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Palladium-Catalyzed Amination of Aryl Chlorides and Bromides with Ammonium Salts

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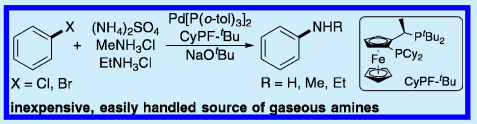
Supporting Information

ABSTRACT: We report the palladium-catalyzed coupling of aryl halides with ammonia and gaseous amines as their ammonium salts. The coupling of aryl chlorides and *ortho*-substituted aryl bromides with ammonium sulfate forms anilines with higher selectivity for the primary arylamine over the diarylamine than couplings with ammonia in dioxane. The resting state for the reactions of aryl chlorides is different from the resting state for the reactions of aryl bromides, and this change in resting states is proposed to account for a difference in selectivities for reactions of the two haloarenes.



The transition-metal-catalyzed amination of aryl electrophiles has become a useful method to construct arylamines. However, the coupling of ammonia is less developed than the coupling of alkylamines, and several properties of ammonia make the coupling of this reagent more challenging than the coupling of alkylamines. Ammonia is a good σ-donor and binds more strongly to metals than do alkylamines, and this binding can lead to catalyst deactivation. In addition, the moderate basicity and low acidity of ammonia disfavor proton exchanges to or from this reagent. Finally, the aniline formed in the reaction of an aryl halide with ammonia is also a reagent for coupling with aryl halides. Therefore, the product of the coupling of ammonia competes with ammonia as the nucleophile, giving rise to mixtures of mono- and diarylamines.[1−3]

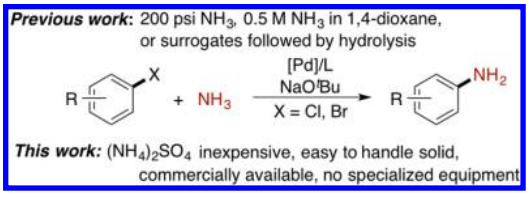
In addition to these chemical properties, the physical properties of ammonia make it a challenging coupling partner to use in palladium-catalyzed chemistry. Because it is a gas at ambient temperature and pressure, reactions performed with anhydrous ammonia often require high-pressure reactors.

One approach to avoid the use of gaseous ammonia and the formation of diarylamine side products is to conduct reactions with ammonia surrogates, such as benzophenone imine,[4,5] amides,[6,7] bis(trimethylsilyl)amide,[8] or carbamates.[9] However, these ammonia surrogates are much more expensive than ammonia, and these methods require a subsequent hydrolysis or hydrogenolysis step to obtain the aniline.

A few reports have been published on the amination of aryl halides with ammonia that occur with high selectivity for the primary arylamine over the diarylamine side product. In these reactions, either ammonia is charged into the reaction vessel directly as a gas[10] or the reaction is conducted with a commercially available solution of 0.5 M ammonia in dioxane.[11−16] Although a convenient alternative to charging reaction vessels with ammonia, the solution is costly and the concentration of the commercial ammonia solution decreases over time. Ammonium hydroxide and ammonium chloride have been used as alternatives to ammonia in copper-catalyzed coupling reactions.[17] However, the scope of electrophiles that undergo these coupling reactions is limited to aryl iodides and activated aryl bromides. The palladium-catalyzed coupling of aryl halides with ammonium hydroxide or ammonium salts has not been reported.

The combination of an inexpensive ammonium salt and base would be an attractive alternative to anhydrous, gaseous ammonia or solutions of ammonia (Scheme 1). Because ammonium salts are only marginally soluble in organic solvents, we considered that the concentration of ammonia could be fine-tuned by the choice of the counterion of the ammonium salt and the base.

Scheme 1. Methods for Palladium-Catalyzed Amination of Aryl Halides with Ammonia



We envisioned multiple benefits to a protocol for the amination of aryl halides involving ammonium salts. A lower concentration of ammonia could reduce catalyst poisoning, leading to lower required loadings of the catalyst. In addition, the low concentration of ammonia at any given time would minimize the safety hazard of heating a sealed vessel containing the reaction. Considering the many benefits of ammonium salts as precursors to ammonia, and to volatile amines, in palladium-catalyzed amination reactions, we sought to develop conditions to conduct palladium-catalyzed amination reactions with ammonium salts.

We report the coupling of ammonium sulfate in the presence of a base to form monoarylamines with selectivities equal to or greater than those from reactions of anhydrous, gaseous ammonia or solutions of ammonia. Moreover, we show that this approach can be extended to the coupling of methyl and ethylamine, which are gases at room temperature and have rarely been used in palladium-catalyzed cross coupling.

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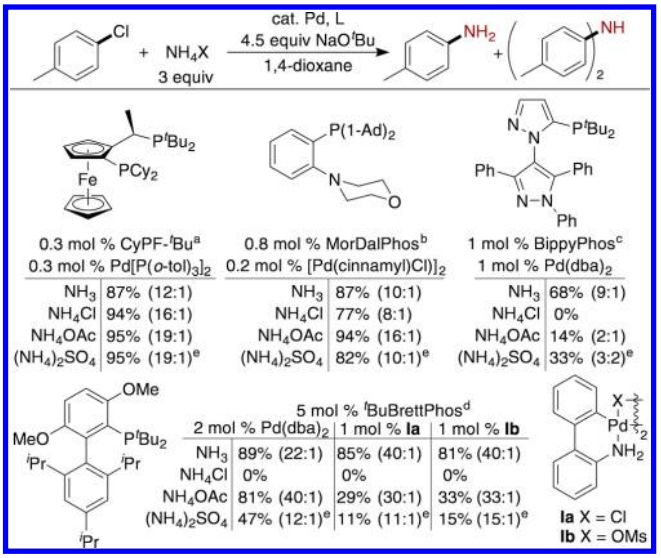
To develop the coupling of ammonium salts, we investigated the reaction of *p*-chlorotoluene with ammonium salts in the presence of several catalysts previously reported for the arylation of ammonia. Ammonia is not a good reductant of Pd(II) precursors, such as $Pd(OAc)_2$ and $PdCl_2$. Therefore, palladium precursors for the coupling of ammonia are typically limited to $Pd(dba)_2$ or $Pd[P(o\text{-tol})_3]_2$, which are air-stable Pd(0) precursors,[18] palladacycles such as **Ia,b**, or allyl complexes (such as $[Pd(cinnamyl)Cl]_2$, or $[Pd(allyl)Cl]_2$) that can be activated under the reaction conditions. For each catalyst, various ammonium salts were examined. The yields of $ArNH_2$ and selectivity ($ArNH_2$:Ar_2NH) with three ammonium salts are shown in comparison to ammonia in dioxane in Scheme 2.

Scheme 2. Evaluation of Ammonium Salts and Palladium Catalysts for the Amination of Aryl Chlorides[a]



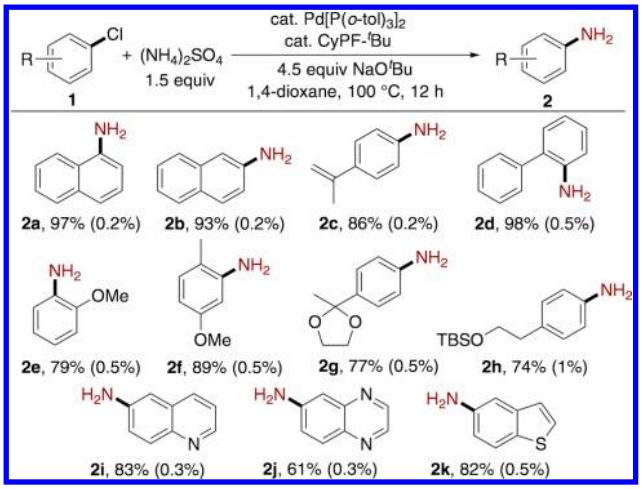
[a]Yields ($ArNH_2$) and selectivities ($ArNH_2$:Ar_2NH) determined by GC analysis using dodecane as an internal standard: (a) 100 °C, 12 h; (b) 110 °C, 4 h; (c) 100 °C, 25 h; (d) 80 °C, 5 h; (e) $(NH_4)_2SO_4$ (1.5 equiv).

The protocols were adapted from those previously reported.[11,13,14,16] The performance of each salt differed with each catalyst system. Ammonium acetate and ammonium sulfate were suitable salts with each catalyst system, and high yields and selectivities were obtained in reactions catalyzed by Pd and ^{t}BuBrettPhos,[13] MorDalPhos,[14] and Josiphos ligand CyPF-^{t}Bu.[11] Reactions catalyzed by Pd and BippyPhos[16,19] either did not form any desired product or formed *p*-toluidine in low yields. Reactions with several ammonium salts catalyzed by $Pd[P(o\text{-tol})_3]_2$ and the Josiphos ligand containing one dicyclohexylphosphino and one di-*tert*-butylphosphino group occurred in high yields and required the lowest catalyst loadings of the systems we studied for this transformation.[11]

These yields and selectivities demonstrate the benefit of maintaining a low effective concentration of ammonia.[20] The concentration of ammonia appears to be affected by the composition of the ammonium salt. Ammonium sulfate is crystalline. Reactions conducted with finely ground ammonium sulfate occurred with lower selectivity (12:1) than those conducted with the salt used as received (20:1).

Results from the reaction of ammonium sulfate with a series of aryl chlorides catalyzed by $Pd[P(o\text{-tol})_3]_2$ and the Josiphos ligand are shown in Scheme 3. Primary arylamines containing *ortho* substituents of varying size, including smaller groups, such as methyl (**2f**) and methoxy (**2e**) groups, and larger groups, such as a phenyl

Scheme 3. Scope of Palladium-Catalyzed Amination of Aryl Chlorides with Ammonium Sulfate[a]



[a]Conditions: ArCl (0.600 mmol), ammonium sulfate (0.900 mmol), $Pd[P(o\text{-tol})_3]_2$ (1.2−6.0 μmol, 0.2−1.0 mol %), CyPF-^{t}Bu (1.2−6.0 μmol, 0.2−1.0 mol %), NaO^{t}Bu (2.70 mmol), 1,4-dioxane (6 mL); 100 °C, 12 h. Isolated yields (catalyst loading in parentheses).

ring (**2d**), were isolated in high yields (79−98%). Styrenyl functionality (**2c**), ketals[21] (**2g**), and silyl-protected alcohols (**2h**) were tolerated by the reaction. Benzo-fused heterocycles containing nitrogen (**2i,j**) and sulfur (**2k**) reacted with the ammonium salt in good yields. The scope of the reaction under these conditions is similar to that of the reaction with the solution of ammonia.[10,11]

The coupling of ammonia with aryl bromides occurs faster and with higher selectivity for the formation of the primary arylamine than does the coupling aryl chlorides.[11] However, we observed that reactions of aryl bromides with ammonium chloride, sulfate, or acetate occurred with lower selectivity (2:1) for the primary arylamine versus the diarylamine than did the reactions of aryl chlorides.

To understand the difference in selectivity between the reactions of aryl chlorides and aryl bromides lacking an *ortho* substituent, and to understand the impact of using the ammonium salts on the rates of different steps in the catalytic cycle, we studied the mechanism of these amination reactions. The mechanism of the amination of aryl halides with ammonia catalyzed by palladium-Josiphos complexes has been studied.[22] Spectroscopic studies showed that $L_2Pd(Ar)(NH_2)$ is the resting state of the catalyst, and kinetic experiments indicated that reductive elimination is the turnover-limiting step.[22]

Because the selectivity varies with the identity of the aryl halide, we considered that the catalyst resting state for the reactions of ammonium salts is not the arylpalladium−amido complex. We monitored the reaction of *p*-chlorotoluene with ammonium sulfate at 80 °C catalyzed by 10 mol % of $(CyPF\text{-}^tBu)Pd(P(o\text{-tol})_3)$, formed in situ, in dioxane. One ligated palladium species was observed by ^{31}P NMR spectroscopy. The chemical shifts and coupling constants of the new complex were different from the reported values for the CyPF-^{t}Bu-ligated arylpalladium chloride[23] or amido[22] complexes. Instead, they were consistent with reported values for the CyPF-^{t}Bu-ligated arylpalladium *tert*-butoxide complex.[23] In contrast, a combination of the arylpalladium *tert*-butoxide complex and the arylpalladium−bromide complex in an 3:4 ratio were observed in solution during the reaction of *p*-bromotoluene with ammonium sulfate (Figure 1).

To understand the effect of the inorganic salts formed in the reaction, we allowed *p*-chlorotoluene to react with ammonium

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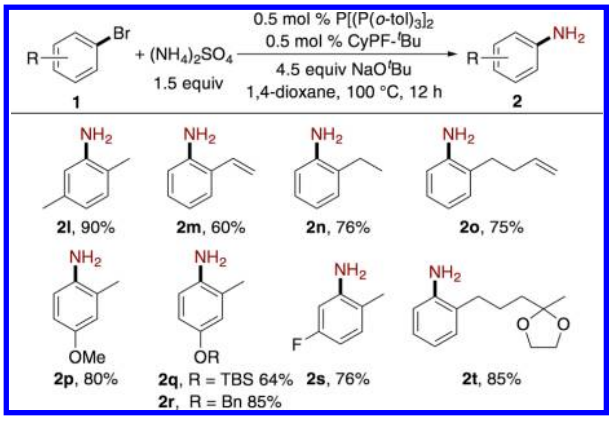
Figure 1. Comparison of the resting states for reactions with ammonia and ammonium sulfate.

Scheme 4. Scope of Palladium-Catalyzed Amination of *Ortho*-Substituted Aryl Bromides with Ammonium Sulfate[a]

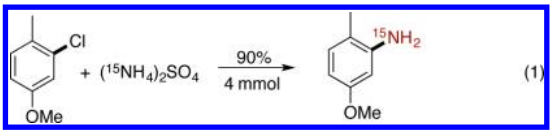


[a]Conditions: ArBr (0.600 mmol), $(NH_4)_2SO_4$ (0.900 mmol), $Pd[P(o\text{-tol})_3]_2$ (3.0 μmol, 0.5 mol %), CyPF-^{t}Bu (3.0 μmol, 0.5 mol %), NaO^{t}Bu (2.70 mmol), 1,4-dioxane (6 mL); 100 °C, 12 h.

sulfate in the presence of the palladium catalyst with 1 equiv of added NaBr. A lower selectivity (9:1) was observed for the reaction with the added bromide salt than was observed for the analogous reaction conducted without the bromide salt (20:1). Stoichiometric reactions with isolated complexes suggest that $L_2Pd(Ar)(O^tBu)$ reacts selectively with ammonia to form the primary arylamine, while $L_2Pd(Ar)(Br)$ selectively reacts with aniline to form diarylamine (Figure 1).[20,24]

Ortho-substituted aryl bromides reacted to provide the primary arylamine in high yields without competing diarylation, presumably due to the large steric difference between the ammonia reagent and an *ortho*-substituted aniline (Scheme 4).

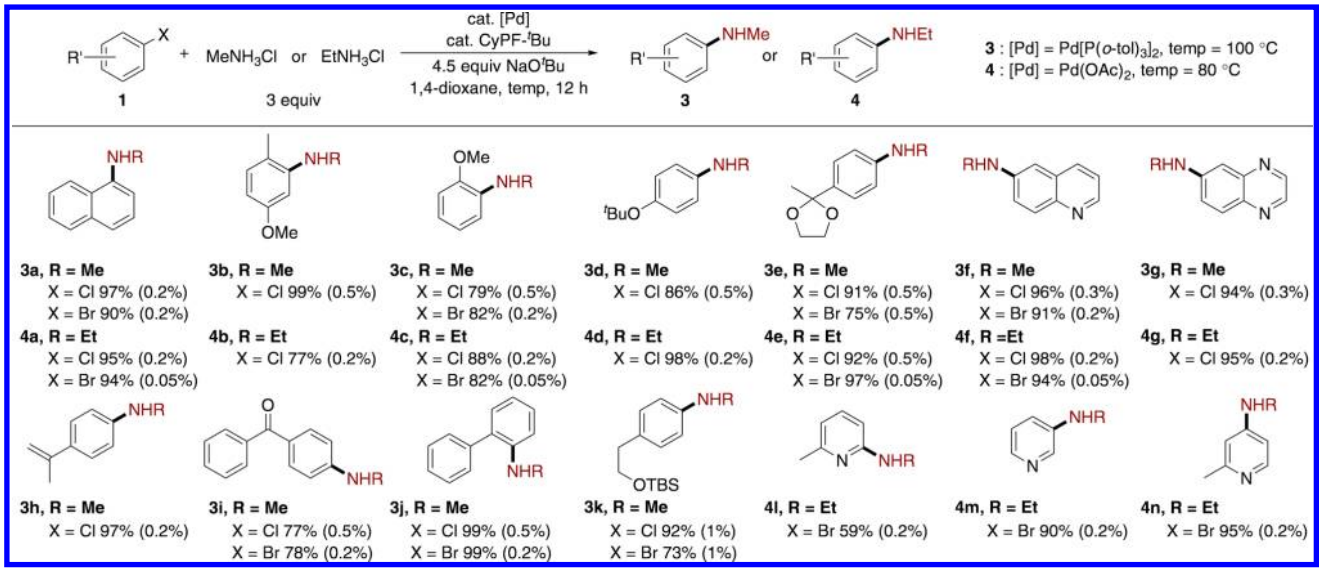
This coupling process provides a convenient method to incorporate ^{15}N into aromatic compounds. The ^{15}N label in anilines is typically installed by nitration and reduction. Such a process is expensive to conduct because it requires solvent quantities of ^{15}N-labeled nitric acid. Ammonium salts are a less expensive and more conveniently handled source of ^{15}N than are nitric acid or ^{15}N-labeled ammonia gas, and our coupling of ammonium salts requires only 3 equiv of solid ^{15}N per mole of substrate. To illustrate this potential application of the coupling of ammonium salts, we prepared ^{15}N-labeled 5-methoxy-2-methylaniline on a 4 mmol scale. This product formed in high yield (eq 1), and the conversion of such products to a range of quinolines[25,26] and indoles[26−28] is well established.



The coupling of aryl halides with ammonium salts was expanded to include that between aryl halides and the ammonium salts of methylamine (bp = −6.3 °C) and ethylamine (bp = 17 °C) to form the corresponding *N*-methyl- and *N*-ethylanilines. There are few reports of the coupling of aryl halides with methylamine, and the source of amine is a commercially available 2.0 M solution in THF.[16,29−34] The reaction of aryl chlorides and bromides with methylamine and ethylamine hydrochloride yielded the corresponding *N*-alkylaniline products in moderate to high yields (59−99%), as shown in Scheme 5.

Because the product of the reaction of methylamine and ethylamine are secondary amines, and the Pd-Josiphos system is selective for reaction of primary amines over secondary amines,[35]

Scheme 5. Pd-Catalyzed Amination of Aryl Chlorides and Bromides with Methylamine and Ethylamine Hydrochloride Salts[a]



[a]Conditions: ArX (0.600 mmol), RNH_3Cl (1.80 mmol), [Pd] (0.30−6.0 μmol, 0.05−1.0 mol %), CyPF-^{t}Bu (0.30−6.0 μmol, 0.05−1.0 mol %), NaO^{t}Bu (2.70 mmol), 1,4-dioxane (6 mL); 12 h.

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diarylamines are not observed in these reactions. *N*-Alkylanilines are less volatile than the corresponding primary arylamines. Therefore, isolated yields from reactions with methyl and ethylamine hydrochloride are slightly higher than those for reactions with ammonium sulfate.

Reactions of ethylamine hydrochloride with aryl halides occur under conditions similar to those previously reported for the coupling of primary alkylamines. In this case, $Pd(OAc)_2$ is a suitable precursor, presumably because of the more facile reduction of the Pd(II) by ethylamine than by methylamine or ammonia.[35] Similarly, aryl halides, including bromopyridines (**4l−n**), coupled with ethylamine hydrochloride to form the corresponding *N*-ethylanilines (Scheme 5).

In summary, we have shown that ammonium salts are practical alternatives to gaseous amines for the aminations of aryl halides and can occur with distinct selectivities, distinct effects of concentration on selectivities, and distinct resting states of the catalyst. We observed a high selectivity for the formation of primary arylamine over diarylamine in reactions of aryl chlorides with ammonium sulfate, but we observed a mixture of mono- and diarylamine in the reactions of aryl bromides with ammonium sulfate. We attribute the difference in selectivity to the difference in resting states in the amination reaction of ammonium sulfate with aryl chlorides and bromides. $L_2Pd(Ar)(O^tBu)$ was observed as the major ligated palladium species during the reaction of aryl chlorides with ammonium sulfate. However, both $L_2Pd(Ar)(O^tBu)$ and $L_2Pd(Ar)(Br)$ were observed in reactions of aryl bromides with ammonium sulfate. The $L_2Pd(Ar)(Br)$ reacts selectively with primary arylamines to afford the diarylamine side product. This method was extended to include other gaseous amines, such as methylamine and ethylamine, to afford *N*-methyl- and *N*-ethylanilines.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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