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# Electronic Supporting Information

## Ionic Liquids in Cross-Coupling Reactions: "Liquid" Solutions to a "Solid" Precipitation Problem

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## Materials

Potassium *tert*-butoxide ($KO^tBu$), phenylboronic acid, aniline, 4-chloroanisole, XPhos, XPhos Pd G1, and 4-methoxybiphenyl were bought from Sigma-Aldrich, Co. LLC (St. Louis, MO, USA). Potassium hydroxide, toluene, and HPLC grade methanol were procured from Fisher Scientific (Fair Lawn, NJ, USA). Trihexyl(tetradecyl)phosphonium chloride ($[P_{66614}]Cl$) was kindly donated by Cytec (Niagara Falls, ON, Canada), whereas 4-methoxy-N-phenylaniline was bought from Toronto Research Chemicals (Toronto, ON, Canada). Potassium carbonate, toluene (to obtain dry toluene), 1,4-dioxane (to obtain dry dioxane), and methanol were purchased from ACP Chemicals Inc. (Montreal, QC, Canada). Cambridge Isotope Laboratories, Inc. (Andover, MA, USA) was the source of DMSO-$d_6$. All materials were used as obtained, unless specified.

## Synthesis of $[P_{66614}]^+$-based ILs

***Synthesis of $[P_{66614}][O^tBu]$ by Metathesis:*** $[P_{66614}]Cl$ was dried (stirring, 60 °C, 6 h, $10^{-4}$ bar) before use. The synthesis was carried out in the glove box under $N_2$ atmosphere. Dried $[P_{66614}]Cl$ (10 mmol) was loaded in a 50 mL Schlenk flask with a magnetic stir bar. $KO^tBu$ (10 mmol) was then added to this reaction flask using a spatula and the flask was capped with a glass stopper. The mixture was allowed to stir at room temperature. The solution changed its color to yellow instantly. After 48 h stirring, dry toluene (5-8 mL) was added to the stirring solution using a Pasteur pipet and stirred overnight. The next day, the liquid was transferred into a centrifuge tube (50 mL) using a Pasteur pipet, the centrifuge tube was capped and removed from the glove box for centrifugation (Thermo Scientific Sorvall Legend XF, Waltham, MA, USA) (15 min, 3000 rpm). A solid phase was observed in the bottom of the centrifuge tube (possibly potassium chloride). The centrifuge tube was reopened inside the glove box, and the upper liquid phase was transferred into another Schlenk flask, while the bottom phase was washed with *ca.* 5 mL dry toluene. Centrifugation and phase separation steps were repeated twice and the toluene phases were collected in the Schlenk flask. Toluene was then evaporated under high vacuum to obtain a faint yellowish wax. The reaction solution and liquid phase were never exposed to air during the synthesis.

***Synthesis of $[P_{66614}][OH]$ by Metathesis:*** $[P_{66614}]Cl$ was dried (stirring, 60 °C, 6 h, $10^{-4}$ bar) before use. Dried $[P_{66614}]Cl$ (10 mmol) was loaded in a 50 mL round bottom flask with a magnetic stir bar. KOH (20 mmol) was then added to this reaction flask, followed by the addition of dry toluene (5-8 mL). The flask was capped with a glass stopper and the mixture was allowed to stir at 40 °C. After 24 h of stirring, *ca.* 5-8 mL dry toluene (5-8 mL) was added to the stirring solution and stirred for 2 h. Thereafter, the liquid was transferred into a centrifuge tube (50 mL) and centrifuged (15 min,

3000 rpm). A solid phase was observed in the bottom of the centrifuge tube (possibly potassium chloride). The upper liquid phase was transferred into another round bottom flask and *ca.* 5 mL toluene were added to the bottom phase. Centrifugation and phase separation steps were repeated twice. Toluene was evaporated by rotary evaporator and finally dried under high vacuum to obtain a white wax.

***Synthesis of [$P_{66614}$][OH]·4MeOH using an Anion-Exchange Resin:*** The anion-exchange was performed as described elsewhere with slight modifications.[1] A known volume of anion-exchange resin (Amberlite IRN-78, 1.2 moles of $[OH]^-$ per L of resin, Alfa Aesar, Ward Hill, MA, USA) was packed in a glass column (of dimension 350 mm × 13 mm) using MeOH and washed with 100 mL MeOH. $[P_{66614}]Cl$ dissolved in MeOH (0.5 moles per mL) was loaded onto the resin bed (in the glass column) such that the molar ratio of $[OH]^-$ of resin to $[P_{66614}]Cl$ was 8. MeOH was used to elute the ion-exchanged cation (pH was monitored using pH strips) and the eluent was collected in a round bottom flask until pH 8 (approx. flow rate: 100 drops per min). This eluent was concentrated using a rotary evaporator (35 °C, 103 mbar) and the concentrate, thus obtained, was dried under high vacuum for 6 h. The product was a yellow liquid.

**Nuclear Magnetic Resonance (NMR) Spectroscopy**

All spectra were recorded as a solution using DMSO-$d_6$ as the lock solvent containing TMS as internal standard. $^1H$ NMRs were recorded using a Bruker Ascend™ 500 (Madison, WI, USA) spectrometer operating at 500 MHz. $^{13}C$ NMR spectra were also obtained with the same instrument at 120 MHz. $^1H$ and $^{13}C$ NMR spectra of all $[P_{66614}]^+$-based ILs used/synthesized in this study are shown in Figures S1-S2.

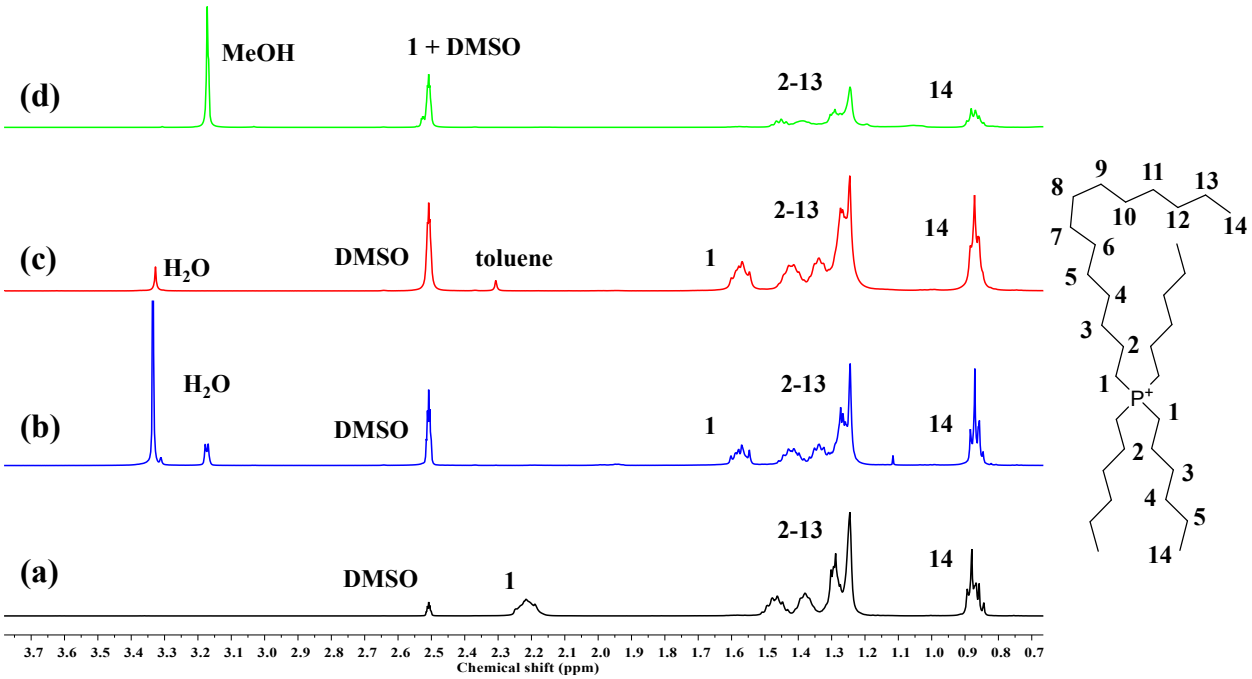


**Figure S1.** $^{1}$H NMR spectra of (a) [$P_{66614}$]Cl, (b) [$P_{66614}$][O$^{t}$Bu], (c) [$P_{66614}$][OH], and (d) [$P_{66614}$][OH]·4MeOH.

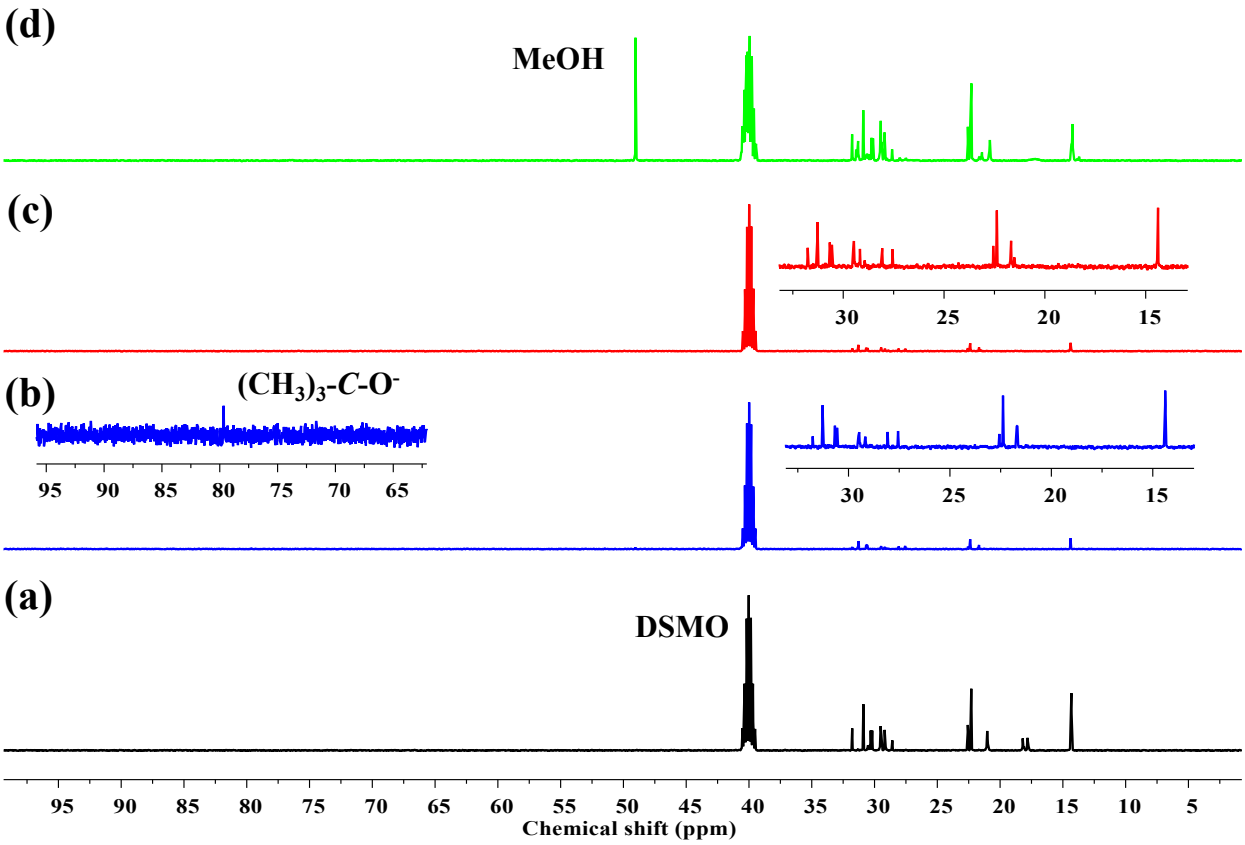


**Figure S2.** $^{13}$C NMR spectra of (a) [$P_{66614}$]Cl, (b) [$P_{66614}$][O$^{t}$Bu], (c) [$P_{66614}$][OH], and (d) [$P_{66614}$][OH]·4MeOH. The signals in (b) and (c) are demonstrated clearly by the enlargement.

**Thermal Gravimetric Analysis (TGA)**

Thermal behavior was determined by TGA on a TA Q500 unit (New Castle, DE, USA) under $N_2$ flow (Figure S3). Samples between 3 and 10 mg were placed in platinum pans and heated from room temperature to 75 °C at a heating rate of 5 °C/min. An isotherm at 75 °C was maintained for 30 min to eliminate all volatiles, if any. After the isothermal step, the temperature was ramped to 800 °C at a heating rate of 5 °C/min. The data was analyzed using TA Universal Analysis software.

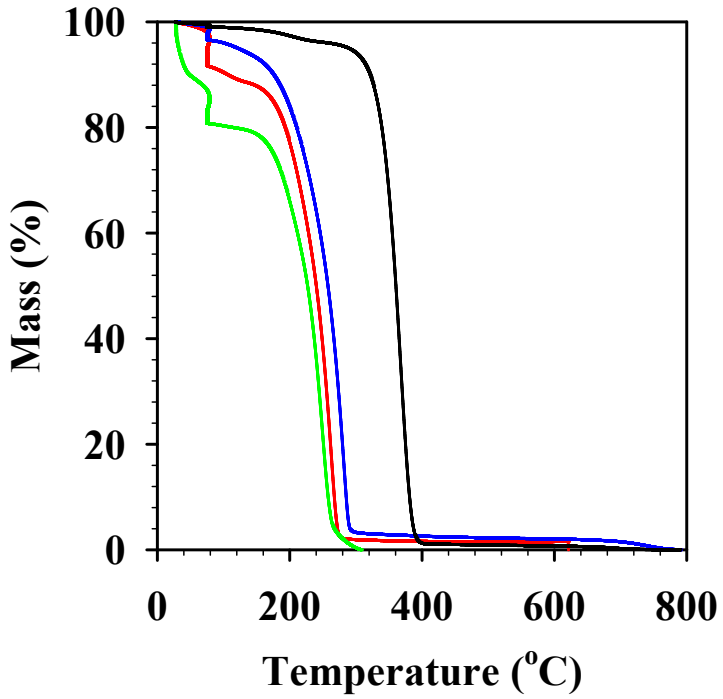


**Figure S3.** TGA profiles of $[P_{66614}][OH]\cdot 4MeOH$ (green), $[P_{66614}][OH]$ (red), $[P_{66614}][O^tBu]$ (blue), and $[P_{66614}]Cl$ (black).

**Differential scanning calorimetry (DSC)**

DSC was performed using a TA Q2000 unit (New Castle, DE, USA) under nitrogen flow (Figure S4). Samples between 5 and 15 mg were placed in $T_0$ Aluminum Hermetic pans (TA Instruments, New Castle, DE, USA) and sealed using a $T_0$ press. The samples were cooled from room temperature to -60 °C at a cooling rate of 5 °C/min, maintained at -60 °C for 5 min, and then heated to 100 °C at a ramp rate of 5 °C/min, followed by an isotherm at 100 °C for 5 min and cooling to -60 °C at 5 °C/min. This cycle was repeated twice to reproduce the results. The data was analyzed using TA Universal Analysis software.

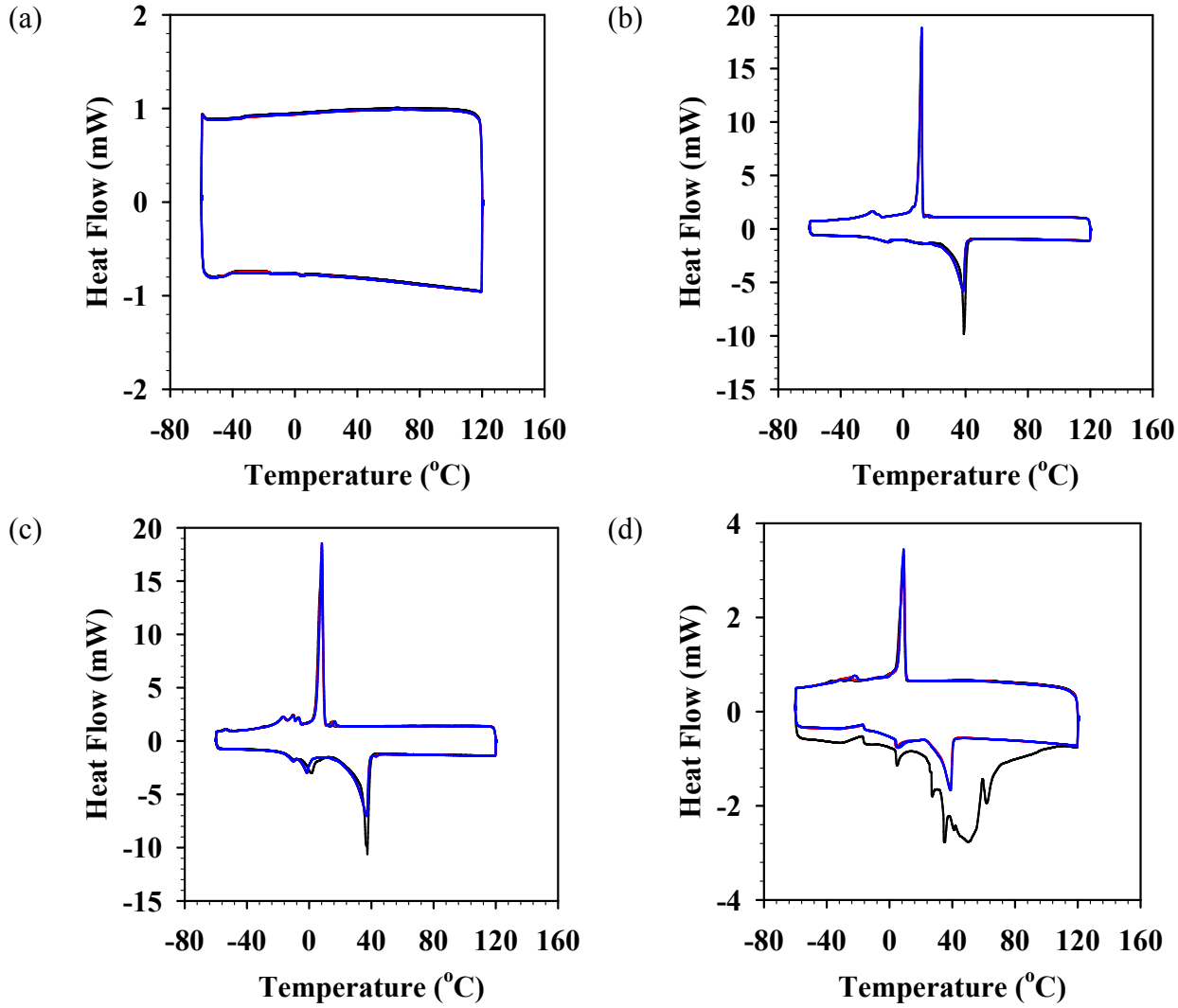


**Figure S4.** DSC profiles (all three cycles overlaid) of (a) $[P_{66614}]Cl$, (b) $[P_{66614}][OtBu]$, (c) $[P_{66614}][OH]$, and (d) $[P_{66614}][OH]\cdot 4MeOH$. Black: 1st cycle. Red: 2nd cycle. Blue: 3rd cycle.

**Solubility Studies**

The solubility of the prepared salts in the representative solvents were determined as described earlier.[2] Typically, 0.2 g sample of each salt was added to a glass vial and 0.5 mL solvent was added and vortexed for 30 sec. If the sample was completely solubilized, it was registered as "soluble". If the sample was not solubilized, an additional 0.5 mL solvent was added and vortexed for 30 sec. If the sample was then completely solubilized, it was still registered as "soluble". If the sample was still not solubilized, another 2 mL solvent (total 3 mL) was added and vortexed for 30 sec. If the sample dissolved in 3 mL, it was registered as "limited solubility". However, if the sample did not dissolve in 3 mL of solvent, then it was registered as "not soluble". The results of the solubility tests for the synthesized ILs in the solvents chosen based on the Snyder's polarity index[3] are listed in Table S1.

**Table S1.** Solubility of Various $[P_{66614}]^+$-based ILs.

| Solvent | P.I.[a] | $[P_{66614}]Cl$ | $[P_{66614}][O^tBu]$ | $[P_{66614}][OH]$ | $[P_{66614}][OH]\cdot 4MeOH$ |
|---|---|---|---|---|---|
| DI water | 9.0 | -[c] | - | - | - |
| Methanol | 6.6 | +[d] | - | + | + |
| DMSO | 6.5 | + | - | - | ±[e] |
| Acetonitrile | 6.2 | + | - | - | + |
| Acetone | 5.1 | + | - | ± | + |
| 1,4-Dioxane | 4.8 | + | - | ± | + |
| IPA[b] | 4.3 | + | - | + | + |
| Ethyl Acetate | 4.3 | + | - | ± | + |
| Chloroform | 4.1 | + | - | + | + |
| Toluene | 2.3 | + | + | + | + |
| Hexane | 0.0 | + | - | + | ± |

[a]Polarity index. [b]Isopropyl alcohol. [c]-, Insoluble (0.2 g in 3 mL solvent). [d]+, Soluble (0.2 g soluble in 1 mL solvent). [e]±, Partly soluble (0.2 g insoluble in 1 mL but soluble in 3 mL solvent).

**Basic Strength Using Indicators**

The basic strengths of $[P_{66614}]^+$-based ILs were determined using color indicators with different p$K_a$ values.[4] For the strength measurements, 0.1 mmol of base was weighed in a glass vial and 1 mL stock solution of indicators (prepared dissolving 0.2 mg in 1 mL of an ethanolic solution (EtOH:$H_2O$ 1:4)) was added. The changes in the color of the indicator solution to the base depicts the p$K_a$ values for each of the $[P_{66614}]^+$-based ILs (Table S2).

**Table S2.** Determination of Basic Strength of Various $[P_{66614}]^+$-based ILs.

| Indicators | p$K_a$ | EtOH:$H_2O$[a] | $[P_{66614}]Cl$ | $[P_{66614}][O^tBu]$ | $[P_{66614}][OH]$ | $[P_{66614}][OH]\cdot 4MeOH$ |
|---|---|---|---|---|---|---|
| Bromothymol Blue | 7.2 | -[b] | - | +[c] | + | + |
| Phenolphthalein | 9.3 | - | - | + | + | + |
| 2,4-Dinitroaniline | 15.0 | - | - | - | - | + |
| 4-Chloro-2-nitroaniline | 17.2 | - | - | - | - | + |
| 4-Nitroaniline | 18.4 | - | - | - | - | - |
| Diphenylmethane | 35.0 | - | - | - | - | - |
| Cumene | 37.0 | - | - | - | - | - |

[a]1:4 v/v. [b]-, Acid-form. [c]+, Base-form.

**Evaluation of Basic Properties in Cross-Coupling Reactions Using 1,4-Dioxane as Solvent**

***Buchwald-Hartwig Amination Reaction:*** Typically, XPhos Pd G1 (catalyst, 0.01 mmol), and XPhos (additive, 0.1 mmol) were weighed in a vial containing a magnetic stir bar. The vial was covered with parafilm with a hole to allow the flow of gases in and out of the vial (during evacuation in the glove box). The base (1.2 mmol) was added to the reaction vial in the glove box ($N_2$ atmosphere) and the vial was sealed with a Teflon sleeve stopper. The vial containing catalyst, additive, and base was then taken out of the glove box, purged with $N_2$ for 15 min, and 1 mL of dry 1,4-dioxane was added to it using a syringe. Meanwhile, 4-chloroanisole (1 mmol) and aniline (1.2 mmol) were weighed separately and 1 mL of 1,4-dioxane was used to dissolve them. The vial under $N_2$ flow was placed into an oil bath preheated at 100 °C. The 1,4-dioxane solution containing halide and amine was added to the stirring solution of catalyst using a syringe, and an additional 0.5 mL 1,4-dioxane was used to rinse the reagents into the reaction vial. The reaction mixture was allowed to stir for 2 h under $N_2$ flow. After 2 h, the vial reaction mixture was allowed to cool to room temperature. The reaction mixture was then diluted to 5 mL with 1,4-dioxane. $^1$H NMR were recorded in DMSO-$d_6$ for qualitative analysis and the product was quantified as described below. Only bases such as KO*t*Bu and [$P_{66614}$][O*t*Bu] were weighed inside the glove box, all other bases were weighed in open air.

***Suzuki-Miyaura Coupling Reaction:*** Typically, XPhos Pd G1 (catalyst, 0.01 mmol), XPhos (additive, 0.1 mmol), and base (1.2 mmol) were weighed in a vial containing a magnetic stir bar. Then 4-chloroanisole (1 mmol) and phenylboronic acid (1.2 mmol) were added to the reaction vial, followed by the addition of 2 mL 1,4-dioxane. The vial was placed into an oil bath preheated at 80 °C. The reaction mixture was allowed to stir for 6 h. After 6 h, the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with 1,4-dioxane to 5 mL. $^1$H NMR were recorded in DMSO-$d_6$ for qualitative analysis and the product was quantified as described below.

***Product Quantification:*** A known aliquot of the reaction mixtures was diluted with HPLC grade methanol for quantitative analysis by LC-ESI-MS (Maxis Impact Q-TOF, Bruker, East Milton, ON, Canada) using a Luna C18 column (50 × 2 mm, 5 μm) from Phenomenex, Inc. (Torrance, CA, USA) attached to a diode array detector. The column was run at 0.3 mL min$^{-1}$ at 25 °C with 0.1% formic acid in water as mobile phase A and 0.1% formic acid in acetonitrile as mobile phase B using a gradient of 2% B to 100% B over 10 min. The product from the

reaction was quantified based on the absorbance signal (UV absorption at 260 nm and 290 nm for products from BHA and SMC reactions, respectively) using calibration curves, and identified by MS. The calibration curve for product were made using 5 different concentrations in the range of 1 μg/mL – 1 mg/mL on a LC-MS instrument and the peak area obtained because of the UV absorbance for the molecule was plotted against the concentration to obtain $R^2$> 0.999. The calibration curves were made every two months.

**Evaluation of Basic Properties in Cross-Coupling Reactions Using $[P_{66614}][OH]\cdot 4MeOH$ as Base and Solvent**

***Buchwald-Hartwig Amination Reaction:*** Typically, XPhos Pd G1 (catalyst, 0.01 mmol), XPhos (additive, 0.1 mmol), 4-chloroanisole (1 mmol), and aniline (1.2 mmol) were weighed in a vial containing a magnetic stir bar. Finally, IL (1.2 mmol) was added to the reaction vial and the vial was sealed with a Teflon sleeve stopper. The vial under $N_2$ flow was lowered into a preheated oil-bath at 100 °C. The reaction mixture was allowed to stir for 2 h under $N_2$ flow. After 2 h, the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with 1,4-dioxane to 5 mL. $^1$H NMR were recorded in DMSO-$d_6$ for qualitative analysis. The product was quantified and identified by LC-ESI-MS, as described above.

***Suzuki-Miyaura Coupling Reaction:*** Typically, XPhos Pd G1 (catalyst, 0.01 mmol), XPhos (additive, 0.1 mmol), and IL (1.2 mmol) were weighed in a vial containing a magnetic stir bar. Then 4-chloroanisole (1 mmol) and phenylboronic acid (1.2 mmol) were added to the reaction vial. The vial was mounted in a preheated oil-bath at 80 °C. The reaction mixture was allowed to stir for 6 h. After 6 h, the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with 1,4-dioxane to 5 mL. $^1$H NMR were recorded in DMSO-$d_6$ for qualitative analysis. The product was quantified and identified by LC-ESI-MS, as described above.

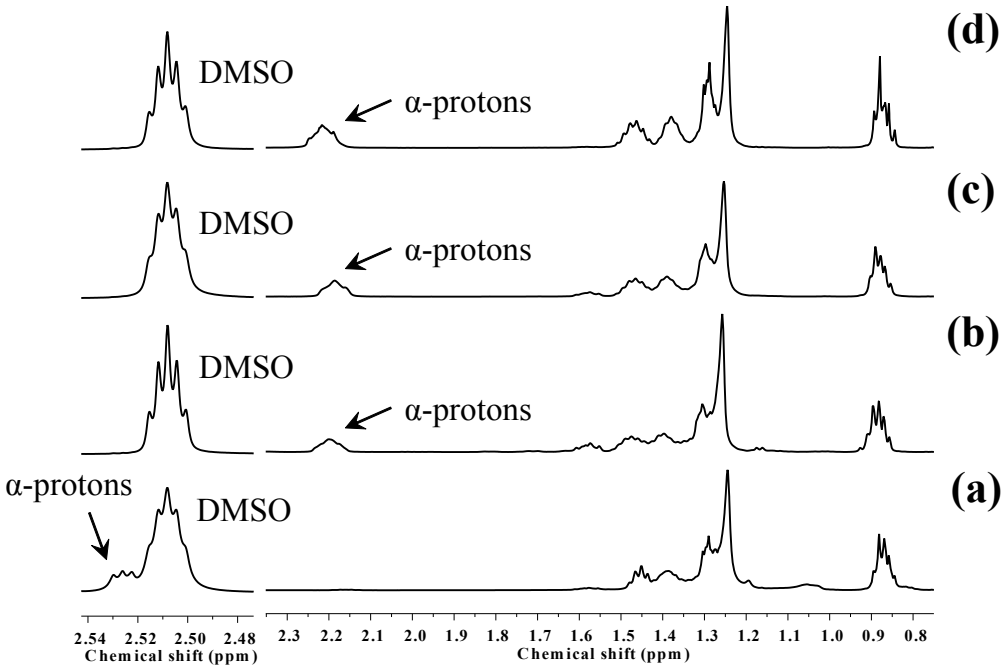


**Figure S5.** $^{1}$H NMR spectra of (a) $[P_{66614}][OH]\cdot 4MeOH$, (b) reaction mixture for Buchwald-Hartwig amination, (c) reaction mixture for Suzuki-Miyaura coupling, and (d) $[P_{66614}]Cl$.

**References**

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4. K. Tanabe, M. Misono, H. Hattori and Y. Ono, Determination of acidic and basic properties on solid surfaces. In *New Solid Acids and Bases*; Elsevier Science: Tokyo, 1989; pp 5-25.