Phenylboronic Ester-Activated Aryl Iodide-Selective Buchwald–Hartwig-Type Amination toward Bioactivity Assay

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ABSTRACT: In this study, a phenylboronic ester-activated aryl iodide-selective Buchwald–Hartwig-type amination was developed. When the reaction of aryl iodides and aryl/aliphatic amines using Ni(acac)$_2$ is carried out in the presence of phenylboronic ester, the Buchwald–Hartwig amination proceeds smoothly to afford the corresponding amines in high yields. This reaction does not proceed in the absence of phenylboronic ester. A wide variety of aryl iodides can be applied in the presence of aryl chlorides and bromides, which remain intact during the reaction. The mechanistic studies of this reaction suggest that the phenylboronic ester acts as an activator for the amines to form the "ate complex". Chemical kinetics studies show that the reaction of aryl iodides, base, and Ni(acac)$_2$ follows first-order kinetics, while that of amines and phenylboronic ester follows zero-order kinetics. The bioactivity screening of the corresponding products showed that some amination products exhibit antifungal activity.

INTRODUCTION

Carbon–nitrogen bond-forming aminations are one of the most important research topics in modern synthetic organic chemistry.$^1$ Among the various C–N bond-forming reactions, the Buchwald–Hartwig reaction is a well-known palladium-catalyzed C–N bond-forming cross-coupling reaction.$^2$ However, palladium is expensive and not an earth-abundant metal; therefore, the replacement of palladium with nickel, an inexpensive earth-abundant metal, is desirable for this reaction. Indeed, many nickel-catalyzed carbon–nitrogen bond-forming reactions have been reported.$^3$ Nickel-catalyzed cross-coupling reactions usually require a bulky ligand bearing a large bite angle, which assists the reductive elimination step.$^3.a–c$ Recently, a ligand-free nickel-photocatalyst dual-catalyzed amination reaction was also reported.$^3$ Here, the photocatalyst assists nickel to undergo reductive elimination. In both cases, reductive elimination is the rate-determining step.$^3.a–c$

We recently reported a nickel-iodide-catalyzed activator-promoted halogen-dependent chemoselective cross-coupling reaction of aryl halides.$^5.a$ In this reaction, the aryl chlorides undergo the Suzuki–Miyaura-type coupling, which is activated by the aryl amines (Scheme 1a, bottom). In contrast, aryl iodides undergo a C–N bond-forming Buchwald–Hartwig-type amination, which is activated by phenylboronic acids/esters (Scheme 1a, top). A boron-amine ate complex (Scheme 1a) appears to be a common intermediate in both reactions. Although these phenomena are interesting in terms of catalytic selectivity, reactions with multi-halide-containing substrates, such as 4-iodo-1-bromobenzene or 4-iodo-1-chlorobenzene, produce a complex reaction mixture, indicating the non-selective nature of the nickel iodide catalyst toward aryl halide species (Scheme 1b). Because halogen-containing N-aryl aniline derivatives exhibit pharmaceutical and biological activities,$^6$ aryl iodide-selective nickel catalysis should provide straightforward access to bromo- or chloro-containing biologically active molecules. In this study, a highly aryl iodide-selective C–N bond-forming cross-coupling reaction was developed using Ni(acac)$_2$ as the catalyst (Scheme 1c). Moreover, mechanistic studies and biochemical assay screening of the synthesized C–N bond-forming cross-coupling products were performed.

RESULTS AND DISCUSSION

Nickel catalysts were screened for the aryl iodide-selective C–N bond-forming amination (Table 1, entries 1–8; for more details, see the Supporting Information (Section 2)). When the reaction of 1-chloro-4-iodobenzene (1b) and toluidine (2a) was carried out with phenylboronic ester (3a) and 0.5 mol % Ni in the form of Ni(acac)$_2$, the C–I bond selectively reacted with 2a to give the corresponding amination product 4b with 94% yield. Here, the C–Cl bond was almost intact (entry 1).
The same reaction did not proceed in the absence of 3a (entry 2). These results suggest that phenylboronic ester acts as an activator. The reaction of nickel iodide (NiI₂) provided halogen-dependent chemoselective cross-coupling, 5a afforded a 21% yield of 4b, where the C−I and C−Cl bonds underwent the reaction (entry 3). While NiI₂ reacts with both aryl iodides and chlorides unselectively, Ni(acac)₂ does only with aryl iodides (for more details, see the Supporting Information (Section 2.4)). NiCl₂ and NiCl₂(dme) produced 59 and 72% yields of 4b, respectively (entries 4 and 5). Nickel(0) catalysts, Ni(PPh₃)₄ and Ni(cod)₂, promoted the formation of 4b in 19 and 11% yields, respectively (entries 6 and 7). The chemical yield of the Ni(acac)₂·2H₂O-catalyzed reaction was significantly lower than that of the anhydrous Ni(acac)₂-catalyzed reaction (entries 1 and 8). Palladium catalysts were found to be ineffective for this transformation because they promoted the corresponding C−C bond-forming Suzuki−Miyaura-type reaction (entries 9−11).

After optimizing the reaction conditions, we investigated the substrate scope of several aryl iodides (Table 2). The reactions of the multi-halide-substituted aryl iodides exhibited high selectivity for the C−I bond. When 1-bromo-4-iodobenzene 1a was reacted with toluidine (2a) under the optimized reaction conditions, a 78% yield of 4-bromo-N-(p-tolyl)aniline 4a was obtained. Similarly, p-chloro-, 1,3-dichloro-, and p-fluoro-substituted aryl iodides also selectively underwent the desiredamination reaction to afford 4b−4d in 80−91% yield. The steric perturbations of the benzene ring of the aryl iodide had no significant effect on the product outcome. The reaction of 1-iodo-3,5-dimethyl benzene (1e) generated the desired amination product 4e in 97% yield. Substrates bearing electron-donating groups, such as p-methoxy (1f) or p-ethoxy (1g) groups, furnished the desired products in 95% yield. However, electron-withdrawing groups such as p-CF₃ (1h) had no significant effect on the product outcome and provided the desired 4h in 96% yield. The substrate with the bulky butyl group at the para-position furnished the product with a 95% yield (4i). The reaction with o-, p-, and m-tolyl iodides afforded amination products 4j, 4k, and 4l with 92, 95, and 94% yields.

Table 2. Amination of Various Aryl Iodides

| Entry | Catalyst | Yield 4b (%) | Yield 5b (%) |
|-------|----------|--------------|--------------|
| 1     | Ni(acac)₂ | 94           | trace        |
| 2     | Ni(acac)₂ | 0            | 0            |
| 3     | NiI₂      | 21           | 12           |
| 4     | NiCl₂     | 59           | 13           |
| 5     | NiCl₂(dme)| 72           | 4            |
| 6     | Ni(PPh₃)₄ | 19           | 3            |
| 7     | Ni(cod)₂  | 11           | 5            |
| 8     | Ni(acac)₂·2H₂O | 62         | trace        |
| 9     | Pd(acac)₂ | 0            | 98           |
| 10    | PdCl₂     | trace        | 94           |
| 11    | Pd(OAc)₂ | 0            | 91           |

“Reaction conditions: aryl halide 1 (1.0 mmol), p-toluidine 2a (3.0 mmol), phenylboronic ester 3a (1.3 mmol), and K₃PO₄ (3 mmol). All yields presented here are isolated yields. **Ni(acac)₂ (2 mol %) and 2a (5 mmol).”
respectively. This catalytic reaction can also tolerate heterocyclic substrates. The amination reaction of 3-iodopyridine (1m) afforded 4m in 86% yield. Although only a trace amount of the product was obtained from 1-iodo-4-nitrobenzene (1n), p-iodoacetophenone (1o) provided the desired amination product 4o with 61% yield. Phenylboronic ester 3a was recovered from all reaction mixtures with up to 91% yield.

Furthermore, we examined the substrate scope of the aryl amines (Table 3). Electronic variation of aniline derivatives also afforded a good iodide (Table 4). Aniline also afforded a good iodide (Table 3). Electronic variation of aniline derivatives 

| Table 3. Amination of a Variety of Aryl Amines |
|-----------------------------------------------|
| **Ni(acac)** (0.5 mol%) | **3a** (1.3 mol equiv) | **K**<sub>3</sub>P<sub>O</sub> <sub>4</sub> (3 mol equiv) | **1 + 2** | **4** | **1,4-dioxane** | **115 °C, 24 h** |
| (4f) 91% | (4p) 82% | (4q) 73% |
| (4a) 74% | (4b) 80% | (4r) 74% |
| (4s) 71%<sup>a</sup> | (4t) 56% | (4v) 56% |
| (4u) 55%<sup>b</sup> | (4w) 70%<sup>c</sup> | (4y) 55%<sup>d</sup> |
| (4x) 83% | (4j) 88% | (4i) 81% |
| (4o) 48% | (4n) trace |

<sup>a</sup>Reaction conditions: aryl iodide 1 (1.0 mmol), aryl amine 2 (3.0 mmol), phenylboronic ester 3a (1.3 mmol), and K<sub>3</sub>P<sub>O</sub> <sub>4</sub> (3 mmol). All yields presented herein are isolated yields.  
<sup>b</sup>1.5 mol % Ni(acac)<sub>2</sub>.  
<sup>c</sup>1 mol % Ni(acac)<sub>2</sub>.  
<sup>d</sup>2 mol % Ni(acac)<sub>2</sub>.  
<sup>e</sup>Reaction time: 48 h.

| Table 4. Reactivity of Aliphatic Amines |
|----------------------------------------|
| **Ni(acac)** (0.5 mol%) | **3a** (1.3 mol equiv) | **K**<sub>3</sub>P<sub>O</sub> <sub>4</sub> (3 mol equiv) | **1 + 2** | **4** | **1,4-dioxane** | **115 °C, 24 h** |
| (4a) 86% | (4ad) 84% | (4ae) 66% |

<sup>a</sup>Reaction conditions: aryl iodide 1 (1.0 mmol), aliphatic amine 2 (3.0 mmol), phenylboronic ester 3a (1.3 mmol), and K<sub>3</sub>P<sub>O</sub> <sub>4</sub> (3 mmol). All yields presented herein are isolated yields.

exhibited no effect in terms of reactivity. The reaction of p-methoxyaniline successfully afforded 4f and 4p in 91 and 82% yields, respectively. Aniline also afforded a good iodide selective amination reaction (4q) in 73% yield. Interestingly, several halogen-containing anilines successfully underwent the desired amination reaction. p-Chloroaniline underwent the desired amination reaction with iodobenzene (4q), electron-rich aryl iodides (4b, 4r, and 4s), halogen-containing aryl iodides (4t–4v), and heterocyclic aryl iodide 4-iodopyridine (4w). Similarly, p-bromoaniline produced the C–N cross-coupled product (4v, 4x, and 4y). The amination reaction of 4-iodotoluene and 4-fluoroaniline produced 4-fluoro-N-(p-tolyl) aniline (4d) in 81% yield. A heterocyclic amine (pyridin-3-amine) was also tolerated under these reaction conditions to afford N-(pyridin-3-amine) (4m) in 83% yield. The o- and m- substituted aniline derivatives were also able to provide the amination products 4j and 4i in 88 and 91% yield, respectively. The reaction of p-aminoacetophenone afforded the desired amination product 4o in 48% yield, whereas the reaction of p-nitroaniline was not successful.

The reactivity of aliphatic amines was also investigated (Table 4). Notably, both aromatic amines and aliphatic amines underwent the amination reaction. The amination products N-dodecyl-4-methylaniline (4x) and 4-bromo-N-dodecylaniline (4aa) were obtained in 95 and 60% yields, respectively. Similarly, 4-chloro-N-octylaniline (4ab) was produced in 71% yield. Nitrogen-containing heterocyclic compounds 4ac–4ae were obtained in 86, 84, and 66% yields, respectively.

The effect of phenylboronic ester on this reaction was investigated. Previously, we observed the formation of a B–N<sup>+</sup>ate complex through <sup>11</sup>B NMR and <sup>15</sup>N NMR studies. In this study, we examined the effect of phenylboronic ester (3a) by plotting the initial rate of the reaction with the amount of phenylboronic ester used. As the amount of phenylboronic ester (3a) increased, the initial rate of amination also increased (Figure 1) until a stoichiometric amount of ester (Scheme 2a) was added. It is clear that the addition of a stoichiometric amount of phenylboronic ester is essential for this transformation.

While surveying the catalytic species, pale blue crystals of Ni(acac)<sub>2</sub>·(4-tolNH)<sub>2</sub> were obtained from the complexation of Ni(acac)<sub>2</sub> and 2a (Scheme 2a). The structure of this nickel complex was unambiguously determined by single-crystal X-ray analysis (CCDC 2084381; for more details, see the Supporting Information (Section 6)). When the reaction of 1k and 2a was performed with 0.5 mol % of Ni(acac)<sub>2</sub>·(4-tolNH)<sub>2</sub> the desired amination proceeded smoothly to afford 4k in 93% yield (Scheme 2b). These results suggest the in situ generation of Ni(acac)<sub>2</sub>·(TolNH)<sub>2</sub> via the complexation of Ni(acac)<sub>2</sub> and toluidine to promote amination.
Radical trapping experiments were performed to determine the catalytic pathway of the reaction (Scheme 3). Reactions with either BHT (2,6-di-tert-butyl-p-cresol) or TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl proceeded smoothly in 79 and 88% yields, respectively. These experiments suggest that there are no radical intermediates involved in this experiment.

Chemical kinetics studies showed that the reaction of aryl iodide, Ni(acac)$_2$, and K$_3$PO$_4$ follows first-order kinetics, while that of phenylboronic ester and amine follows zero-order kinetics (for more details, see the Supporting Information (Section 4)).

A plausible catalytic pathway is as follows (Scheme 4): Ni(II) species (A) is reduced by PhB(OR)$_2$ to produce an Ni(0) species (B) and biphenyl (detected with GC), where K$_3$PO$_4$ stabilizes this in situ generated Ni$^{0}$ catalyst.$^{7,8}$ The oxidative addition of Ar$_1$-I affords Ar$_1$-Ni(II)-I (C), which reacts with a boron-amine ate complex (D) to give Ar$_2$-Ni(II)-NH-Ar$_2$ (E). Reductive amination of E affords product 4 and regenerates Ni(0) (B).

BIOACTIVITY ASSAY AGAINST YEASTS

To explore the antifungal properties of the products, 15 compounds were tested for growth inhibitory activities against the yeast species Saccharomyces cerevisiae and Candida albicans. All 15 compounds showed no significant inhibitory activities against the S. cerevisiae wild-type cells at 10 μM. Three compounds (4t, 4v, and 4x) inhibited the growth of S. cerevisiae drug-sensitive cells, in which the drug-efflux pumps were removed, and C. albicans cells (Table 5 and Table S1 (Supporting Information)). In addition, we tested the antiproliferative activity of these compounds against a mammalian cell line, HL-60, and bacteria (Staphylococcus aureus and Escherichia coli). The data showed that only 4ac inhibited the growth of S. aureus, a Gram-positive bacterium, and none of them affected the growth of HL-60 at a dose of more than 30 μM, indicating their selective antifungal activity. Further studies will be required to analyze the structure−activity relationships of these products in terms of the importance of bromo- and chloro-groups and their target identification. Notably, target molecules of a compound can be predicted and identified by a "chemical genomics" technique, in which the synthetic lethality between a compound and gene is comprehensively examined using the S. cerevisiae drug-sensitive strain.$^{8}$ Overall, these compounds can be considered as candidates for antifungal agents in that they inhibit the growth of the pathogenic Candida species but do not affect human cells.

Scheme 3. Radical Trapping Experiments

| entry | compound | S. cerevisiae (drug-sensitive) | C. albicans |
|-------|----------|-------------------------------|------------|
| 1     | 4t       | 3.3 ± 0.4                     | 6.1 ± 1.5  |
| 2     | 4v       | 2.1 ± 0.4                     | 5.3 ± 0.5  |
| 3     | 4x       | 7.1 ± 1.2                     | 6.4 ± 0.6  |
CONCLUSIONS

In summary, we demonstrated a Ni(acac)2-catalyzed amination that allows rapid access to a wide range of N-aryl aniline derivatives with good to excellent yields. The reaction exhibits very high selectivity for aryl iodides in case of multi-halide-containing substrates. The use of phenylboronic ester as an activator is essential for this transformation. Several mechanistic studies have been conducted. We also performed bioactivity assays of the synthesized products and found that halogen-containing N-aryl anilines could be candidates for antifungal agents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at 10.1021/acsomega.2c01092.

Experimental details and analytical data (compound characterization, 1H NMR, 13C NMR, MS-EI) for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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