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

Received 00th January 20xx, Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

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To alleviate the problem of solid salt precipitation when using inorganic bases in cross-coupling reactions, basic anions were combined with the trihexyl(tetradecyl)phosphonium ($[P_{66614}]^+$) cation to ensure an ionic liquid byproduct. If the starting base is also an ionic liquid, as is the case for $[P_{66614}][OH]$ ·4MeOH, it can be used as both base and solvent.

Transition metal-catalyzed cross-coupling reactions have been an integral part of our industrialized society since their first appearance in the 1970s, due to the possibility to form C-C or Cheteroatom σ -bonds involving electrophiles (typically halides) and nucleophiles (e.g., amines, olefins, organoborons, etc.).¹ Among these, Suzuki-Miyaura coupling (SMC; C-C coupling) and Buchwald-Hartwig amination (BHA; C-N coupling) reactions have become a ritual in the industrial organic synthesis of natural products. pharmaceuticals, and supra-molecular assemblies, to name a few.¹ All of these cross-coupling reactions require stoichiometric amounts of inorganic or alkali-metal alkoxide bases to afford satisfactory yields;^{2,3} however, the use of inorganic bases results in the formation of solid salts that are either insoluble or have limited solubility in the solvents most suited for these reactions, resulting in precipitation. On an industrial scale, these reactions, when performed under continuous mode, rather than batch mode, can offer significant processing/economic advantages that include energy efficiency, multistep synthesis, scalability, improved thermal and mixing controls, and much more.^{1,4,5,6} However, the generation of insoluble solid salt byproducts is highly incompatible for continuous synthesis, as it will affect the flow rate, increasing the energy consumption, and demanding regular maintenance.

Significant attention has been paid to overcome the formation of insoluble salts during continuous/flow cross-coupling reactions. For example, mixtures of polar protic solvents have been proposed for the dissolution of reagents/products/byproducts.⁷ Acoustic irradiation of microfluidic flow reactors and specialized reactors were designed and employed for the amination of 4-chloroanisole with aniline was attempted earlier to prevent clogging.⁸⁻¹⁰ Still, most of these strategies focus on the solubility of the byproduct salt, while limited efforts have been made to prevent the byproduct from being a solid at all during the coupling reaction. Nevertheless, it should be noted that a soluble base/byproduct will not be an optimal solution to this critical issue as the solubility of a substrate may vary depending on the reaction parameters.

The use of ionic liquids (ILs, organic salts with melting points below 100 °C¹¹) has been extensively reported for catalytic reactions, either as catalysts and/or solvents.^{12,13} In 2003, BASF launched the first industrial process based on ILs, the Biphasic Acid Scavenging utilizing Ionic Liquids (BASIL) process, which uses a molecular organic base to react with acids produced in the reaction (that may decompose the target product) and results in the generation of an IL. Imidazole-based ILs (imidazole either as cation or anion) have also been employed as base in various base-catalyzed organic reactions, leading to undesired transformations.¹⁶ Still, no attempts have been made to design the byproducts in cross-coupling reactions to be room temperature ILs by the use of a suitable cation in the basic salt.

The combination of an IL-forming cation with a basic anion to obtain a basic salt (which does not have to be an IL itself) can avoid the use of conventional inorganic or alkali metal alkoxide bases (e.g., potassium *tert*-butoxide, KOtBu). This approach would allow employment of base with the appropriate basicity and stability, generating a liquid halide salt during the catalytic cycle of coupling reactions (**Scheme 1**).¹ It is important to point out that as long as the byproduct is liquid, its solubility/miscibility in/with the solvent employed will not interfere with continuous processing. It must also be noted that a liquid base is *not essential* just a liquid byproduct, but if the base is also liquid at the reaction temperature, it adds some flexibility and design space.

Selecting the pair of ions that will form the *final* IL with the required properties is the first and crucial step to evaluate these molten salts as bases in catalytic reactions. The choice of the cation here was made based on the following considerations: (a) the halide form (especially the chloride form) of the cation should be liquid, and (b) it should have reasonable thermal stability.

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^{*}Electronic Supplementary Information (ESI) available: Materials and methods, NMRs, TGAs, DSCs, basic strength and solubility data. See DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C7CC09635F Journal Name

Trihexyl(tetradecyl)phosphonium $([P_{66614}]^{\dagger})$ satisfied the above criteria and was thus chosen as the model cation in this study.¹⁷ Anions such as $[OtBu]^{-}$ and hydroxide $([OH]^{-})$ were selected as the counter ions to impart the IL's basic properties.

Pd Catalyst [IL-forming Cation][Basic Anion]

R-X + R-FG [IL-forming Cation][Dask Anton] ➤ R-R' + [IL-forming Cation]X where, X = Cl, Br, or I (liquid) R and R' = alkyl, alkenyl, allyl, or aryl

FG = functional group

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Scheme 1. Reaction scheme demonstrating the formation of a liquid [Cation]X salt after the Pd catalyzed cross-coupling reaction.

The ILs [P₆₆₆₁₄][OH] and [P₆₆₆₁₄][OtBu] were synthesized using [P₆₆₆₁₄]Cl as a cation source via metathesis reactions, with the appropriate potassium salts to make [P₆₆₆₁₄][OH] and [P₆₆₆₁₄][OtBu] (ESI for detailed description of the syntheses). While [P₆₆₆₁₄]Cl is liquid at room temperature, without a documented melting point, and a glass transition temperature of -69.8 °C,¹⁷ both [P₆₆₆₁₄][OH] and [P₆₆₆₁₄][OtBu] are solids, with melting points of ca. 40 °C (ESI). Nuclear magnetic resonance (NMR, ¹H and ¹³C) was used to confirm the synthesis and purity of the [P₆₆₆₁₄]⁺-based ILs (see ESI).

An ion exchange resin was also used as an alternate route in an attempt to simplify the synthesis of $[P_{66614}][OH]$ (see ESI).¹⁸ However, this IL was liquid even after exposing the synthesized product to high vacuum at room temperature for 12 h, indicating differences in the products depending on the synthetic route. Integration of the NMR signals for this product suggested the final formula to be $[P_{66614}][OH]$ ·4MeOH. Thermogravimetric analysis confirmed this formula with a ca. 20% weight loss at 70 °C, which is equivalent to ca. 4 moles of MeOH per mole of [OH]. This compound could only be prepared by ion exchange, even when the metathesis reactions were attempted in methanol (*vide infra*).

The analysis of the ¹H NMR spectra suggests different interactions between the ions of the synthesized ILs, particularly noticeable due to the changes in the chemical shift values of the α protons of $[P_{66614}]^{+}$ (Figure 1). These signals were observed as a multiplet at 2.14-2.28 ppm in [P₆₆₆₁₄]Cl corresponding to 8 protons, while there was an upfield shift to 1.52-1.63 ppm for the ILs synthesized through metathesis ([P_{66614}][OH], and [P_{66614}][OtBu]). This would seem to confirm stronger interactions between the ions in these ILs which is in keeping with their isolation as solids. On the other hand, the ¹H NMR spectrum of [P₆₆₆₁₄][OH]·4MeOH obtained using the anion-exchange resin was different and the signal for the α -protons of the cation had a downfield shift, almost merging with the signals for the lock solvent deuterated dimethyl sulfoxide (DMSO-d₆; Figure 1). The signal corresponding to the methyl group of methanol (MeOH), used as solvent in this synthetic route, was also observed (Figures S1-S2). The solvation of hydroxide by MeOH during anion-exchange through strong charge-assisted hydrogen bond and thereby a decreased (or negligible) interaction with phosphonium ions could explain the downfield shift of the α protons, and also have important implications in the activity of this base as explained later.

The $[P_{66614}][OH]$ synthesized by metathesis was mixed with MeOH and stirred for 24 h in an attempt to obtain $[P_{66614}][OH]$ ·4MeOH, however, the downfield shift for the α -protons was not observed in the compound obtained from the mixing, suggesting that MeOH is only incorporated into the IL during the synthesis using the anion-exchange resin. A similar phenomenon was noted during the synthesis of 1-ethyl-3-methylimidazolium



fluoride hydrofluoride ([C2mim][F]·xHF), where excess of

hydrofluoric acid (HF) could not be removed and indeed the

synthesized compound was found to be [C₂mim][F]·1.6HF·2.1H₂O

based on NMR, IR, elemental analyses, and Karl Fischer titration.

Figure 1. ¹H NMR spectra of (a) $[P_{66614}]CI$, (b) $[P_{66614}][OtBu]$, (c) $[P_{66614}][OH]$, and (d) $[P_{66614}][OH] \cdot 4MeOH$. Shifts in the signal of the α -protons from the $[P_{66614}]^+$ cation are noted (See ESI for full spectra).

The thermal stability of all of the synthesized ILs was much lower than $[P_{66614}]Cl$, with the onset of 5% mass fraction loss temperatures $(T_{5\%onset})$ of 300.6, 163.8, 158.7, and 166.5 °C for $[P_{66614}]Cl$, $[P_{66614}](OtBu]$, $[P_{66614}][OH]$, and $[P_{66614}][OH]$ -4MeOH, respectively (**Figure S3**). A melting point (T_m) was also observed in all cases, $T_m = 38.5$ and $36.8^{\circ}C$ for $[P_{66614}][OtBu]$ and $[P_{66614}][OH]$, respectively. Interestingly, DSC showed that $[P_{66614}][OH]$ -4MeOH converts to $[P_{66614}][OH]$ in the first heating cycle with multiple endothermic and exothermic transitions, after which the DSC thermograms match $[P_{66614}][OH]$ on all subsequent cycles (**Figure 2**). This suggest several conversion steps with the ultimate loss of all methanol in the first heating cycle (**Figure S4**).



Figure 2. DSC plots of $[P_{66614}][OH] \cdot 4MeOH 1^{st}$ cycle (solid line), $[P_{66614}][OH] \cdot 4MeOH 2^{nd}$ cycle (dashed line), $[P_{66614}][OH] 2^{nd}$ cycle (dotted line).

Similar pK_a values for MeOH and water have been reported in the past using conductivity, with the conclusion that MeOH could be a stronger acid than water.²⁰ Based on the pK_a values and acid strength of MeOH and water, the presence of both hydroxide and methoxide in [P₆₆₆₁₄][OH]·4MeOH can be expected as shown in equ. (1). This is important as this could be indicative of the co-existence of hydroxide and methoxide in equilibrium.

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$OH_{(methanolic)}^{-} + MeOH_{(l)} \implies H_2O_{(methanolic)}^{-} + MeO_{(methanolic)}^{-}$ (1)

The basic strength of the ILs was determined using indicators in the pK_a range of 7.2 to 37.0 (see ESI).²¹ The overall order of basic strength was [P₆₆₆₁₄][OH]·4MeOH > [P₆₆₆₁₄][OtBu] ~ [P₆₆₆₁₄][OH] >> [P₆₆₆₁₄][Cl. As indicated by the NMR data, the weakest cation/anion interactions occur for [P₆₆₆₁₄][OH]·4MeOH, which might explain its greater basicity. When the IL [P₆₆₆₁₄][OH] was stirred in MeOH for 30 min, the basic strength of the mixture was not similar to [P₆₆₆₁₄][OH]·4MeOH, highlighting the importance of the anion-exchange resin that probably facilitates the solvation of each hydroxide ion. The dilution of [P₆₆₆₁₄][OH] with weakly acidic MeOH failed to shift the equilibrium in equation (1) to right supposedly due to the stronger interaction of [OH]⁻ anion with [P₆₆₆₁₄]⁺ cation.

Before using the ILs in our catalytic reactions, we tested their solubility in various organic solvents (Snyder polarity index 0-9, from hexane to isopropyl alcohol, to acetonitrile, to DI water).²² As expected, all $[P_{66614}]^{t}$ -based ILs were insoluble in water (see ESI). While $[P_{66614}]CI$ was soluble/miscible in/with all solvents under investigation except water, $[P_{66614}][OtBu]$ was soluble only in toluene. Both $[P_{66614}][OH]$ and $[P_{66614}][OH]$ -4MeOH had similar solubilities in the solvents employed.

To assess the performance of each IL as a base, we used the widely employed cross-coupling reactions such as SMC and BHA (Scheme 2). Generally, chloro-derivatives have low reactivity as compared to bromo- or iodo-derivatives, due to the strength of the C-Cl bond (bond dissociation energies, C-Cl: 96 kcal mol⁻¹; C-Br: 81 kcal mol⁻¹; C-I: 65 kcal mol⁻¹).²³ Nevertheless, the chloroarenes are industrial favorites as substrates for cross-coupling reactions, considering the economy of the process. The reactivity can be improved in conjunction with electron-deficient moieties, whereas chloroarenes are less reactive in the presence of electron-donating groups like methoxy (-OCH₃). 4-chloroanisole (deactivated chloroderivative) was chosen as a model substrate to undergo reactions with aniline and phenylboronic acid for the BHA and SMC reaction, respectively.



Scheme 2. Catalytic reaction scheme of Buchwald-Hartwig amination and Suzuki-Miyaura coupling studied in this report. Inorganic base: KOtBu for BHA and K_2CO_3 for SMC reactions. Reaction conditions: halide: nucleophile: base: catalyst: ligand= 1: 1.2: 1.2: 0.01: 0.1 (molar ratio).

The catalytic tests were carried out using the catalyst XPhos Pd G1 (((2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-amino-ethyl)phenyl)]palladium(II) chloride), in the presence of the additive XPhos (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl).²⁷ The reactivity of chloroarenes was measured relative to the yield of the products achieved with conventional bases; KOtBu for BHA and potassium carbonate (K₂CO₃) for SMC (**Scheme 2** and ESI).²⁴

When the synthesized ILs were used as bases using 1,4-dioxane as solvent, only $[P_{66614}][OH]$ -4MeOH assisted the Pd-catalyzed BHA and SMC reactions, while both $[P_{66614}][OH]$ and $[P_{66614}][OtBu]$ worked poorly (**Figure 3**). The higher reactivity of 4-chloroanisole in the presence of $[P_{66614}][OH]$ -4MeOH can be explained by its higher basic strength.



Figure 3. Effect of $[P_{66614}]^+$ bases vs. inorganic bases on Pd-catalyzed Buchwald-Hartwig amination (black) and Suzuki-Miyaura coupling (gray). Solid bars: 1,4-dioxane as solvent; Crosshatched bars: ILs as both base and solvent; Inorganic base: KOtBu for BHA and K₂CO₃ for SMC. Right: Final reaction mixtures (with magnetic stir bar) for BHA (a) and SMC (b) using $[P_{66614}]$ [OH]-4MeOH as base and dioxane as solvent.

In order to verify the role of MeOH in the enhancement of the product yield, a control experiment with $[P_{66614}][OH]$ as base was performed with externally added MeOH (corresponding to the total amount of MeOH in the catalytic run employing $[P_{66614}][OH] \cdot 4MeOH$ as base). The added MeOH did not affect the reaction yield, again showing that $[P_{66614}][OH] \cdot 4MeOH$ has a unique identity with higher basic strength.

As was hypothesized, no precipitate was observed after the catalytic run for both BHA and SMC reactions using $[P_{66614}][OH]\cdot 4MeOH$ as base (Figure 3, right). The generation of $[P_{66614}]CI$ (confirmed by ¹H NMR, Figure S5), validates the proposed reaction pathway (Scheme 1) and explains why there was no precipitation after the catalytic run, since $[P_{66614}]CI$ is liquid at room temperature.

Due to the liquid nature of [P₆₆₆₁₄][OH]·4MeOH, it can also be used as both base and solvent for cross coupling reactions, perhaps improving the catalytic efficiency of Pd compared to reactions in 1,4-dioxane. In fact, when the IL was used as both solvent and base for the selected model reactions, the obtained yields were comparable with those obtained using inorganic salts as bases in 1,4-dioxane (**Figure 3**). It is well-known that a change of reagent (such as base) in cross-coupling reactions requires drastic modification of reaction coordinates,²⁵ and hence, the influence of other parameters such as temperature, time, or solvent type/volume on reaction rate in the presence of the IL base is subject to ongoing research. It is important to note that we envision an increase in the yields with the optimization of the catalytic reaction parameters.

In the case of BHA, the addition of methanol to the reaction mixture allowed a complete separation of the product (biphasic-solid product and IL/MeOH), which is insoluble in MeOH.

DOI: 10.1039/C7CC09635F

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For the selected model reactions, although no salt precipitation was detected after the reaction using IL as base, the replacement of 1,4-dioxane with the IL resulted in the precipitation of the product in the studied BHA reaction, while in the SMC reaction, no precipitation was observed. Hence, when ILs are proposed to be used as base and solvent, several factors need to be considered, including not only basicity, but also the solubility of the reagents and product(s) in the selected IL. Due to the possibility of tuning the IL, other cations can be selected to avoid precipitation of products and reagents, increasing the potent uses of the proposed strategy.

In summary, basic $[P_{66614}]^{\dagger}$ salts were synthesized and employed as the base in cross-coupling reactions, to yield IL byproducts, overcoming the problem of precipitation of solid salts in these reactions. Our evaluation showed the novel IL base, $[P_{66614}][OH] \cdot 4MeOH$, to have the highest basic strength among all synthesized basic salts, and this salt was the most efficient in the Pd-catalyzed BHA and SMC reactions. No precipitate was observed after the catalytic run due to the generation of the room temperature IL $[P_{66614}][CI.$ In addition, since $[P_{66614}]CI$ was used in the synthesis of the active base ($[P_{66614}][OH] \cdot 4MeOH$) in an ion-exchange process, an easy recycling of the generated IL is anticipated simply by elution with methanol on an ion exchange column in a continuous manufacturing mode.²⁶

An added benefit of the basic salt being an IL itself, was demonstrated when [P₆₆₆₁₄][OH]-4MeOH employed as both base and solvent, enhanced the catalytic reaction rates for BHA and SMC reactions over those obtained using 1,4-dioxane as solvent. Depending on the synthesized products, we envision more design flexibility if an IL is used as both base and solvent, allowing one to improve the solubility of products and reagents or to selectively precipitate the desired product from the reaction mixture by choice of ions. This work suggests design rules for ILs suitable for many other reactions that have similar issues of salt (or byproduct) precipitation during continuous/flow reactions.

We thank the Novartis-Massachusetts Institute of Technology (MIT) Center for Continuous Manufacturing (CCM) and Novartis International AG for financial support. This research was undertaken, in part, thanks to funding from the Canada Excellence Research Chairs Program.

Conflicts of interest

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There are no conflicts to declare.

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