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Charge-tagged polar phosphine ligands in Pd-catalysed reactions in aqueous and ionic media

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ABSTRACT

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A new range of polar imidazolium and phosphate-containing ligands was synthesised from readily available starting materials in high yielding multi-step transformations. These ligands were used to generate Pd catalysts for Suzuki and Heck C-C coupling reactions in organic and organic/aqueous media. The catalysts performed well in aqueous media in the Suzuki reaction and less well in the Heck reaction, related to solubility of the substrates in the aqueous media. When moving to ionic liquids, the Heck reaction dramatically improved, especially in media compatible with the polar catalysts and the non-polar reagents. In all cases, the catalysts were stable to the formation of Pd black, a form of degradation that frequently befalls Pd catalysts. The catalysts could be successfully recycled without loss of activity.

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1. Introduction

The primary role of ligands in the context of homogeneous catalysis is to modify the metal in question towards stability, activity, product selectivity, isolation, and recycling. The role that ligands play in determining many of the features of metal-based catalysts has led to a prolific number and wide variety of ligands being prepared,¹ including those that are phase-switchable,² which are highly useful in the mechanistic study of catalysed reactions.^{1a} While heterogeneous catalysts are readily recovered and reused,³ homogeneous catalysts suffer a persistent disadvantage because of the difficulties associated with recovering and recycling them. Polar phosphine ligands assist the recovery and reuse of catalysts in several possible ways. Firstly, if the ligands are sufficiently polar, they may be extracted into an aqueous phase post-reaction, having been held in the organic phase during the reaction.² Secondly, they may be held in altogether a separate phase, which may be aqueous or another non-miscible phase such as, for example, an ionic liquid.⁴ Such biphasic systems facilitate the recovery and reuse of catalysts,⁵ a pertinent example being the Rhône-Poulenc process. Here, a Rh catalyst is used in a biphasic medium to convert lower alkenes into higher value aldehydes and alcohols.⁶ Triphenylphosphine trisulphonate is the ligand,⁶ and it imparts to the catalyst a level of water solubility which reduces leaching of Rh into the organic reaction product to very low levels. Polar ligands also assist the move towards more benign solvent systems, even if recovery of the catalyst is not under consideration,

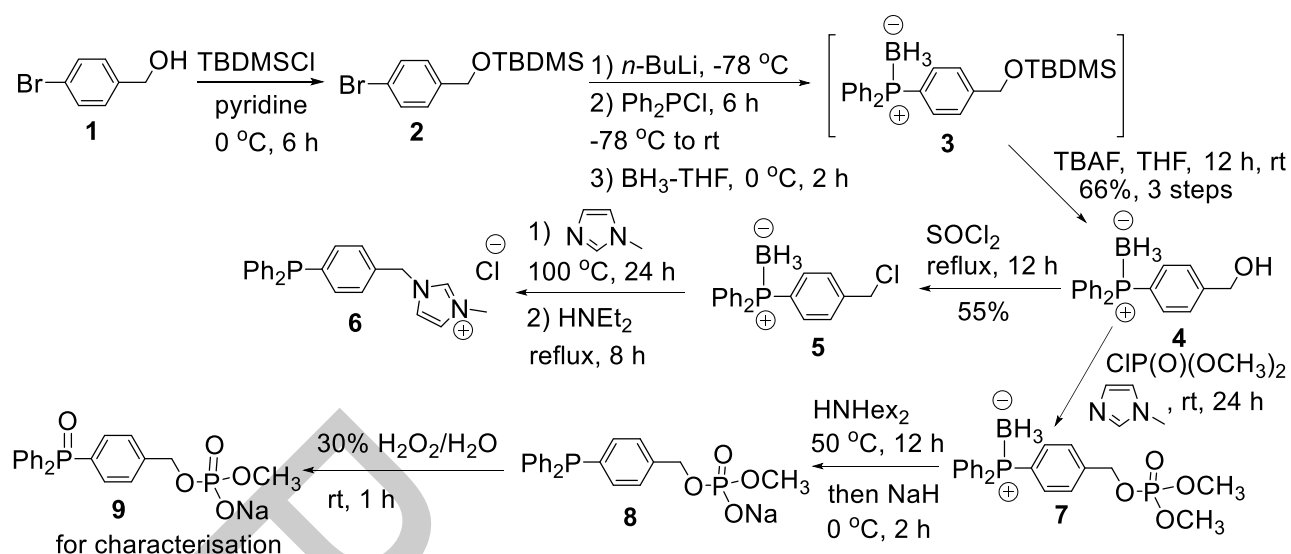
because aqueous or ionic liquid-based solvents can be employed.⁷ Thus, it was an objective of the present study to investigate the synthesis, and application in catalysis, of different P-type ligands with the polarity being derived from phosphate-containing and imidazolium-containing moieties. These ligands would be assessed in Pd-catalysed C-C bond-forming Heck⁸ and Suzuki⁹ reactions in polar organic, organic aqueous and ionic liquid systems, including recycling experiments.

2. Results and discussion

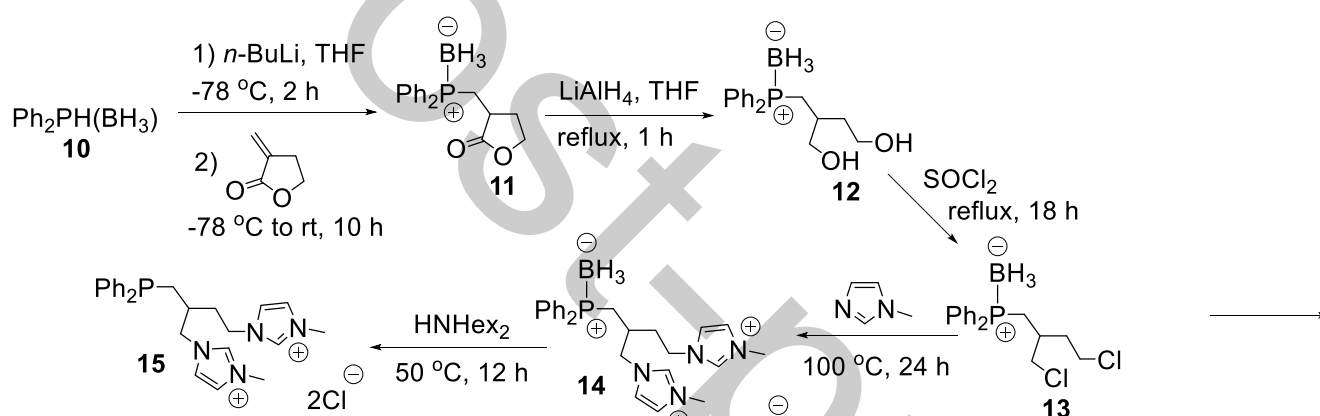
The synthesis of these ligands was achieved by multi-step sequences which converted suitable starting materials into more complex derivative structures, making use of Ph₂PCl and Ph₂PH as sources of the P atom. These two reagents are useful as electrophiles and nucleophiles, respectively. In the case of Ph₂PCl as the substrate, a nucleophile may attack the P atom, ejecting chloride to form a new P-C bond. In the latter, the P-H is deprotonated thereby converting it into a nucleophile suitable for reactions with, for example, α,β -unsaturated esters. In all cases, the products of these reactions were transformed into polar entities.

4-Bromobenzyl alcohol (**1**) was protected as its silyl ether **2** (Scheme 1), and the resulting product was subjected to lithium-halogen exchange with *n*-butyllithium.¹⁰ Reaction of the lithiated intermediate with Ph₂PCl, and P-protection of the reaction product with BH₃-THF, afforded the triphenylphosphine derivative **3**. If the P-atom was left unprotected during conversion of the benzyl

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Scheme 1. Synthesis of mono phosphate-based polar ligands.

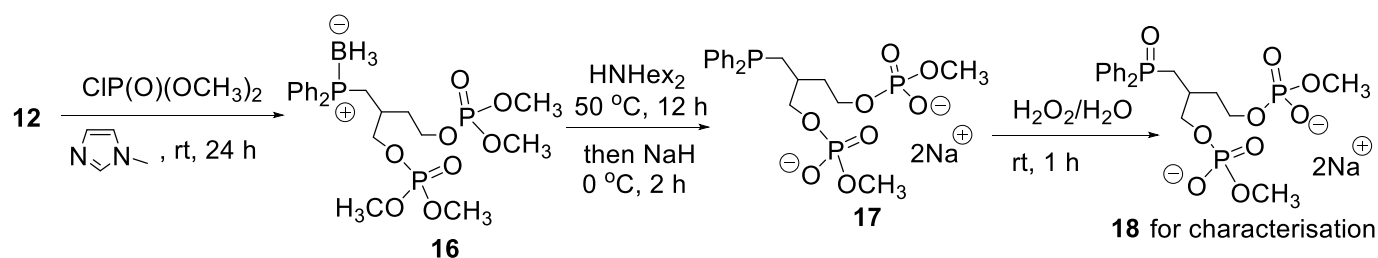


Scheme 2. Synthesis of bis imidazolium-based polar ligands.

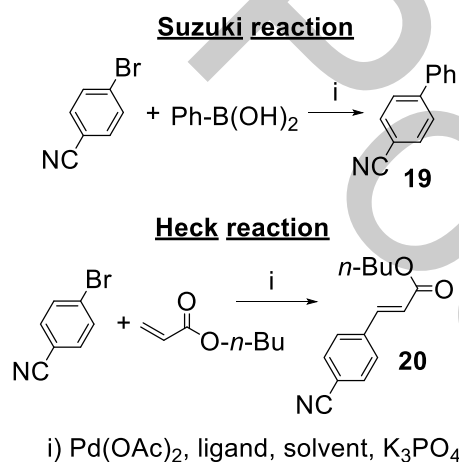
alcohol into its corresponding chloride under the action of thionyl chloride (see below), the P atom was oxidised into its unwanted P(O) derivative. Unmasking of the OH group under the action of tetra-*n*-butyllammonium fluoride on **3** furnished benzyl alcohol **4** in 66% overall yield from **1**, after column chromatography on silica gel. A two proton singlet at 4.72 ppm in the ^1H NMR spectrum of the product was consistent with the anticipated benzyl alcohol CH_2 group. This product afforded the anticipated broad doublet signal at 20.8 ppm ($J = 61.3$ Hz) in the ^{31}P NMR spectrum thereof, accompanied by a range of doublet signals in the aromatic region of the ^{13}C NMR spectrum, caused by P-C coupling over a number of bonds. Uneventful conversion of the benzyl alcohol into its chloride analogue **5** under the action of thionyl chloride and reaction of **5** with excess *N*-methylimidazole at 100°C , followed by P-deprotection with neat diethylamine,¹¹ afforded the desired imidazolium-containing phosphine **6** in 60% yield from **4**. The free phosphine and the diethylamine-borane complex were readily separated by extraction with CH_2Cl_2 and water: the phosphine was soluble in the organic phase while the amine-borane complex was soluble in the aqueous phase. Compound **6** produced diagnostic signals for the imidazolium moiety in the ^1H NMR and ^{13}C NMR spectra thereof, accompanied by a sharp singlet at -5.1 ppm in its ^{31}P NMR spectrum, which provided evidence for deprotection of the P atom. Alternatively, benzyl alcohol **4** could be reacted with

dimethyl chlorophosphate (CAUTION! This substance is highly toxic and requires special handling techniques.) to convert it into phosphate **7**. Deprotection of the P atom and partial hydrolysis of the phosphate ester of **7** with neat dihexylamine, followed by cation exchange with NaH, afforded the corresponding sodium phosphate **8**, which was characterised as its phosphine oxide **9**. In this instance, dihexylamine was chosen for the P deprotection step because the ligand would be soluble in the aqueous layer and it was desirable for the amine-borane complex to be soluble in the organic phase. The ^1H NMR spectrum of the P=O product **9** showed a characteristic two proton doublet at 4.88 ppm ($J_{\text{H,P}} = 8.2$ Hz) and a three proton doublet at 3.56 ppm ($J_{\text{H,P}} = 9.5$ Hz), while the ^{31}P NMR spectrum thereof showed two sharp singlet signals at 31.7 ppm (P(O)) and 1.1 ppm (OPO).

In a second approach towards polar phosphines, diphenylphosphine-borane **10** was lithiated using *n*-butyllithium and the lithium phosphide was subsequently reacted with α -methylene- γ -butyrolactone in a Michael-type reaction to produce adduct **11** (Scheme 2). The lactone was readily reduced to the corresponding diol by reaction thereof with LiAlH_4 to produce the desired product **12** in a yield of 85%. Reaction of the diol with thionyl chloride followed by treatment of the dichloro intermediate **13** with *N*-methylimidazole at elevated temperature produced bisimidazolium chloride **14**. The P atom was released



Scheme 3. Synthesis of bis phosphate-based polar ligands. immediately prior to the catalysis by treatment of **14** with dihexylamine to deliver free phosphine **15**, which was not characterised due to its sensitive nature. Diol **12** was also reacted with dimethyl chlorophosphate (CAUTION! This substance is highly toxic and requires special handling techniques.), the product of which was deprotected, partially hydrolysed and subjected to cation exchange to produce the water soluble bisphosphate **17** (76% from **12**), which was characterised as its P=O derivative **18** (Scheme 3).



Scheme 4. Suzuki and Heck reactions using polar catalysts.

The ligands were then employed in Pd-catalysed Suzuki- and Heck reactions (Scheme 4, Table 1) as set out in Table 1. Reactions were performed in polar organic medium and in organic/aqueous medium, and the catalysts were benchmarked against baseline systems which were devoid of ligands. In all instances, the ligands produced catalysts that were stable and from which no Pd black was formed. It is clear from the results that the ligands produce catalysts that are consistently good for the Heck and Suzuki reactions performed in DMF. The catalysts all performed well to mediate the Suzuki reaction in DMF/H₂O. In contrast, the Heck reactions performed in DMF/H₂O did not fare so well. It is most likely that the difference in outcome is due to the polarity of the reaction partners, and it is unlikely that the 4-bromobenzonitrile, used as a substrate for the oxidative addition step that initiates both the Heck and the Suzuki reaction, causes the difference. Rather, for the Heck reaction the nonpolar butyl acrylate is used as the substrate while in the Suzuki reaction the polar phenylboronic acid is used as the substrate. Presumably, it is the low solubility of the former that hampers the progress of the Heck reaction in the polar organic/aqueous binary solvent. These outcomes are consistent with our previous results using simpler catalyst systems in polar organic and in aqueous media.⁸

Additional Heck reactions were therefore performed in ionic liquids (Table 2) in an attempt to improve the outcome. As a general comment on the outcomes of the reactions, the catalysts constituted from the new ligands performed as well as or better

Table 1. Pd-catalysed Heck- and Suzuki reactions^{a,b}

Entry	Ligand	Suzuki product 19		Heck product 20	
		DMF	DMF/H ₂ O	DMF	DMF/H ₂ O
1	–	55%	60%	10%	5%
2	8	73%	75%	65%	20%
3	9	75%	76%	72%	20%
4	6	74%	78%	67%	25%
5	12	77%	80%	72%	28%
6	14	86%	86%	76%	45%
7	17	75%	75%	75%	43%

^a Suzuki reaction: Pd(OAc)₂ (5 mol%), ligand (10 mol%), DMF or 1:1 DMF/H₂O (2 mL), K₃PO₄ (1.0 equiv.), 4-bromobenzonitrile (1.0 equiv.), phenylboronic acid (1.0 equiv.), 100 °C, 24 h.

^b Heck reaction: Pd(OAc)₂ (5 mol%), ligand (10 mol%), DMF or 1:1 DMF/H₂O (2 mL), Et₃N (1.0 equiv.), 4-bromobenzonitrile (1.0 equiv.), butyl acrylate (1.0 equiv.), 110 °C, 24 h.

than the triphenylphosphine benchmark reaction. The ionic liquid of choice was [bmim]BF₄ (see Table 2 footnote for definition of the abbreviations for the ionic liquids), which is the most polar of the ionic liquids employed. While the [bmim] and [hmim] ionic liquids could conceivably form carbene structures with Pd, the [C8dmim] ionic liquid cannot because the 2-position is blocked. That there was little difference between the outcomes when using this ionic liquid and those where the 2-position is free, would point towards the notion that carbenes potentially generated from the ionic liquids are not involved in the catalysis. The ligands demonstrate their real usefulness during recycling experiments, though. Firstly, no Pd black was noted for any of the new ligands during four consecutive runs, indicating that stable catalysts were formed. Secondly, NMR spectra of concentrates of the organic extracts (post reaction in each of the four runs) failed to show the presence of the ligands, demonstrating minimal leaching thereof, along with the Pd, into the organic phase. Recharging the substrates to the Pd/**6**/[bmim]BF₄ catalyst medium in the four consecutive runs, once the organic phase had been decanted, allowed the recyclability of the catalysts to be assessed. These runs afforded yields of the Heck products of 88%, 83%, 84% and 81%, respectively. The high level of repeatability of the runs when making use of the recycled catalyst indicates the retention of high levels of the catalyst in the ionic liquid phase and that it suffered little or no degradation or inactivation.

3. Conclusion

Imidazolium and phosphate-containing phosphines, produced in good overall yield in several steps from readily accessible starting materials, form stable Pd catalysts that are capable of effecting C-C bond-forming reactions in polar organic and organic/aqueous mixed solvent systems. All ligands form stable

Table 2. Pd-catalysed Heck reactions in ionic liquids^{a,b}

Ligand	[bmim]BF ₄	[hmim]BF ₄	[C8dmim]BF ₄	[bmim][NSO ₂ CF ₃] ₂	[hmim][NSO ₂ CF ₃] ₂	[C8py][NSO ₂ CF ₃] ₂
TPP	74%	61%	58%	58%	48%	51%
6	88% (83%, 84%, 81%) ^c	63%	68%	65%	48%	55%
15	81%	59%	56%	59%	45%	52%

^a TPP = triphenylphosphine, bmim = 1-butyl-3-methylimidazolium, hmim = 1-hexyl-3-methylimidazolium, C8dmim = 2,3-dimethyl-1-octylimidazolium, C8py = *N*-octylpyridinium.

^b Heck reaction: Pd(dba)₂ (5 mol%), ligand (10 mol%), ionic liquid (1 mL), Et₃N (1.0 equiv.), 4-bromobenzonitrile (1.0 equiv.), butyl acrylate (1.0 equiv.), 110 °C, 24 h.

^c Values in parentheses represent recycling experiments in which the catalyst was used in a total of four runs.

and active catalysts for Suzuki and Heck reactions in ionic liquids and the outcomes of the reactions are less linked with the nature of the Pd-ligand system than they are with the solubility of the substrates. If the substrates are only slightly soluble in the organic/aqueous medium, then the reactions are plagued by low yields. The presence of the imidazolium or the phosphate groups clearly does not hamper the catalyst activity. Recycling experiments revealed an ability to reuse the catalysts over several runs without loss of activity.

Acknowledgement

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Graphical Abstract

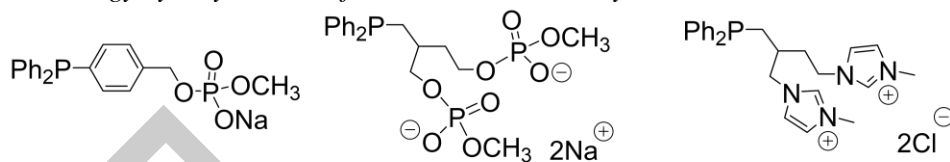
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Ligands for Suzuki, Heck reactions in aqueous and ionic media using a recyclable catalyst.