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# A Pronounced Anionic Effect in the Pd-Catalyzed Buchwald–Hartwig Amination Reaction Revealed in Phosphonium Salt Ionic Liquids

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The Pd-mediated Buchwald–Hartwig amination reaction of aryl halides in a phosphonium salt ionic liquid consisting of a trihexyl(tetradecyl)phosphonium cation with a range of anions has been investigated. A pronounced anionic effect was uncovered with the reaction proceeding readily with weakly nucleophilic diarylamines only in the presence of noncoordinating anions. A mechanism is postulated to explain these results and it involves a rate-limiting ligand exchange step that proceeds through a dissociative pathway.



## Introduction

The use of transition metal complexes to catalyze cross-coupling reactions between aryl and vinyl halides or their equivalents with amines has become a standard tool for the construction of complex amines.[1–5] Classic protocols utilizing copper salts (Ullmann reaction)[2] suffer from many drawbacks in terms of reactivity. These methods require high loadings of copper catalyst, high reaction temperatures and/or times, the use of excess amine and the reactions often result in the formation of side products. Tedious, expensive and wasteful product purification and the disposal of metal-containing waste are further environmental concerns of the classic Ullmann reaction, which accentuates the need for the development of "green" alternatives for obtaining these valuable intermediates and products. On the basis of initial reports by Buchwald and Hartwig,[3] a plethora of methods utilizing Pd complexes (now known as Buchwald–Hartwig amination) coupled with a variety of electron rich, bulky ligands have appeared over the last few years.[4] A major impetus for these developments is the potential utility of efficient amination protocols in the synthesis of dyes, high-value pharmaceuticals[5] and functionalized triarylamines, which are the key components in a variety of materials including organic photoconductors, light-emitting diodes and photovoltaic cells.[6] An expanding variety of arylamines have now been prepared under mild conditions and in a controlled, chemoselective manner by utilizing this methodology. Many factors contributing to the success of this reaction have been investigated including solvent effects,[7] where the superiority of noncoordinating solvents was demonstrated. To the best of our knowledge, no reports specifically on anionic effects have been reported on the production of arylamines under Buchwald–Hartwig conditions.

## Results and Discussion

Recently, we have been interested in developing applications of Pd-catalyzed[8] and other[9] cross-coupling reactions in phosphonium salt ionic liquids (ILs). Phosphonium-based ILs are very thermally stable,[10] nonvolatile, economical and available on an industrial scale. Most IL research has been conducted in nitrogen-based solvents, especially alkyl imidazolium salts,[11] whereas the phosphonium analogues represent a largely unexplored area. We have reported the efficient Suzuki cross-coupling of aryl halides, including chlorides, with a variety of boronic acids in the IL trihexyl(tetradecyl)phosphonium chloride. Efficient recovery and recycling of the palladium catalysts was demonstrated,[8a] and this work has been extended to Suzuki and other Pd-mediated reactions employing an organic solvent nanofiltration technology.[12] In addition to the "green" potential of these processes, an interesting feature when utilizing these IL solvents is the tunability of the reaction that is available through altering the nature of either the anion or phosphonium cation. For example, trihexyl(tetradecyl)-phosphonium bis(trifluoromethylsulfonyl)imide (bistriflimide) IL proved to be the optimal choice in a series of alklyation reactions investigated,[9a,13] whereas with this same cation, the chloride IL proved optimal in Suzuki[8a] and Heck[8b] cross-coupling reactions, and finally, the decanoate salt was optimal in the catalysis of carbonyl addition

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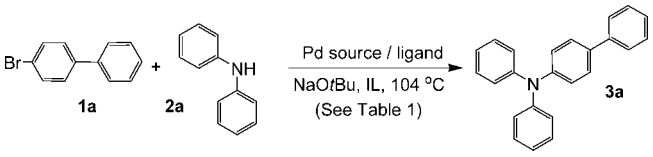
reactions.[9b] As an extension of this work, we recently investigated a Pd-mediated Buchwald–Hartwig amination reaction of an aryl bromide in trihexyl(tetradecyl)phosphonium chloride and were surprised that little cross-coupling took place (Scheme 1).




Scheme 1. Screening Pd sources and ligand in trihexyl(tetradecyl)-phosphonium bistriflimide IL.

This was surprising because this same substrate, under otherwise similar conditions, readily enters into Suzuki cross-coupling reactions with the same Pd source [$Pd_2(dba)_3 \cdot CHCl_3$], the only difference being the nature of the nucleophile (amine versus boronic acid). This negative result prompted us to further explore the reaction parameters in order to gain a deeper insight into this dichotomous observation. Prior to this work, Pd-mediated amination[14a] and direct nucleophilic amination of activated aryl halides[14b] was reported in imidazolium ionic liquids, both cases utilize tetrafluoroborate or hexafluorophosphate counteranions. In this paper, we report the use of phosphonium-based ILs in Pd-mediated Buchwald–Hartwig-type amination reactions and uncover a pronounced anionic effect and discuss its mechanistic implications.

The target compound central to our investigation was biphenyl-substituted triarylamine **3a**, Scheme 1. The most direct route for its synthesis and structural analogues would be from 4-bromobiphenyl (**1a**) and a diphenylamine such as **2a** by using a Buchwald–Hartwig amination protocol.[6] The cross-coupling shown (Scheme 1) did not proceed significantly in trihexyl(tetradecyl)phosphonium chloride IL; however, we quickly determined that it proceeded rapidly in the bistriflimide analogue, which allowed complete conversion of the aryl bromide. The reaction independently requires the addition of ligand and base. We screened two $Pd^0$ sources and several ligands (Table 1) in this IL solvent and determined that the source of the active palladium catalysts was not crucial, although the combination of $Pd_2dba_3 \cdot CHCl_3$ with the tertiary phosphane 1-isobutyl-2,2,6,6-tetramethylphosphorinane proved optimal. We have recently found this ligand to be valuable in various Pd-mediated cross-coupling reactions, including amination reactions conducted in toluene solvent.[15] Further experiments on the nature of the anionic effect were carried out with this optimal catalyst–precursor combination.

The cross-coupling reaction was screened in nine different trihexyl(tetradecyl)phosphonium ILs by varying the electronic and, to some extent, the steric nature of the anion; the results are summarized in Table 2 (Scheme 2). The superiority of the bistriflimide derivative is striking; this reaction went to completion within two hours, whereas even other partly successful anions, decanoate and tetrafluoroborate, provided only 57 to 59% conversion over 24 h under otherwise identical conditions. The saccharide (imide) derivative was also successful but reacted slower to give 90% conversion over a 24 h reaction period. The inactivity of the chloride and bromide derivatives is also startling, particularly in view of the success of these media in promoting other Pd-mediated cross-coupling reactions.[8a,8b] The Buchwald–Hartwig amination reaction in tetradecyl(trihexyl)phosphonium bistriflimide was also successfully conducted by coupling 4-methoxyaniline (**2b**) (Scheme 3) with bromobenzene derivatives **1b**–**1d** (Table 3). The reaction appears to be general and indicates that oxidative addition of the catalyst to both electron-rich and electron-deficient halides proceeds without difficulty.

In general, the results in Table 2 show that nucleophilic "coordinating" counteranions are detrimental to the success of the amination reaction whereas diffuse, weakly or noncoordinating anions, particularly the bistriflimide and saccharide derivatives, are superior. This result is in agreement with the solvent effect study recently reported in which donor solvents were seen to be an inferior media.[7] It appears that the weakly nucleophilic nature of the diarylamine employed in the present study inhibits its participation in the Pd-mediated catalytic cycle where coordinating anions and/or solvent are present. These results contrast the success of the chloride-containing IL in the Suzuki cross-coupling reaction.[8a] It seems unlikely that a different Pd-catalyst is operative in the chloride-containing IL during the Suzuki process given the similarity of the reaction conditions. The above results and the generality of the amination reaction to variously substituted aryl halides (Table 3) indicate that there is no problem with the oxidative addition step in either catalytic cycle and that the explanation for the dichotomy rests upon the nature of the ligand exchange step involving the weakly nucleophilic diarylamine (vide infra).

Table 1. Screening different palladium sources and ligands in bistriflimide IL.

| Entry | Palladium source | Ligand | Temperature [°C] | Time [h] | Conversion[a] [%] |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | tri(*tert*-butyl)phosphane | 104 | 15 | 89 |
| 2 | $Pd_2(dba)_3$ | isobutylphosphorinane | 104 | 2 | 98 |
| 3 | $Pd_2(dba)_3$ | tri(*o*-tolyl)phosphane | 104 | 2 | 71 |
| 4 | $Pd(OAc)_2$[b] | tri(*tert*-butyl)phosphane | 104 | 2 | 90 |
| 5 | $Pd(OAc)_2$ | isobutylphosphorinane | 104 | 15 | 36 |
| 6 | $Pd(OAc)_2$ | tri(*o*-tolyl)phosphane | 104 | 15 | 20 |

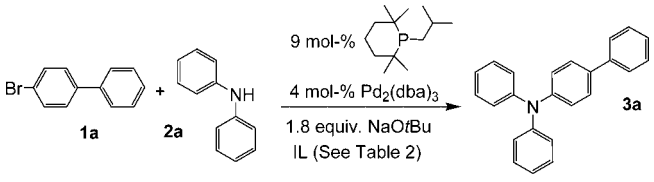
[a] Conversion determined by HPLC analysis. [b] 5 mol-% of palladium catalyst used.

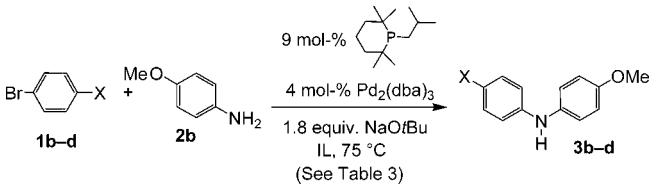
Table 2. Phosphonium-based ionic liquid screen in a standard amination reaction.

| Entry | Ionic liquid | Overnight conversion[a] [%] | Isolated yield [%] |
|---|---|---|---|
| 1 | trihexyl(tetradecyl)phosphonium chloride | 1 | NA |
| 2 | trihexyl(tetradecyl)phosphonium bromide | 2 | NA |
| 3[b] | trihexyl(tetradecyl)phosphonium dicyanamide | 2 | NA |
| 4 | trihexyl(tetradecyl)phosphonium decanoate | 57 | 42 |
| 5 | trihexyl(tetradecyl)phosphonium tosylate | 2 | NA |
| 6 | trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)imide | 98[b] | 73 |
| 7 | trihexyl(tetradecyl)phosphonium tetrafluoroborate | 59 | 35 |
| 8 | trihexyl(tetradecyl)phosphonium dibutylphosphate | 15 | 9 |
| 9 | trihexyl(tetradecyl)phosphonium saccharide | 90 | 65 |

[a] Conversion determined by HPLC analysis. [b] This reaction was complete in 2 h.




Scheme 2.

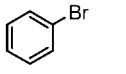
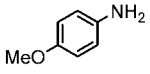
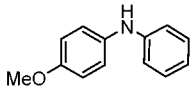
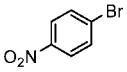
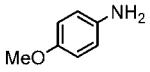
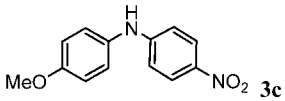
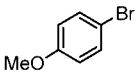
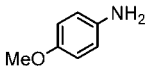
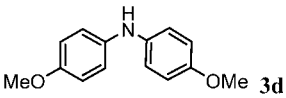



Scheme 3.

Having uncovered the anionic effect in the phosphonium salt ILs, we probed the effect in a typical organic solvent in order to ascertain if this effect is general or just a manifestation of the overall polar or atypical nature of the reaction medium. Further evidence for the general nature of the anionic effect described above was gained from the following reactions. The cross-coupling reaction between 4-bromobiphenyl (**1a**; 1 equiv.) and diphenylamine (**2a**, 1.05 equiv.) also proceeded smoothly in toluene as solvent with the same catalyst, ligand and base combination as shown in Scheme 1. The addition of trihexyl(tetradecyl)phosphonium bistriflimide in various proportions ranging from 1.0 to 5.0 equiv. (relative to 4-bromobiphenyl) to the amination reaction in toluene had no effect on the reaction, with 98% conversion being observed in the latter case. In contrast, the addition of trihexyl(tetradecyl)phosphonium chloride poisoned the operative catalytic cycle in the cross-coupling reaction in toluene. Although 1.0 equiv. of the chloride IL was tolerated, the reaction did not proceed at all in toluene when 5.0 equiv. of this soluble chloride were added. These results correlate precisely with the activity observed in the cross-coupling reaction as described purely in the IL solvent, which confirms the generality of the anionic effect.

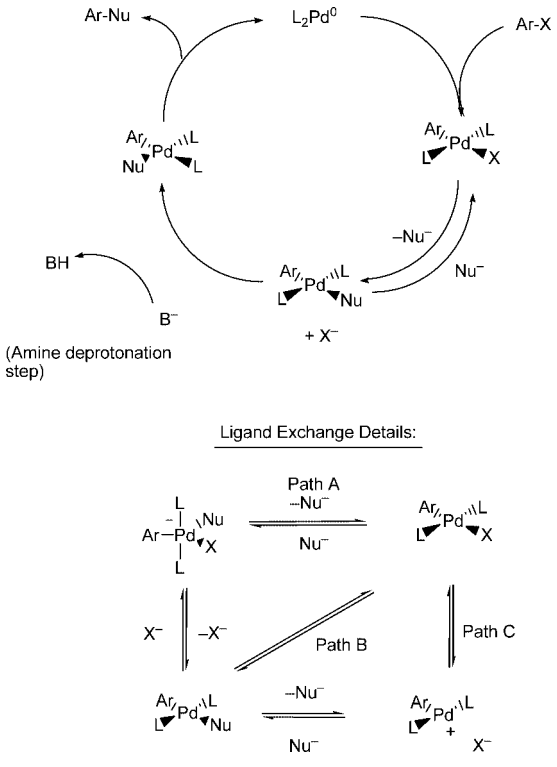
Extensive work has been carried out on the effects of halides and other coordinating anions in palladium-mediated cross-coupling reactions. The work of Amatore, Jutand et al.[16a] indicates that in the presence of such anions an anionic complex of type $L_2PdX^-$ is formed and that this is an active species in the oxidative addition to the aryl halide. At least two catalytic cycles are now generally accepted for such a cross-coupling reaction in the absence or presence of added halide or other coordinating species.[16b] In contrast to the above catalytic cycles, cases are known where added chloride retards the rate of a Pd-mediated cross-coupling reaction,[17] alters the regioselectivity in the case of a Heck reaction[18] or may promote the formation of complexes of type $LPdX^-$ that undergo rapid oxidative addition.[19] In addition, excess salt can modify the process by simply increasing the polarity of the medium. These catalytic cycles also present an overall dichotomy; whereas added halide may expedite the initial steps of the cycle through the intermediacy of $L_2PdX^-$ and rapid oxidative addition to the Ar–X bond, a high concentration of halide is expected to hinder

Table 3. Cross-coupling of 4-methoxyaniline with aryl bromides.

| Entry | Aryl halide | Aniline | Product | Time [h] | Isolated yield [%] |
|---|---|---|---|---|---|
| 1 |  |  |  **3b** | 24 | 72 |
| 2 |  |  |  **3c** | 24 | 75 |
| 3 |  |  |  **3d** | 24 | 75 |

subsequent ligand exchange steps that involve halide dissociation. Since halide anions are released during many cross-coupling reactions, oxidative addition is expected to accelerate, while ligand exchange is expected to become self-poisoning to the cycle as the reaction proceeds. The contributing effect of anions on a given catalytic cycle is therefore far from clear-cut and must depend on the nature of the active catalyst, the medium and intimate details of the contributing steps. In the present case, the bistriflimide IL is considered to be a dipolar, halide-free medium. Rapid cross-coupling takes place with a weakly nucleophilic diarylamine. When this reaction is performed in toluene, 5.0 equiv. of a soluble chloride are enough to poison the catalytic cycle with this amine under conditions where stronger nucleophiles like arylboronic acids readily participate. The most likely explanation involves the nature of the ligand-exchange step, the details of which are outlined in Scheme 4. In principle, this may take place through either an associative (Path A), interchange (Path B) or dissociative (Path C) mechanism.[20] In the case of the bistriflimide IL, the polar medium, absence of halide and excess of noncoordinating anion are likely to promote the ionization of the halide from the oxidative addition intermediate to yield a cationic $L_2PdAr^+$ complex.[21] This complex can then combine with the weakly nucleophilic diarylamine, which provides the next intermediate that undergoes N-deprotonation[22] and finally reductive elimination to complete the cycle.




Scheme 4. Proposed catalytic cycle and dissociative ligand exchange (Path C) with weak nucleophiles in noncoordinating media.

The presence of excess halide or other coordinating anion in the reaction conducted in the IL or toluene is expected to hinder this ionization step (Path C) in accord with Le Chatelier's principle and thus hinder cross-coupling with weak nucleophiles. In contrast, a strong nucleophile, such as an arylboronic acid/base combination, could allow ligand exchange (or transmetallation) by a nucleophilically assisted process through either association to form an anionic palladium intermediate or directly through an interchange pathway. A modification of the "textbook" catalytic cycle for halide-free cross-coupling taking into account the details of the ligand exchange is presented in Scheme 4. This process also offers a satisfactory explanation for the successful Suzuki cross-coupling reactions reported in the chloride-containing IL and hence Scheme 4 may describe a unified view of Pd-mediated cross-coupling reactions in phosphonium salt ILs; the differences is accounted for by the nature of the ligand exchange processes available and competing strong or weak nucleophiles present. While the Suzuki cross-coupling conducted in the chloride IL could take place via the involvement of the anionic complex ($L_2PdCl^-$), the lack of coordinating solvent and high chloride ion concentration are expected to retard subsequent ligand exchange processes, which raises doubt that such a cycle is operative.

Taken together, the overall results of the amination reaction conducted in phosphonium salt ILs and toluene with the addition of soluble anions show that the general anionic effect uncovered in our investigations in IL media are also applicable to typical Buchwald–Hartwig amination reactions conducted in a standard solvent such as toluene. In retrospect, the use of the phosphonium salt IL media as the solvent coupled with either coordinating or noncoordinating anions proved to be an ideal media in which to isolate, uncover and probe the anionic effect in this cross-coupling reaction. The use of a media consisting of a diffuse phosphonium cation coupled to anions varying from Lewis-basic to noncoordinating has provided insight into the nature of the Buchwald–Hartwig amination cycle. The anionic effects indicate ionization in noncoordinating media and the intervention of a cationic palladium intermediate with the weakly nucleophilic amine. Further investigations into the nature of the active catalyst described in the bistriflimide IL and its oxidative addition product, as well as the synthesis of a variety of triarylamines by the cross-coupling of weakly nucleophilic diarylamines utilizing this process, is under investigation in our laboratories.

## Experimental Section

**General Information**: Reactions were carried out under an argon atmosphere in oven-dried glassware. All ionic liquids used were obtained from Cytec Canada Inc., Niagara Falls, Ontario. Ionic liquids were degassed under high vacuum for at least one hour immediately prior to use. All other solids were dried under high vacuum. Toluene was distilled from sodium metal with benzophenone indicator. CIMS were obtained with a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (CI) were performed with a Micromass Q-Tof Ultima spectrometer. $^1H$ and $^{13}C$ NMR spectra

were recorded with a Bruker 500 or AV 700 spectrometer with TMS as the internal standard. Chemical shifts are reported in ppm downfield of TMS.

**General Procedure for Table 2**: To a vial containing degassed trihexyl(tetradecyl)phosphonium bis(trifluoromethylsulfonyl)imide (1.00 mL), 4-bromobiphenyl (100 mg, 0.44 mmol), sodium *tert*-butoxide (77.5 mg, 0.79 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (18.46 mg, 4 mol-%), and 2,2,6,6-tetramethyl-1-isobutylphosphorinane ligand $HBF_4$ salt (12.2 mg, 9 mol-%) were sequentially added, followed by the addition of diphenylamine (80 mg, 0.47 mmol) under an argon atmosphere. The vial was capped and heated at either 75 or 104 °C for the duration specified. Reactions were terminated when TLC or HPLC indicated full consumption of the bromoarene. The reaction mixture was cooled to room temperature. The product was isolated by using a hexane/water protocol. This results in partitioning of the central ionic liquid phase between the lower water and upper hexane layers with the palladium complex remaining in the ionic liquid layer. The combined hexane fractions were dried with $Na_2SO_4$, the solvent was removed under reduced pressure and the product was isolated from a silica column (hexane) to give the desired product in 73% yield.

***N*-Biphenyl-*N*-diphenylamine (3a):** The general procedure was followed throughout Table 2 with the various ionic liquids at 104 °C. White solid. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.57 (d, $J$ = 7.5 Hz, 2 H), 7.48 (d, $J$ = 8.5 Hz, 2 H), 7.41 (t, $J$ = 7.6 Hz, 2 H), 7.28 (m, 6 H), 7.14 (d, $J$ = 8.4 Hz, 5 H), 7.03 (t, $J$ = 7.4 Hz, 2 H) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 147.7, 147.1, 140.6, 135.1, 129.2 (4 C), 128.7 (2 C), 127.7 (2 C), 126.7 (2 C), 126.6 (2 C), 124.4 (4 C), 123.9 (2 C), 122.9 (2 C) ppm. EIMS (70 eV): *m*/*z* (%) = 321 $[M]^+$ (100), 243 (15), 167 (10), 77 (10), 43 (10). HRMS (EI): calcd. for $C_{24}H_{19}N$ 321.1517; found 321.1508.

***N*-(4-Methoxyphenyl)-*N*-phenylamine (3b):** The general procedure was followed, and the reaction was heated at 75 °C (Table 3, Entry 1). Yellow solid. M.p. 103–104 °C, Ref.[23] 104–105 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.26 (t, $J$ = 8.4, 7.5 Hz, 2 H), 7.12 (d, $J$ = 8.7 Hz, 2 H), 6.86 (m, 5 H), 5.56 (br. s, 1 H), 3.84 (s, 3 H) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 155.3, 145.1, 135.7, 129.2 (2 C), 122.2 (2 C), 119.5 (2 C), 115.6 (2 C), 114.6, 55.5 ppm. CIMS (70 eV): *m*/*z* (%) = 199 $[M]^+$ (50), 184 (40), 105 (100). HRMS (CI): calcd. for $C_{13}H_{13}NO$ 199.0997; found 199.0995.

***N*-(4-Methoxyphenyl)-*N*-(4-nitrophenyl)amine (3c):** The general procedure was followed, and the reaction was heated at 75 °C (Table 3, Entry 2). Orange solid. M.p. 152–153 °C, Ref.[24] 152–152.5 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.10 (d, $J$ = 9.2 Hz, 2 H), 7.18 (d, $J$ = 8.9 Hz, 2 H), 6.96 (d, $J$ = 8.9 Hz, 2 H), 6.78 (d, $J$ = 9.2 Hz, 2 H), 6.15 (s, 1 H), 3.85 (s, 3 H) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 157.6, 151.9, 139.2, 132.2, 126.5 (2 C), 125.6 (2 C), 115.1 (2 C), 112.6 (2 C), 55.7 ppm. CIMS (70 eV): *m*/*z* (%) = 244 $[M]^+$ (35), 214 (100), 199 (60). HRMS (CI): calcd. for $C_{13}H_{12}N_2O_3$ 244.0848; found 244.0854.

***N,N*-Bis(4-methoxyphenyl)amine (3d):** The general procedure was followed, and the reaction was heated at 75 °C (Table 3, Entry 3). Pale yellow solid. M.p. 102–103 °C, Ref.[24] 99.5–101.5 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 6.97 (d, $J$ = 8.9 Hz, 4 H), 6.85 (d, $J$ = 9.0 Hz, 4 H), 5.32 (s, 1 H), 3.79 (s, 6 H) ppm. $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ = 154.4 (2 C), 138.1 (2 C), 119.7 (4 C), 114.9 (4 C), 55.8 (2 C) ppm. CIMS (70 eV): *m*/*z* (%) = 229 $[M]^+$ (100), 214 (90), 199 (10). HRMS (CI): calcd. for $C_{14}H_{15}NO_2$ 229.1103; found 229.1102.

**Toluene, Ionic Liquid Doping Experiments:** Trihexyl(tetradecyl)phosphonium chloride (1 equiv.): To a vial containing degassed trihexyl(tetradecyl)phosphonium chloride (22 mg, 1.0 equiv.) and dry toluene (3.0 mL), 4-bromobiphenyl (10 mg, 1 equiv.), sodium *tert*-butoxide (7.7 mg, 1.8 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mg, 4 mol-%), 2,2,6,6-tetramethyl-1-isobutylphosphorinane ligand $HBF_4$ salt (1.3 mg, 9 mol-%) and diphenylamine (8 mg, 1.05 equiv.) were sequentially added under an argon atmosphere. The vial was capped and heated at 70 °C for 16 h at which time analysis (TLC or HPLC) indicated the absence of 4-bromobiphenyl (limiting reagent) and complete conversion to the triarylamine.

**Trihexyl(tetradecyl)phosphonium Chloride (5 equiv.):** To a vial containing degassed trihexyl(tetradecyl)phosphonium chloride (115 mg, 5 equiv.) and dry toluene (3.0 mL), 4-bromobiphenyl (10 mg, 1 equiv.), sodium *tert*-butoxide (7.7 mg, 1.8 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mg, 4 mol-%), 2,2,6,6-tetramethyl-1-isobutylphosphorinane ligand $HBF_4$ salt (1.3 mg, 9 mol-%) and diphenylamine (8 mg, 1.05 equiv.) were sequentially added under an argon atmosphere. The vial was capped and heated at 70 °C for 16 h at which time analysis (HPLC or TLC) indicated that only starting materials were present.

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