Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface

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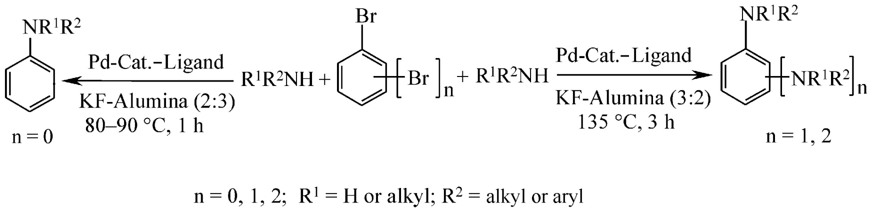
Abstract: An efficient palladium-catalyzed amination, including polyaminations of aromatic bromides mediated on a surface of KF-alumina, is reported. The solvent-free one-pot protocol avoids the use of a strong base (sodium *tert*-butoxide) making it applicable to substrates containing a base-sensitive functional group. It proceeds without concomitant reductive bromination and provides access to selective amination of polyhaloaromatics.

Key words: aryl halides, aryl amines, amination, palladium, KF-alumina

Aromatic amines are an integral part of pharmaceuticals, dyes, polymers, organic materials with important electronic properties, and ligands for transition metals.[1] The preparation of aryl amines is therefore important to synthetic organic chemists. The palladium-catalyzed cross-coupling of aryl halides with amines, developed independently by Buchwald[2] and Hartwig,[3] represents a mild alternative to the classical construction[4] of aryl amines. The Buchwald–Hartwig reaction has emerged during the last decade as a very powerful tool for the synthesis of aryl amines. The hetero cross-coupling reaction is normally carried out in the presence of a palladium catalyst, most commonly a bis-phosphine ligand and a base (3–5 equiv), preferably sodium *tert*-butoxide.[2d] Many advances have been made in this palladium-catalyzed amination reaction since it was reported by Buchwald and Hartwig.[5] The use of sodium *tert*-butoxide as the base eliminates a number of common functional groups such as esters, enolizable ketones, aldehydes, nitriles and nitro groups, and efforts have been made to replace it with a milder base. In the presence of other bases such as KOH or Cs_2CO_3, the double amination proceeds slowly and leads to an increased amount of the reductive product.[6,8a] Furthermore, several groups have employed this protocol to synthesize polyanilines[1d,7] and polyamino-substituted benzenes.[8] Although anilines gave high yields of double amination products, primary amines did not afford the desired *bis*-amination due to competing reductive debromination. While studying double amination of *o*-dibromobenzene with primary amines, Diver et al. reported formation of imine as the byproduct besides concomitant reductive debromination.[8a] Recently, we reported a procedure for palladium-catalyzed amination of heteroaryl halides using KF-alumina as the base.[9] The solvent-free dry reaction has been found to have advantages in the case of halopyridines. While extending the preparative advantages for amination of haloaromatics, we conducted KF-alumina mediated palladium-catalyzed C–N cross couplings between the aryl bromides and amines. We envisaged that the Buchwald–Hartwig C–N couplings should be studied with polyhalobenzenes to extend the scope and the amelioration of the various parameters of this amination process. We report herein our observations, which finally constitute not only a mild and efficient procedure for amination of aromatic bromides on a solvent-free surface of KF-alumina but also provide an expedient route for selective amination of polyhaloaromatics.

In the course of developing synthetic protocol toward amination of polyhaloaromatics on a KF-alumina surface, we first employed similar conditions to those developed for mono-amination of bromopyridines [amine (2 mmol), KF-alumina (1:4; 1 g/mmol), palladium-phosphine catalyst (2 mol%) for bromopyridines (1 mmol)]. Although amination of bromobenzene with secondary amines worked well under the conditions, the reaction with



n = 0, 1, 2; R^1 = H or alkyl; R^2 = alkyl or aryl
Pd-Cat.–Ligand = $Pd_2(dba)_3$–BINAP

Scheme 1

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primary amines was sluggish and poor yields were obtained. The conditions were optimized and the best results were achieved with KF impregnated on alumina was used in a ratio of 2:3. In the presence of $Pd_2(dba)_3$/BINAP as the catalytic system, bromobenzene underwent amination with both primary (Table 1, entries 3 and 4) and secondary amines (Table 1, entries 1 and 2) quite rapidly at moderate temperatures (80–90 °C/1 h) yielding the corresponding anilines in 73–88% yields (Table 1). Since the use of other bases can affect groups like enolizable ketones, we tested the amination of *p*-bromoacetophenone using the solvent-free KF-alumina surface. Gratifyingly, amination occurred effectively without any changes to the base-sensitive functionality (Table 1, entry 5). In a typical experiment,[10] the catalyst $Pd_2(dba)_3$/BINAP (2 mol%) was admixed intimately with KF-alumina (2:3; 2 g), heated at 80–90 °C for 15 minutes, and then treated with a mixture of aryl bromide (2 mmol) and amine (5 mmol). The solid mixture was stirred at 80–90 °C for 1 hour. The desired product was then isolated by column chromatography over silica gel.

Table 1 Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface

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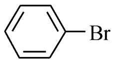
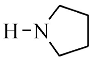
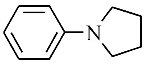
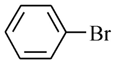
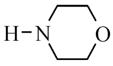
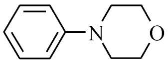
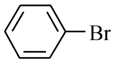
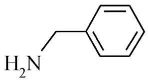
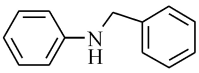
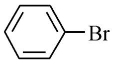
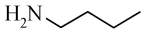
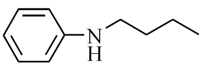
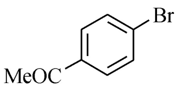
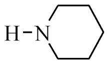
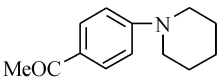
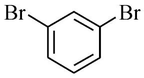
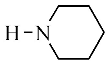
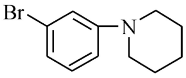
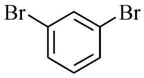
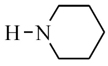
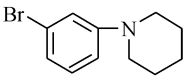
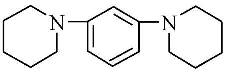
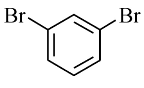
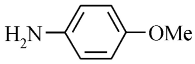
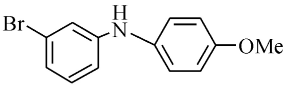
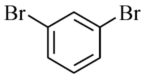
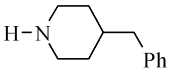
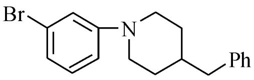
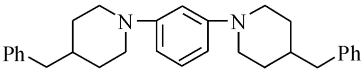
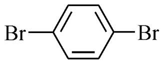
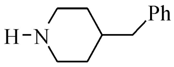
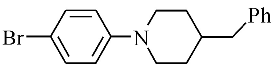
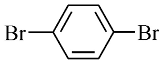
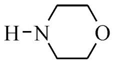
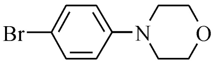
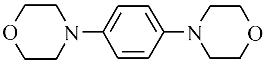
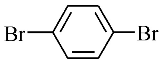
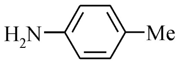
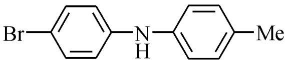
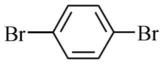
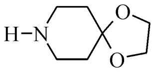
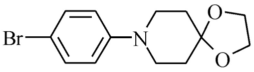
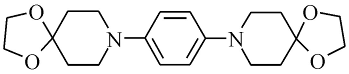
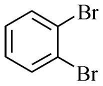
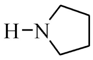
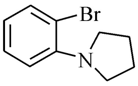
				Monoamine	Yield (%)	Bisamine	Yield (%)
1			A		83		
2			A		88		
3			A		78		
4			A		73		
5			A		80		
6			A		86		
7			B		12		78
8			A		75		
9			B		14		73
10			A		90		
11			B		17		72
12			A		80		
13			B		23		56
14			A or B		80		

Table 1 Palladium-Catalyzed Selective Amination of Haloaromatics on KF-Alumina Surface (continued)

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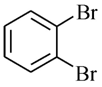
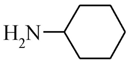
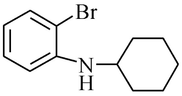
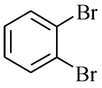
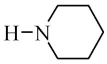
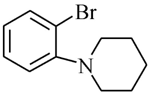
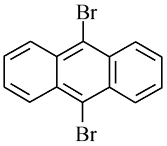
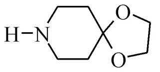
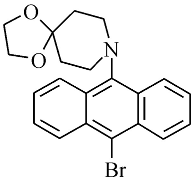
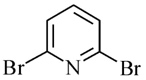
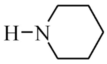
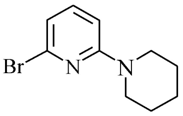
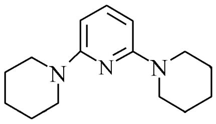
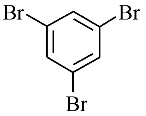
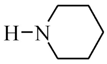
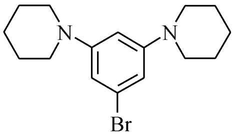
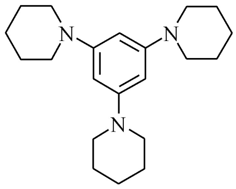
15			A or B		65		
16			A or B		90		
17			A		64		
18			B		5		90
19			B		18		67

[a] A: KF-Al_2O_3 (1:4 or 2:3), Pd_2dba_3/BINAP, 80–90 °C, 1 h; B: KF-Al_2O_3 (3:2), Pd_2dba_3/BINAP, 135 °C, 3 h.

[b] Isolated products; structure determined by IR, ^1H NMR, and ^{13}C NMR spectra.[11]

Since polyaminobenzenes are important compounds for various industries, we wanted to employ the reaction conditions to effect polyamination of polyhaloaromatics. While applying similar conditions to dibromobenzenes, mono-aminated products only resulted (Table 1, entries 6, 8, 10, 12, and 17). Earlier we observed similar results in the case of dibromopyridines.[8] In order to obtain the bis-aminated products we examined various proportions of KF-alumina and different catalytic systems. The combination of KF-alumina in the ratio of 3:2 and $Pd_2(dba)_3$/BINAP as the catalyst was found to be suitable for bis-, or tris-aminations in a one-pot reaction (Table 1, entries 7, 9, 11, and 13). Under similar conditions, 2,6-dibromopyridine and 1,3,5-tribromobenzene yielded the corresponding bis- and tris-aminated products (Table 1, entry 18 and 19) in 90% and 67% yields, respectively. Neither reductive debromination nor the formation of imine was observed under these conditions, indicating that the possible β-elimination might not be favorable, and thus contamination with any other byproducts is avoided. The amination occurs quite rapidly for mono-amination (1 h) while polyamination requires a longer time (3 h) and higher temperatures (135 °C). In the case of polyaminations, partial mono-aminated products remained in the reaction mixtures, which were easily isolated by column chromatography (Table 1). Interestingly, 1,2-dibromobenzene did not produce the 1,2-bis-amines in either condition, possibly due to steric crowding (Table 1, entries 14–16). Several variations in terms of the catalytic system, the surface (KF-alumina), and temperatures did not change the course of the reactions.

In conclusion, we have demonstrated that it is possible to effect palladium-catalyzed amination of halobenzenes on a solvent-free surface of KF-alumina without using any strong bases such as sodium *tert*-butoxide. The base-sensitive functional groups remained unaffected under this condition. The procedure is also effective for one-pot mono- or poly-aminations selectively, depending on the conditions used, and thus constitutes a mild and benign method for the synthesis of polyaminobenzenes. No reductive bromination leading to other byproducts has been observed in this procedure.

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(10) **General Procedure for the Amination Reactions:**
A: A mixture of $Pd_2(dba)_3$ (2 mol%) and BINAP (4 mol%) was admixed intimately with KF-Alumina (2:3; 2 g) and heated at 80–90 °C for 15 min. Aryl bromide (2 mmol) and amine (5 mmol) were added to the solid surface and the mixture was stirred at 80–90 °C for 1 h. An orange color developed while mixing and gradually disappeared over 1 h. The solid mass was then cooled, packed on a column of silica gel and eluted with EtOAc–light petroleum (1:19) to afford the mono-aryl amines. All the products were identified by IR, ^1H and ^{13}C NMR spectral data.
Condition B: The reaction conditions were identical except the quantity of amine was increased to 7–8 equiv, KF-alumina was used in the ratio of 3:2, and the solid mixture was heated at 135 °C for 3 h. Pure bis-amines were obtained by chromatography over silica gel and elution with EtOAc–light petroleum (1:9). The spectral data were consistent with the assigned structures.

(11) **Selected Spectral Data for Mono- and Bis-Coupled Products**
Table 1, Entry 5: 1-(4-Piperidin-1-yl-phenyl)ethanone: IR (Nujol): 1675, 1206.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.65$ (m, 6 H), 2.50 (s, 3 H), 3.34 (m, 4 H), 6.84 (d, 2 H, $J = 9.0$ Hz), 7.85 (d, 2 H, $J = 9.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 24.3$, 25.3, 26.0, 48.6, 113.3, 126.7, 130.5, 154.4, 196.4.
Table 1, Entry 7: 1, 3-Dipiperidino Benzene: IR (Nujol): 1201.6, 1124.4 cm^{-1}.
^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.55–1.62$ (m, 4 H), 1.70–1.78 (m, 8 H), 3.16 (t, 8 H, $J = 5.4$ Hz), 6.49 (dd, 2 H, $J = 8.1$, 2.2 Hz), 6.61 (s, 1 H), 7.15 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 24.4$, 26.0, 51.2, 106.1, 108.7, 129.3, 153.2.
Table 1, Entry 11: 1,4-Dimorpholino Benzene: IR (Nujol): 1234.4, 1120.6 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 3.01$ (t, 8 H, $J = 4.7$ Hz), 3.80 (t, 8 H, $J = 4.7$ Hz), 6.85 (s, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 50.5$, 66.9, 117.4, 145.8.
Table 1, Entry 13: 1,4-Di-[8-(1,4-dioxa-8-aza-spiro[4,5]decane)]benzene: IR (Nujol): 1125 cm^{-1}. ^1H NMR (acetone-d_6, 300 MHz): $\delta = 1.76$ (t, 8 H, $J = 5.7$ Hz), 3.16 (t, 8 H, $J = 5.7$ Hz), 3.94 (s, 8 H), 6.88 (s, 4 H). ^{13}C NMR (acetone-d_6, 75MHz): $\delta = 34.7$, 48.6, 63.9, 107.5, 117.9.
Table 1, Entry 15: (2-Bromophenyl)cyclohexylamine: IR (Nujol): 1321.1, 1016.4 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.20–1.44$ (m, 6 H), 1.75–1.79 (m, 2 H), 2.02–2.1 (m, 2 H), 3.30 (m, 1 H), 4.26 (br s, 1 H), 6.5 (m, 1 H), 6.6 (d, 1 H, $J = 8.1$ Hz), 7.14 (m, 1 H), 7.40 (d, 1 H, $J = 8.8$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 24.8$, 25.8, 33.0, 51.6, 109.8, 111.8, 117.1, 128.3, 132.5, 144.
Table 1, Entry 17: 8-(10-Bromoanthracene-9-yl)-1,4-dioxa-8-aza-spiro[4,5]decane: IR (Nujol): 1122.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.05$ (t, 4 H, $J = 5.3$ Hz), 3.57 (t, 4 H, $J = 5.3$ Hz), 4.10 (s, 4 H), 7.48–7.60 (m, 4 H), 8.48 (d, 2 H, $J = 8.7$ Hz), 8.56 (d, 2 H, $J = 8.7$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 36.4$, 49.9, 64.4, 107.6, 125.2, 125.3, 126.9, 128.3, 131.2, 131.4, 134.1, 145.3.
Table 1, Entry 19: 1,3,5-Tripiperidino Benzene: IR (Nujol): 1199.6, 1122.5 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.51–1.58$ (m, 6 H), 1.66–1.73 (m, 12 H), 3.10 (t, 12 H, $J = 5.3$ Hz), 6.14 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta =$ 24.3, 26.0, 51.5, 99.2, 153.7.