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# The Buchwald–Hartwig Amination of Nitroarenes

Fumiyoshi Inoue, Myuto Kashihara, M. Ramu Yadav, and Yoshiaki Nakao*

**Abstract**: The Buchwald–Hartwig amination of nitroarenes has been achieved for the first time by using palladium catalysts bearing dialkyl(biaryl)phosphanes. The cross-coupling reactions of nitroarenes with diarylamines, arylamines, and alkylamines are demonstrated to afford the corresponding substituted arylamines. A catalytic cycle involving the oxidative addition of Ar–$NO_2$ bond to palladium(0) followed by the reaction with amines is proposed based on a stoichiometric reaction.

The arylamine moiety represents a prevalent motif in a variety of pharmaceuticals and functional materials. The Buchwald–Hartwig amination is a highly efficient and versatile method to access substituted arylamines.[1] In these reactions, aryl halides have originally been used as electrophiles for the cross-coupling with organotin amides[2] and amines[3] in the presence of Pd-based catalysts to furnish arylamines. Subsequently, various aryl pseudohalides, including aryl sulfonates, such as aryl triflates,[4] tosylates,[5] ethers,[6] esters,[7] sulfamates,[8] and carbamates,[9] have been introduced as electrophilic coupling partners to surrogate the aryl halides, which may cause undesirable halogen-based contamination.[10] The use of nitroarenes as pseudohalides in the Buchwald–Hartwig amination may also circumvent these problems and thus be useful in an academic and industrial context, as nitroarenes are readily available and serve as building blocks for functionalized arenes.[11] Herein, we report the first example of the Pd-catalyzed Buchwald–Hartwig amination.

Following our recent studies on the Suzuki–Miyaura coupling of nitroarenes,[12] we examined the reaction of 4-nitrotoluene (**1a**; 0.20 mmol) with diphenylamine (**2a**; 0.30 mmol) in the presence of $Pd(acac)_2$ (5.0 mol%), phosphane ligands (15 mol%), and $K_3PO_4$•n$H_2O$ (0.60 mmol)[13] in *n*-heptane at 130 °C for 24 h (Table 1). Among the ligands examined for the aminations by Buchwald, BrettPhos[14] (**L1**) was the most effective to afford 4-methyl-*N*,*N*-diphenylaniline (**3aa**) in 55% yield (entry 1). XPhos (**L2**) also furnished **3aa** in 41% yield (entry 2), while CPhos (**L3**), SPhos (**L4**), RuPhos (**L5**), and CyJohnPhos (**L6**) were not as effective as **L1** and **L2** (entries 3–6). Other phosphane ligands conventionally employed in the Buchwald–Hartwig amination such as DPPF, BINAP, and P(*t*-Bu)$_3$ did not generate **3aa** (entries 7–9). A subsequent investigation of bases (entries 10–14) revealed that pre-dried $K_3PO_4$ raised the yield of **3aa** to 75% (entry 10), whereas $K_2CO_3$ and $Cs_2CO_3$ resulted in poorer yields (entries 11 and 12). Strong bases such as KO*t*-Bu and NaO*t*-Bu, which are commonly used in the amination, did not afford **3aa** (entries 13 and 14), presumably due to a competitive reduction of the nitro group via electron transfer. The formation of triarylamines proceeded in higher yields when the reaction was performed in less polar solvents such as toluene (43%; entry 15), whereas 1,4-dioxane and DMF resulted in lower yields (entries 16 and 17).

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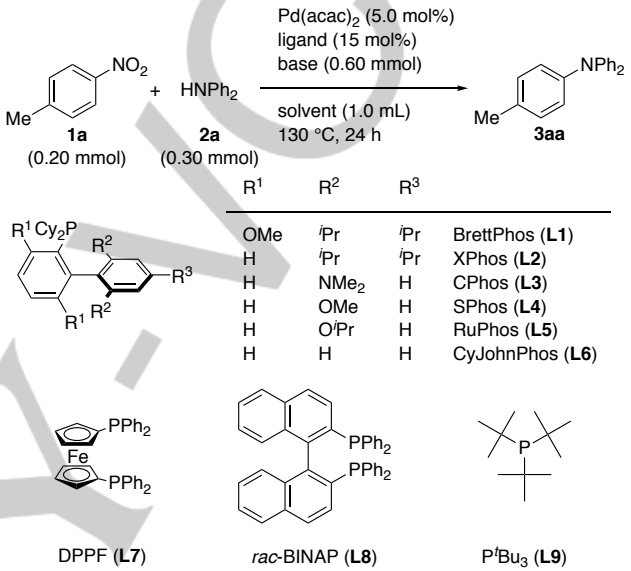
**Table 1.** Optimization of the Reaction Conditions for the Amination of **1a** with **2a**.[a]




| $R^1$ | $R^2$ | $R^3$ | |
|---|---|---|---|
| OMe | *i*Pr | *i*Pr | BrettPhos (**L1**) |
| H | *i*Pr | *i*Pr | XPhos (**L2**) |
| H | $NMe_2$ | H | CPhos (**L3**) |
| H | OMe | H | SPhos (**L4**) |
| H | O*i*Pr | H | RuPhos (**L5**) |
| H | H | H | CyJohnPhos (**L6**) |

DPPF (**L7**) *rac*-BINAP (**L8**) P*t*Bu$_3$ (**L9**)

| Entry | Ligand | Base | Solvent | Yield (%) |
|---|---|---|---|---|
| 1 | **L1** | $K_3PO_4$•n$H_2O$ | *n*-heptane | 55 |
| 2 | **L2** | $K_3PO_4$•n$H_2O$ | *n*-heptane | 41 |
| 3 | **L3** | $K_3PO_4$•n$H_2O$ | *n*-heptane | 6 |
| 4 | **L4** | $K_3PO_4$•n$H_2O$ | *n*-heptane | 2 |
| 5 | **L5** | $K_3PO_4$•n$H_2O$ | *n*-heptane | 19 |
| 6 | **L6** | $K_3PO_4$•n$H_2O$ | *n*-heptane | <1 |
| 7[b] | **L7** | $K_3PO_4$•n$H_2O$ | *n*-heptane | <1 |
| 8[b] | **L8** | $K_3PO_4$•n$H_2O$ | *n*-heptane | <1 |
| 9 | **L9** | $K_3PO_4$•n$H_2O$ | *n*-heptane | <1 |
| 10 | **L1** | $K_3PO_4$[c] | *n*-heptane | 75 |
| 11 | **L1** | $K_2CO_3$ | *n*-heptane | 2 |
| 12 | **L1** | $Cs_2CO_3$ | *n*-heptane | 56 |
| 13 | **L1** | KO*t*-Bu | *n*-heptane | 1 |
| 14 | **L1** | NaO*t*-Bu | *n*-heptane | <1 |
| 15 | **L1** | $K_3PO_4$[c] | toluene | 43 |
| 16 | **L1** | $K_3PO_4$[c] | 1,4-dioxane | 17 |
| 17 | **L1** | $K_3PO_4$[c] | DMF | 5 |

[a] Yields were calculated by GC analysis with $C_{15}H_{32}$ (19.0 mg, 0.090 mmol) as an internal standard. [b] 7.5 mol% of the ligand was used. [c] $K_3PO_4$•n$H_2O$ was dried under reduced pressure (<1.0 mmHg) at 160 °C for 3 h prior to use.

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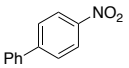
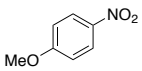
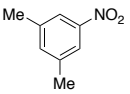
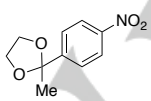
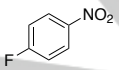
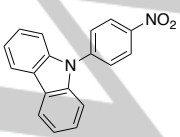
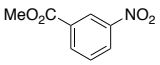
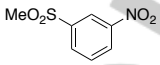
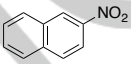
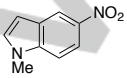
Subsequently, we studied the scope of the nitroarenes in this reaction, using **2a** as the amine-coupling partner under the previously established optimized reaction conditions (Table 2). The amination of **1a**, nitrobenzene (**1b**), 4-nitrobiphenyl (**1c**), 4-methoxynitrobenzene (**1d**), and 3,5-xylylnitrobenzene (**1e**) on a 0.60 mmol scale afforded the corresponding aryldiphenylamines in good yields (entries 1–5). An acetal-protected acetyl group was tolerated (entry 6), and the nitro group of 4-fluoronitrobenzene (**1g**) was substituted exclusively by **2a** (entry 7). It should be noted here that classical aromatic nucleophilic substitution reactions usually convert the fluoro group of **1g** to an amino functionality as in 9-(4-nitrophenyl)-9*H*-carbazole (**1h**), which would subsequently react with **2a** under modified reaction conditions (entry 8). Modifications of the aminations, i.e., choice of ligands and/or base, allowed nitroarenes bearing sterically demanding substituents **1i** and **1j** (entries 9 and 10) or a Lewis-basic functional group **1k** and **1l** (entries 11 and 12) to participate in the transformation. Nitronaphthalenes **1m** and **1n** can be cross-coupled with bis(4-*tert*-butylphenyl)amine (**2b**) to give the corresponding diarylnaphthylamines (**3mb** and **3nb**; entries 13 and 14). Heteroaromatic nitro compounds such as 3-nitropyridine and 2-nitrothiophene did not afford the corresponding triarylamines, whereas 1-methyl-5-nitroindole (**1o**) furnished the corresponding amination product in 52% (entry 15).

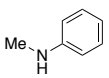
**Table 2.** Scope of Nitroarenes.

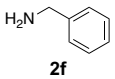
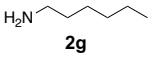
| Entry | Nitroarenes | Diarylamines | Yield (%)[a] |
|---|---|---|---|
| 1 | **1a** | **2a** | 73 (**3aa**) |
| 2 |  **1b** | **2a** | 83 (**3ba**) |
| 3[b] |  **1c** | **2a** | 74 (**3ca**) |
| 4 |  **1d** | **2a** | 66 (**3da**) |
| 5 |  **1e** | **2a** | 77 (**3ea**) |
| 6 |  **1f** | **2a** | 56 (**3fa**) |
| 7 |  **1g** | **2a** | 62 (**3ga**) |
| 8[b],[c],[d],[e] |  **1h** | **2a** | 57 (**3ha**) |
| 9[d],[f] |  | **2a** | 64 (**3ia**) |
| | **1i** | | |
| 10[f] |  **1j** | **2a** | 78 (**3ja**) |
| 11[b],[c],[g] |  **1k** | **2a** | 51 (**3ka**) |
| 12[b],[c],[d],[g] |  **1l** | **2a** | 50 (**3la**) |
| 13[b],[h] |  **1m** | **2b** | 74 (**3mb**) |
| 14[h] |  **1n** | **2b** | 65 (**3nb**) |
| 15[b] |  **1o** | **2a** | 52 (**3oa**) |

[a] Isolated yields. [b] 1.8 mmol of diarylamine was used. [c] **L3** was used instead of **L1**. [d] $K_3PO_4$•n$H_2O$ was used instead of dried $K_3PO_4$. [e] 1,4-Dioxane was used instead of *n*-heptane. [f] **L2** was used instead of **L1**. [g] Toluene was used instead of *n*-heptane. [h] **2b** was used instead of **2a**.

Thereafter, we examined the scope of amines using 4-nitroanisole (**1d**) as an electrophile, $K_3PO_4$•n$H_2O$, and 1,4-dioxane as a reaction solvent, which gave superior yields in these cases (Table 3). We discovered that polar solvents were necessary due to the limited solubility of the amines in other solvents, and that $K_3PO_4$•n$H_2O$ performed better than $K_3PO_4$ in polar solvents. Indeed, the reaction of aniline (**2c**) afforded the corresponding diarylamine **3dc**, while the corresponding triarylamine was not detected, i.e., **3dc** was not consumed as a nucleophile, probably on account of steric reasons (entry 1). *N*-Methylaniline (**2d**) participated in the amination albeit in modest yield (entry 2). Piperidine (**2e**) can also be used in this transformation and furnish the corresponding tertiary amine in 61% yield (entry 3). 3,5-Xylylnitrobenzne (**1e**) was efficiently aminated by benzylamine (**2f**) (entry 4), whereas simple alkylamines such as hexylamine (**2g**) were also suitable for this reaction (entry 5). In both cases, tertiary amines were not obtained.

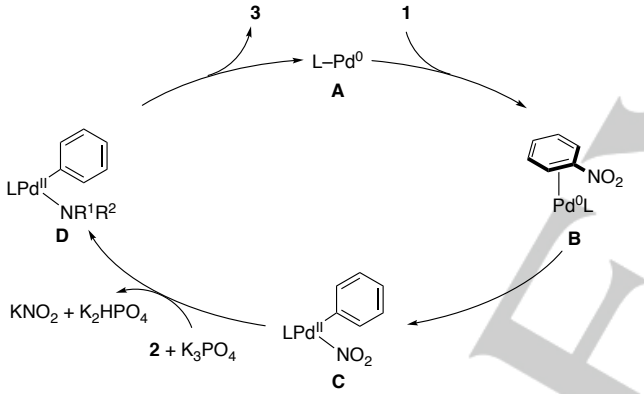
**Table 3.** Scope of Amines.

| Entry | Amines | Yield (%)[a] |
|---|---|---|
| 1[b] |  **2c** | 64 (**3dc**) |
| 2 |  **2d** | 41 (**3dd**) |
| 3 |  **2e** | 61 (**3de**) |

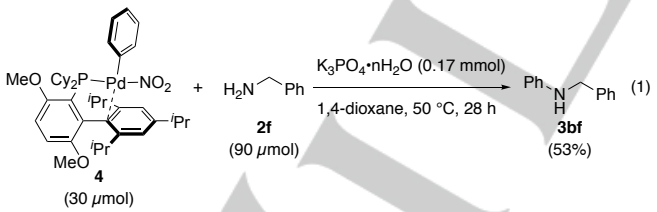
| | | |
|---|---|---|
| 4[c] |  **2f** | 81 (**3ef**) |
| 5 |  **2g** | 72 (**3dg**) |

[a] Isolated yields. [b] DMF was used instead of 1,4-dioxane. [c] **1e** was used instead of **1d**.

A plausible reaction mechanism for the amination of nitroarenes is described in Scheme 1. As previously demonstrated, nitroarenes react with palladium(0) comlex **A** to form $\eta^2$-arene–palladium(0) complexes such as **B**. This step is followed by oxidative addition the C–$NO_2$ bond to afford **C**. Subsequently, an amine nucleophile could react with **C** in the presence of a base to afford arylpalladium amide **D**, which could reductively eliminate arylamine **3** and concomitantly exchange the arene ligands to regenerate **A**. Oxidative adduct **4** was prepared according to our previous report[12] and was reacted with **2f** at 50 °C in the presence of $K_3PO_4$•n$H_2O$ to furnish *N*-benzylaniline in 53% yield (eq. 1). This result supports the proposed catalytic cycle, in which the oxidative addition is turnover-limiting.




**Scheme 1.** Plausible Mechanism for the Buchwald–Hartwig Amination of Nitroarenes.




In summary, we have developed the Pd-catalyzed Buchwald–Hartwig amination of nitroarenes. Using conventional Buchwald–Hartwig ligands allowed us to transform a range of substituted nitrobenzenes into triarylamines, diarylamines, alkylarylamines, and dialkylarylamines in moderate to good yields. Further efforts to develop novel coupling processes through Ar–$NO_2$ bond cleavage are currently underway in our laboratories and will be reported in due course.

## Experimental Section

A 15-mL vial was charged with $Pd(acac)_2$ (9.1 mg, 0.030 mmol), BrettPhos (0.090 mmol), **1** (0.60 mmol), and brought into a nitrogen-filled glovebox. In the glovebox, to the vial $K_3PO_4$ (382 mg, 1.8 mmol), **2** (0.90 mmol or 1.8 mmol), and *n*-heptane 3.0 mL) were added. The vial was sealed with a Teflon screw cap and taken out of the glovebox. The resulting mixture was stirred for 24 h at 130 °C. After the reaction, the mixture was filtered through a pad of Celite®. All volatiles were removed in vacuo and the residue was purified by medium pressure liquid chromatography (MPLC) using Biotage® SNAP Ultra to give the corresponding product. The following manipulations were performed before purification in some cases: To the crude, $Et_2O$ (10 mL) and $H_2O_2$ (30 wt% in $H_2O$, 1.5 mL) were added and the resulting mixture was stirred for 10 minutes at room temperature. $H_2O$ (10 mL) was added and the organic layer was separated. The remained aqueous layer was washed with EtOAc (10 mL) and the organic layer was combined, dried over $MgSO_4$, and filtered.

## Acknowledgements

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**Keywords:** C–N activation • amination • palladium

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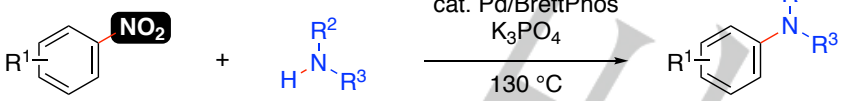


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