

Synthetic Methods

Synthesis of Hindered Anilines: Copper-Catalyzed Electrophilic Amination of Aryl Boronic Esters**

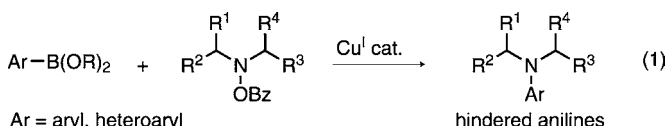
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The synthesis of aromatic and heteroaromatic amines has attracted considerable attention in the last two decades as a result of the numerous applications of these compounds in the pharmaceutical industry and medicinal chemistry.^[1] The development of several transition-metal-catalyzed couplings of aryl halides with amines^[2] has provided a practical method for the preparation of a wide range of anilines.^[3] However, some important challenges remain. For example, bromo- and iodo-substituted anilines cannot be prepared directly using these methods. More importantly, the preparation of hindered anilines is still a major challenge,^[4] as illustrated by problems recently encountered by Baran et al. in the total synthesis of (+)-psychotetramine.^[5]

Currently available methods for the synthesis of hindered anilines require the formation of highly reactive intermediates, such as benzynes^[6] or organometallic reagents.^[7,8] The most general of these reactions was reported by Knochel and co-workers, and involves oxidative coupling of organometallic reagents with hindered lithium amides in the presence of stoichiometric amounts of copper.^[7b] In a rare instance of catalytic synthesis of hindered anilines, Berman and Johnson reported three examples of the electrophilic amination of aryl zinc reagents by hindered electrophiles.^[7a,9] A common feature of the procedures reported by the groups of Johnson and Knochel is that a significant excess (≥ 2 equivalents) of one of the coupling components is necessary. Furthermore, both methods use a stoichiometric amount of an aryl Grignard or an aryl lithium reagent.



Aryl boronic acids and their derivatives offer significant advantages over the organometallic reagents currently used in the synthesis of hindered anilines. They are stable, readily available, and compatible with a wide range of functional groups. However, previous attempts by Berman and Johnson^[7a] and others^[10] to develop electrophilic amination of these compounds have been unsuccessful. A related oxidative amination of organoboron reagents developed by the groups of Lam,^[11] Chan,^[12] Evans,^[13] and others^[14] is highly sensitive to the steric properties of amine substrates and cannot be used for the synthesis of hindered anilines.^[15] Herein, we

describe a catalytic method for the synthesis of hindered anilines from aryl and heteroaryl boronic esters compatible with a wide variety of functional groups, including aryl iodides and bromides [Eq. (1); Bz = benzoyl].



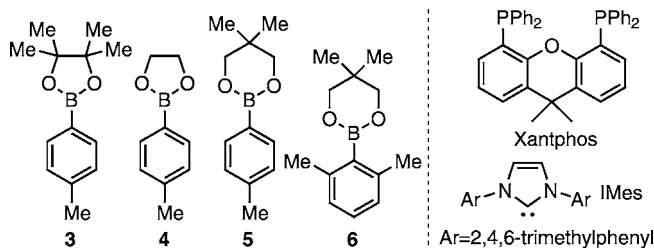
In an initial experiment, we explored the reactivity of aryl boronic ester **3** and 4-benzoyloxymorpholine (**1**), in the presence of sodium *tert*-butoxide and IMesCuOtBu as a catalyst.^[16] Upon full conversion of the electrophile, the desired aniline was obtained in less than 5 % yield (Table 1, entry 1).

Table 1: Developing the electrophilic amination of aryl boronic esters.

| Table 1. Developing the electrophilic catalytic system for α -aryl carboxylic esters. | | | | | | |
|--|---|-----------------------|----------|----|--------------------|--------------------------|
| Ar—B(OR') ₂ + BzONR ₂ | | LCuOtBu (5 mol %) | | | Ar—NR ₂ | |
| | | MOtBu, solvent | | | | |
| Entry ^[a] | BzONR ₂ | ArB(OR') ₂ | L | M | Solvent | Yield [%] ^[b] |
| 1 | | 3 | IMes | Na | THF | < 5 |
| 2 | | 4 | IMes | Na | THF | 16 |
| 3 | | 5 | IMes | Na | THF | 72 |
| 4 ^[c] |  | 5 | Xantphos | Na | 1,4-dioxane | 99 |
| 5 | 1 | 6 | Xantphos | Na | 1,4-dioxane | 8 |
| 6 | 6 | 6 | Xantphos | Li | 1,4-dioxane | 56 |
| 7 | 6 | 6 | Xantphos | Li | toluene | 74 |
| 8 ^[d] |  | 6 | Xantphos | Li | toluene | 81 |
| 9 ^[e] | 2 | 6 | Xantphos | Li | toluene | 94 |


[a] ArB(OR')₂ (1.2 equiv), BzONR₂ (1.0 equiv), MOtBu (1.0 equiv), 25 °C, 12 h. [b] Determined by GC analysis of the crude reaction mixture.

[c] Catalyst was formed in situ from Xantphos and $(\text{CuOtBu})_4$. [d] Reaction performed at 45 °C. [e] 60 °C, 1.0 M, toluene used to prepare the catalyst.



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We speculated that the low yield of the aniline was a consequence of slow transmetalation of the aryl boronic ester. Indeed, reactions with ethylene glycol (**4**) and neopentyl glycol (**5**) esters, which are known to undergo transmetalation faster than the corresponding pinacol esters,^[17] provided the aniline product in 16 and 72 % yield, respectively (Table 1, entries 2 and 3),

In a catalyst screen performed with boronic ester **5** and electrophile **1**,^[18] we identified XantphosCuOtBu, a complex prepared from Xantphos ligand and (CuOtBu)₄,^[19] as the best catalyst. In a reaction performed in 1,4-dioxane, the desired aniline was obtained in 99 % yield (Table 1, entry 4). Unfortunately, a reaction with the more hindered boronic ester **6** resulted in the formation of the desired aniline in only 8 % yield, together with 83 % yield of *tert*-butyl benzoate (Table 1, entry 5).

In fact, a control experiment revealed that *tert*-butyl benzoate forms in nearly quantitative yield in a reaction of **1** with sodium *tert*-butoxide after only 10 minutes at room temperature. We found that the decomposition of the electrophile can be suppressed if lithium *tert*-butoxide is used in a noncoordinating solvent.^[18] Consistent with these findings, a reaction with the boronic ester **6** and electrophile **1** performed in toluene in the presence of lithium *tert*-butoxide afforded the desired aniline in 74 % yield (Table 1, entry 7). The same reaction conditions could also be used to prepare highly hindered *N,N*-diisopropyl-2,6-dimethyl aniline from boronic ester **6** and electrophile **2** (Table 1, entry 8). Finally, the best result (94 % yield) was obtained when this reaction was performed in a concentrated isooctane solution using a catalyst prepared from Xantphos and (CuOtBu)₄ in toluene (Table 1, entry 9).

The optimized reaction conditions proved to be remarkably general. We found that reactions with the diisopropylamine-derived electrophile **2** could be performed in the presence of a number of functional groups, including formyl, carbomethoxy, nitro, methoxy, trifluoromethyl, iodo, and bromo groups (Table 2, **7–14**). As the synthesis of anilines **16** and **17** suggests, hindered boronic esters are well tolerated in the reaction. In addition, a variety of heteroaromatic boronic esters, including 2-chloropyridine-3-boronic ester, can also be used as nucleophiles (**18–21**). In most reactions, 2.5 mol % of the catalyst was sufficient to accomplish the full conversion in less than 12 hours, whereas the sterically hindered boronic esters required a higher catalyst loading (5 mol %). Finally, as the synthesis of **8** demonstrates, the reaction can be successfully performed on a 5 mmol scale.

To establish the full scope of the amination reaction, we explored the reactivity of various electrophiles. *O*-benzoyl hydroxylamines derived from common cyclic amines, such as pyrrole, piperidine, morpholine, and piperazine can be used in the reaction (Table 1, **23–25** and **31**). Electrophiles bearing functionality, such as nitro, carbomethoxy, bromo, and chloro groups are also viable substrates and provide the aniline products in excellent yields. The steric properties of an electrophile have no significant effect on the outcome of the reaction. Both 2-methylpyrrole- and decahydroquinoline-derived electrophiles provide the expected anilines in high yield (**30** and **31**). Even a highly hindered electrophile derived

Table 2: The scope of electrophilic amination.^[a]

| ArBneop 1.2 equiv | + R ₂ NOBz 1.0 equiv | Xantphos (2.5 mol %) CuOtBu (2.5 mol %) LiOtBu (1.0 equiv) isooctane, 60 °C | Ar–NR ₂ | |
|----------------------------------|--|---|----------------------------------|-------------------|
| | X OMe ^[b] Cl ^[c] CO ₂ Me CHO I Br | 7 85% 8 82% 9 89% 10 94% 11 82% 12 84% | 13 84% | 14 88% |
| 15 85% | 16 84% | 17 ^[b] 94% | 18 ^[b] 87% | |
| 19 ^[b] 88% | 20 ^[d] 87% | 21 ^[d] 78% | 22 95% | |
| 23 81% | 24 80% | 25 76% | | |
| 26 ^[d] 80% | 27 ^[d] 87% | 28 ^[d] 92% 29 ^[d] 81% | 29 ^[d] 81% | |
| 30 95% | 31 ^[d] 90% | 32 95% | 33 ^[d] 60% | |

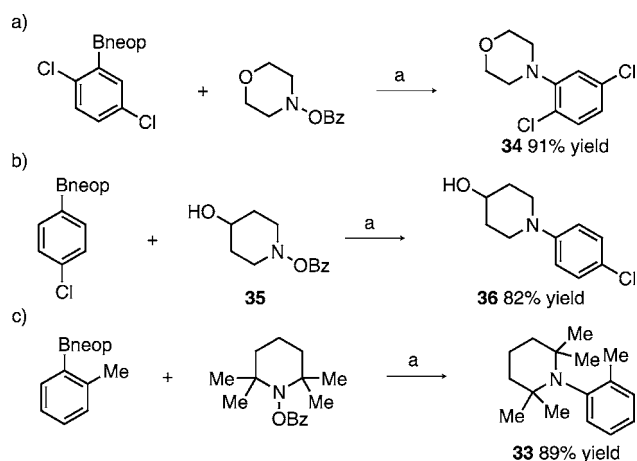
[a] Reactions performed on a 0.5 mmol scale. Yields of isolated products are reported. Catalyst was added as a 0.1 M solution in toluene.

[b] 5 mol % of the catalyst was used. [c] The reaction was performed on a 5.0 mmol scale. [d] 2.5 mol % of the catalyst was used at 45 °C.

Boc = *tert*-butoxycarbonyl, neop = neopentyl glycol.

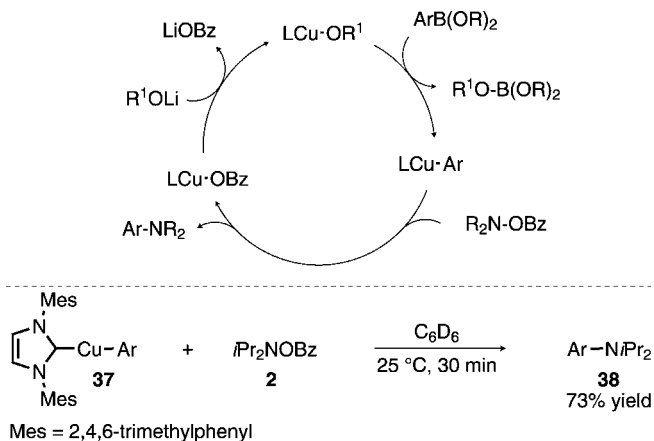
from 2,2,6,6-tetramethylpiperidine could be coupled with nitrophenyl boronic ester in 87 % yield (**32**), and the 2-methylphenyl boronic ester provided **33** in 60 % yield.

An extension of the substrate scope could be achieved if lithium *tert*-butoxide is replaced with CsF. This change was particularly beneficial in coupling *ortho*-substituted boronic esters with less hindered electrophiles (Scheme 1 a).^[20] Furthermore, CsF allowed the reaction to be performed in the presence of acidic functional groups, as demonstrated by the reaction of the 4-hydroxypiperidine-derived electrophile shown in Scheme 1 b. Finally, the extremely hindered aniline **33** could be prepared in 89 % yield using this procedure (Scheme 1 c).



Scheme 1. Reactions with CsF as an additive. a) ArBneop (1.2 equiv), R_2NOBz (1.0 equiv), Xantphos (5 mol%), $CuOtBu$ (5 mol%), CsF (5.0 equiv), toluene, 60 °C, 72 h.

We propose that the amination reaction proceeds according to the mechanism shown in Scheme 2. The reaction involves transmetalation from boron to copper, with subsequent electrophilic amination of the aryl copper intermediate. Finally, the reactive copper alkoxide is regenerated with lithium alkoxide.



Scheme 2. Proposed reaction mechanism.

With the transmetalation of aryl boronic esters to copper well documented in the literature,^[16,21d-e] we focused our attention on the electrophilic amination of the putative aryl copper intermediate (Scheme 1). A reaction of electrophile **2** with the IMes-supported copper aryl complex **37**^[16] resulted in a 73 % yield of aniline **38**, in less than 30 minutes, at room temperature. In addition, when used as a catalyst, **37** provided results indistinguishable from those obtained with IMes- $CuOtBu$ catalyst.^[22]

In conclusion, we have developed a mild copper-catalyzed reaction for the synthesis of sterically hindered anilines from aryl and heteroaryl boronic esters. The new method is compatible with a wide range of functionalities, including chloro, bromo, iodo, carbomethoxy, nitro, hydroxyl, formyl,

and methoxy groups. Overall, an exceptionally broad scope and reliability of this new procedure, together with the availability of a wide variety of aryl boronic esters, make it a significant addition to the existing methods for aniline synthesis.

See the Supporting Information for full experimental details, including full characterization for new compounds.

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