid layer, the coupled product in the organic layer and any salts in the aqueous layer. Purification simply

Keywords: Ionic liquids; Heck reaction.

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Table 1. Phosphonium based ionic liquid screen for a standard Heck reaction

Entry	Ionic liquid	Percent conversion (%) ^a	
		X = I ^b R = H; R' = CH ₃	X = Br ^c R = OMe; R' = ^t Bu
1	Trihexyl(tetradecyl)phosphonium bromide	13	0
2	Trihexyl(tetradecyl)phosphonium chloride	78	61
3	Trihexyl(tetradecyl)phosphonium dicyanamide	34	0
4	Trihexyl(tetradecyl)phosphonium-bis(trifluoromethane sulfonyl)amide	23	0
5	Trihexyl(tetradecyl)phosphonium decanoate	75	72
6	Trihexyl(tetradecyl)phosphonium-bis(2,4,4,-trimethylpentyl)phosphinate	16	74
7	Trihexyl(tetradecyl)phosphonium hexafluorophosphate	11	0
8	Trihexyl(tetradecyl)phosphonium tetrafluoroborate	17	0
9	Triisobutyl(methyl)phosphonium tosylate	27	NA ^d
10	Tributyl(methyl)phosphonium methylsulfate	16	NA ^d

^a Conversion determined by GC analysis.

^b 1.0 equiv 4-iodotoluene, 1.5 equiv methylacrylate, 2% Pd₂dba₃·CHCl₃, 1.5 equiv Et₃N, 50 °C, 2h.

^c 1.0 equiv 4-bromoanisole, 1.4 equiv *t*-butylacrylate, 1% Pd(OAc)₂, 1.5 equiv Et₃N, 100 °C, 4h.

^d Not attempted.

required separation of the phases. However, use of the decanoate IL allowed for the separation of only two phases thereby requiring additional purification.

Further optimization of reaction conditions revealed that Pd(OAc)₂ was the ideal palladium source. The reaction proceeds in the presence of a number of organic bases (Et₃N, DMAP, etc.) but was found to be most efficient when sodium acetate and water (added for salt solubility) were employed. The combination also simplified purification as the desired triphasic system was more readily achieved. The optimal conditions (THP-Cl, aryl iodide, 1.4 equiv olefin, 4% Pd(OAc)₂, 1.5 equiv NaOAc, H₂O)¹¹ were then applied to a series of aryl iodides and a number of Heck coupling partners.¹² As can be seen from Table 2 (entries 1–7), reactions can be carried out with activated, deactivated and more sterically challenging aryl iodides at 50 °C in very high isolated yields in approximately 2h. Of particular note is the complete regioselectivity for the β-position. In addition, no *cis* olefin products were observed.

In addition, the IL layer containing the Pd catalyst was shown to be active and reusable. For example, repetition of the coupling protocol was carried out for entry 6 with additional quantities of methyl acrylate, 4-iodoanisole and NaOAc but *no further catalyst* added to the isolated ionic liquid. The system was used three times to give yields of 98%, 95% and 94% in each of the recycled rounds. It is clear that a competent palladium catalyst remains fully dissolved in the phosphonium salt allowing its efficient reuse.

When the Heck reaction was carried out on aryl bromide substrates using the optimal conditions developed for the aryl iodides, low yields of the coupled product were obtained (e.g., *p*-bromotoluene was coupled with methylacrylate and α-methyl-methacrylate in 45% and

Table 2. Heck reaction of aryl halides using THP-Cl

Entry	Aryl Halide	Olefin	Yield
1 ^a			98
2 ^a			95
3 ^a			99
4 ^a			99
5 ^a			98
6 ^a			98
7 ^a			99
8 ^b			88
9 ^b			82
10 ^b			81

^a THP-Cl, 1.0 equiv aryl iodide, 1.4 equiv olefin, 4% Pd(OAc)₂, 1.5 equiv NaOAc, 50 μL H₂O, 50 °C, 2h.

^b THP-Cl, 1.0 equiv aryl bromide, 1.4 equiv olefin, 1% Pd(OAc)₂, 1.5 equiv Et₃N, 100 °C, 4h.

34% yield, respectively). An increase in temperature had little effect on the overall yield. As a result, a new screening and optimization program was undertaken. We quickly determined that organic bases were much better at promoting the coupling of aryl bromides than sodium acetate. In fact when the IL library (Table 1, X = Br) was screened in the reaction of 4-bromoanisole and *t*-butylacrylate using Et₃N and Pd(OAc)₂ at 100 °C, reasonable conversions were obtained for both the THP-Cl and THP-decanoate. Interestingly, the phosphinate counter anion of entry 6 also allowed for reasonable turn over. Addition of additives such as NaOAc or PPh₃, were ineffective at lower concentrations (2–15%) and deleterious at higher concentrations (above 20%). However, small amounts of chloride or decanoate could be added to allow for turnovers from ILs that did not normally facilitate the Heck reaction. For example, when 10% decanoate was added to THP-bromide, the conversion after 2h increased to 43%. Optimal conditions for the coupling of aryl bromides were determined (1% Pd(OAc)₂, Et₃N and 1.4equiv of olefin) and applied to a series of coupling partners. A few representative examples appear in Table 2 (entries 8–10).

In conclusion, it has been demonstrated that judicious choice of phosphonium salt ionic liquid provides an economical, recyclable media for the Heck cross-coupling reaction. Further analysis of the active Pd-catalytic species formed by dissolution of Pd(OAc)₂ in the phosphonium salt ionic liquid and applications of the process to other coupling partners are currently under investigation in our laboratories.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (Collaborative Research and Development Award) and Cytec Canada Inc. for financial support.

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11. Smaller amounts of palladium can be used, however, 4% Pd(OAc)₂ allowed for excellent turnovers in roughly 2h.
12. Samples of THP-Cl (trade name CYPHOS 3653) and other ionic liquids described may be obtained by contacting Cytec at the address given. A representative procedure for the Heck reaction is as follows. Into an oven dried 5mL reaction vessel equipped with a stir bar were added trihexyl(tetradecyl)phosphonium chloride (THP-Cl, 520mg, 1.0mmol), Pd(OAc)₂ (4%, 11.2mg, 0.05mmol), sodium acetate (123.0mg, 1.5mmol) and placed under vacuum for 1h before exposure to a nitrogen atmosphere. The aryl halide (1.0mmol), the olefin (1.5mmol) and H₂O (50μL) were added and the flask heated to 50 °C with stirring. After the appropriate amount of time (approximately 2h), the reaction mixture was cooled and treated with brine (1mL) and hexane (2mL). The mixture was stirred vigorously, then allowed to separate over 30min. Both the aqueous and organic layers were collected and the IL layer extracted with fresh hexane and brine for a total of five times. The organic layers were combined and concentrated under reduced pressure and the residue purified via flash silica gel chromatography if necessary (5–25% ethyl acetate in hexane). Use of this method allowed for efficient catalyst recycling. For example, in the case of entry 6, the ionic liquid was degassed then recharged with methylacrylate, 4-iodoanisole and NaOAc and heated as indicated above. Aryl bromides were run under identical conditions in a sealed vessel using 1% Pd(OAc)₂, 1.4equiv *tert*-butyl acrylate and 1.5equiv triethylamine (no water was added) and heated to 100 °C for 4–8h.