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# Reliable and Diverse Synthesis of Aryl Azides through Copper-Catalyzed Coupling of Boronic Acids or Esters with TMSN$_3$

Yu Li,[a, b] Lian-Xun Gao,[a] and Fu-She Han*[a]

Organic azides are versatile compounds in a wide spectrum of areas. They are commonly used as photoaffinity labeling reagents for biomolecules,[1] and they also serve as a latent group for accessing a rich variety of functional groups including amines, amides, and carbamates, as well as aziridines, the ring-opening and expansion reactions of which are extremely attractive for constructing numerous N-containing structural motifs.[2] Particularly, with the recent advent of the click chemistry of azides and alkynes for accessing triazoles,[3] and the [3+2] cycloaddition of azides and cyanides for the construction of structurally more interesting tetrazoles,[4] azides have found widespread applications in drug discovery,[5] biochemistry,[6] materials science,[7] and supramolecular chemistry.[8]

Thus, practical routes to access various azides are required. Although a myriad of approaches for the synthesis of aliphatic azides are available,[9] methods for the preparation of aryl azides are rather limited, with the conversion of amines to the azides through their diazonium salts[9,10] or the reactions of organometallic aryls with *p*-tosyl azide[11] being the major choice. However, general use of these processes is restricted owing to the poor functional-group compatibility and harsh reaction conditions. Recently, copper-catalyzed couplings of aryl amines,[12] halides,[13] and boronic acids[14] with an azide source such as TfN$_3$[12a] and NaN$_3$,[13,14] have been reported. Although powerful, the generality of these methods remains to be determined. More significantly, hazards associated with the azide sources[12–14] and *t*BuONO[10] are important deterrents to their practical use. Herein, we present a less hazardous, simple, and highly efficient protocol for the diverse synthesis of aryl azides through copper-catalyzed coupling of boronic acids or esters with TMSN$_3$. Although TMSN$_3$ is a more reliable azide source,[9b] its use in metal-catalyzed organic azide formation is virtually unknown.

In the initial studies, coupling of 4-methoxylphenylboronic acid (**1**) with TMSN$_3$ was carried out to optimize the reaction conditions. As shown in Table 1, either in the absence or in the presence of tetrabutylammonium fluoride (TBAF), the CuI-catalyzed coupling was inefficient in MeOH at room temperature (Table 1, entries 1 and 2). The reaction was also sluggish by heating under reflux without using TBAF (Table 1, entry 3). Pleasingly, when TBAF was added under reflux conditions, the desired coupling reaction occurred quite smoothly to give the 4-methoxylphenyl azide (**2**) in 89 % yield (Table 1, entry 4). The control experiment showed that no reaction occurred in the absence of CuI (Table 1, entry 5).[15] It is thus evident that in addition to the catalyst, the use of TBAF as an additive coupled with an elevated reaction temperature plays a pivotal role in effecting the reaction. Here, TBAF is assumed to promote the cleavage of the N−Si bond in TMSN$_3$ to form a more nucleophilic N$_3^-$ anion.

With these preliminary results in hand, we investigated further the effect of catalysts, additives, and solvents on this transformation. A survey of the catalysts revealed that although FeCl$_2$ was inefficient (Table 1, entry 6), rapid conversion as well as excellent yields were observed for various copper catalysts that have different redox states (e.g., Cu$^{I}$ and Cu$^{II}$) and counter ions (Table 1, entries 7–11), and CuCl appeared to be the most appealing catalyst in terms of the yield and reaction time (Table 1, entry 7). Thus, by using CuCl as the catalyst, the effect of additives was then evaluated. The results showed that TBAF was more effective than KF, CsF, and NH$_4$F as shown by a comparison of the corresponding results (Table 1, entry 7 vs. entries 12–14). More interestingly, we observed a strong dependence of the reaction efficiency on the nature of solvents. Namely, the reaction was completely suppressed when aprotic solvents

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[a] Y. Li, Prof. Dr. L.-X. Gao, Prof. Dr. F.-S. Han
Changchun Institute of Applied Chemistry
Chinese Academy of Sciences, 5625 Renmin Street
Changchun 130022, Jilin (China)
Tel: (+86) 431-85262936
E-mail: fshan@ciac.jl.cn

[b] Y. Li
Graduate School of Chinese Academy of Sciences
Beijing, 100864 (China)

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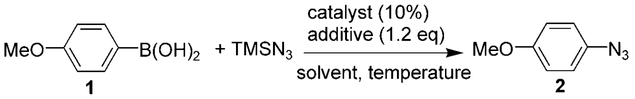
Table 1. Optimization studies for the copper-catalyzed cross-coupling of 4-methoxylphenylboronic acid (**1**) and $TMSN_3$.[a]



| Entry | Catalyst | Additive | Solvent | $T$ [°C] | $t$ [h] | Yield [%][b] |
|---|---|---|---|---|---|---|
| 1 | CuI | –[c] | MeOH | RT | 10 | NR[d] |
| 2 | CuI | TBAF[e] | MeOH | RT | 5 | NR |
| 3 | CuI | –[c] | MeOH | reflux | 25 | trace[f] |
| 4 | CuI | TBAF | MeOH | reflux | 4.5 | 89 |
| 5 | –[g] | TBAF | MeOH | reflux | 22 | NR |
| 6 | $FeCl_2$ | TBAF | MeOH | reflux | 22 | NR |
| 7 | CuCl | TBAF | MeOH | reflux | 4.5 | 94 |
| 8 | CuBr | TBAF | MeOH | reflux | 5.5 | 93 |
| 9 | $CuCl_2·H_2O$ | TBAF | MeOH | reflux | 7 | 85 |
| 10 | $Cu(OAc)_2$ | TBAF | MeOH | reflux | 4 | 90 |
| 11 | $CuSO_4·5H_2O$ | TBAF | MeOH | reflux | 6 | 92 |
| 12 | CuCl | KF | MeOH | reflux | 8 | 83 |
| 13 | CuCl | CsF | MeOH | reflux | 17 | 76 |
| 14 | CuCl | $NH_4F$ | MeOH | reflux | 22.5 | 74 |
| 15 | CuCl | TBAF | THF | reflux | 8 | trace |
| 16 | CuCl | TBAF | dioxane | 70 | 11 | trace |
| 17 | CuCl | TBAF | DMF | 70 | 11 | trace |
| 18 | CuCl[h] | TBAF | THF | reflux | 4 | 93 |
| 19 | CuCl[h] | TBAF | DMF | RT | 10 | 74 |
| 20 | CuCl[h] | TBAF | dioxane | RT | 22.5 | 72 |
| 21 | CuCl | TBAF | MeOH/THF (v/v=1:1.6) | reflux | 15.5 | 79 |
| 22 | CuCl | TBAF | MeOH/THF (v/v=1:1) | reflux | 7 | 87 |
| 23 | CuCl | TBAF | MeOH/THF (v/v=2:1) | reflux | 6 | 96 |

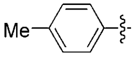
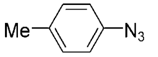
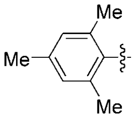
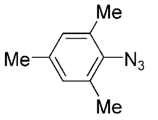
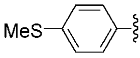
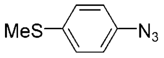
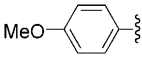
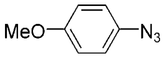
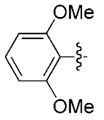
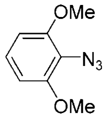
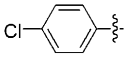
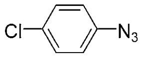
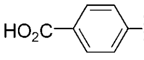
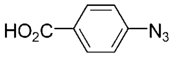
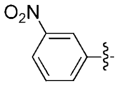
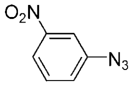
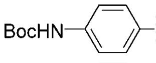
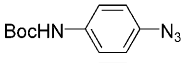
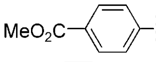
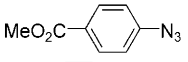
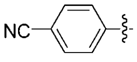
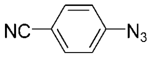
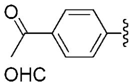
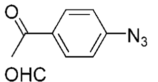
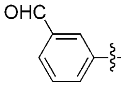
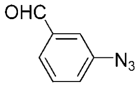
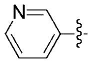
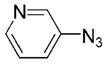
[a] Reaction conditions: 4-methoxylphenylboronic acid (1 mmol), $TMSN_3$ (1.1 mmol for entries 1–3, and 1.2 mmol for entries 4–23), copper catalyst (10 mol%), additives (1.2 mmol), solvent (4 mL). [b] Isolated yields. [c] No additives were used. [d] NR = No reaction. [e] Tetrabutylammonium fluoride (1 mol$L^{-1}$ solution in THF). [f] Monitored by TLC. [g] No CuI catalyst. [h] CuCl (1.0 equiv) was used.

such as THF, DMF, and dioxane were used instead of protic MeOH (Table 1, entries 15–17). Further investigation showed that effective conversion in these aprotic media requires at least a stoichiometric amount of catalyst (Table 1, entries 18–20). Such a marked solvent effect was further confirmed by executing the reaction in a THF/MeOH mixed solvent. In such a solvent system both the reaction rate and the yield were increased gradually as the proportion of MeOH increased (Table 1, entries 21–23), indicating that the choice of protic solvent is crucial for this transformation. The role of MeOH in promoting the coupling reaction is not clear at this stage and deserves a further detailed investigation.

Thus, extensive survey of various reaction parameters that include catalyst, additive, solvent, and temperature led to the identification of an optimal reaction system, that is, CuCl (10 mol%) and TBAF (1.2 equiv) at reflux in MeOH. By applying the optimized conditions, we then defined the scope and functional-group tolerance of this transformation. Accordingly, a variety of boronic acids were examined and the data are listed in Table 2. Simple boronic acids with inert methyl substituents underwent smooth coupling to afford the desired products in excellent yields (Table 2, entries 1 and 2). The reaction was also tolerant of a rich variety of substituents with a strong electron-donating (Table 2, entries 3-5) and electron-withdrawing nature (Table 2, entries 6-13). In addition, the mild and simple reaction conditions permit the synthesis of aryl azides containing various reactive groups such as acid or base-labile Boc, ester, and cyano groups (Table 2, entries 9-11), as well as electrophilic ketone and aldehyde groups (Table 2, entries 12 and 13). Moreover, the sterically congested 2,6-disubstituted substrates could also be coupled efficiently under the optimized

Table 2. Cross-coupling of various boronic acids with $TMSN_3$ under optimized conditions.[a]

$$ArB(OH)_2 + TMSN_3 \xrightarrow[\text{MeOH, reflux}]{\text{CuCl (10\%)}\ \text{TBAF (1.2 eq)}} ArN_3$$

| Entry | $ArB(OH)_2$ | $t$ [h] | $ArN_3$ | Yield [%][b] |
|---|---|---|---|---|
| 1 |  | 4.5 |  | 83[c] |
| 2 |  | 5.0 |  | 97 |
| 3 |  | 4.5 |  | 100 |
| 4 |  | 4.5 |  | 94 |
| 5 |  | 1.5 |  | 77 |
| 6 |  | 4 |  | 90 |
| 7 |  | 22.5 |  | 86 |
| 8 |  | 4.5 |  | 93 |
| 9 |  | 5 |  | 92 |
| 10 |  | 7 |  | 100 |
| 11 |  | 5 |  | 80 |
| 12 |  | 4 |  | 82 |
| 13 |  | 4 |  | 83 |
| 14 |  | 7 |  | 73 |

[a] Reaction conditions: Arylboronic acid (1 mmol), $TMSN_3$ (1.2 mmol), CuCl (10 mol%), TBAF (1.2 mmol; 1 mol$L^{-1}$ solution in THF), MeOH (4 mL) under reflux. [b] Isolated yields. [c] Part of the product was lost during evaporation and drying under reduced pressure owing to the rather volatile property of the product.

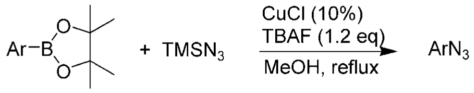
conditions (Table 2, entries 2 and 5). Finally, a heteroaromatic boronic acid proved to be a competent substrate, providing the corresponding heteroaromatic azide in 73 % yield (Table 2, entry 14).

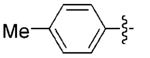
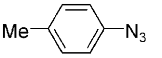
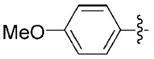
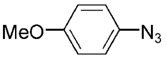
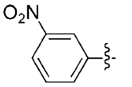
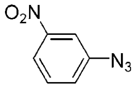
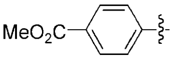
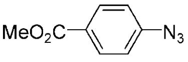
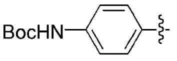
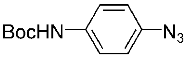
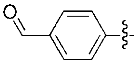
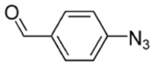
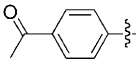
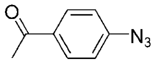
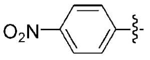
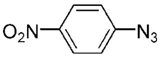
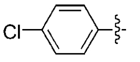
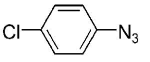
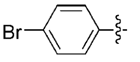
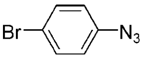
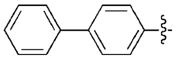
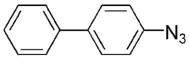
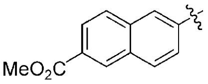
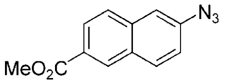
Note that to compare with the reported procedures, the methodology presented here is compatible with a broader range of functional groups. For instance, boronic acids that are substituted with a strong electron-withdrawing group such as 4-cyano or 4-acetyl group are weak nucleophiles but could be converted to the desired cyano and acetylphenyl azides in high yields of over 80 % (Table 2, entries 11 and 12). In sharp contrast, we noted that attempts to realize the same products through the $CuSO_4$-catalyzed cross-coupling of the aniline derivatives with $TfN_3$ was less efficient, producing the desired products only in 7 % and 15 % yields, respectively.[12a] Consequently, the high reaction efficiency, simplified operation, broad applicability, and the less hazardous properties of the process presented herein by employing boronic acids and $TMSN_3$ as substrates appeared to be a more attractive option for the synthesis of aryl azides with structural diversity.

Having established a robust protocol for the synthesis of various aryl azides through the CuCl-catalyzed coupling of aryl boronic acids and $TMSN_3$, we then became interested in extending this method to boronic esters because this class of substrate can now be accessed very readily through the Suzuki–Miyaura approach, either from aryl halides or from phenol derivatives.[16] More significantly, utilizing boronic esters as substrates would omit the acidic hydrolysis step for converting boronic esters to the corresponding acids, which not only makes the pathway for accessing aryl azides more straightforward but also enlarges the scope of the coupling substrates. It should also be mentioned that although direct azidation of aryl halides (I and Br) and $NaN_3$ catalyzed by CuI has been reported,[13] practical application of this technology was limited owing to the relatively harsh reaction conditions such as the utilization of NaOH base under elevated temperature, inert gas atmosphere, and the explosive $NaN_3$.

To examine the feasibility and general applicability of this transformation, a number of boronic esters were subjected to treatment with $TMSN_3$ by employing identical conditions to those of boronic acids (Table 3). The results showed that this procedure exhibits not only high efficiency but also broad applicability to various aryl boronic esters that are substituted by electron-neutral (Table 3, entry 1), electron-donating (Table 3, entry 2), and electron-withdrawing groups (Table 3, entries 3–10). More interestingly, substrates with rather a strong electron-withdrawing nature such as $NO_2$ and carbonyl groups (Table 3, entries 6–8) were also effective. In addition, substrates with a Br group, which has been shown to be a prominent leaving group in numerous transition-metal-catalyzed cross-couplings,[17] also underwent smooth coupling to afford the desired azide in high yield (Table 3, entry 10). Equally interesting is the fact that the high coupling efficiency was also observed for biaryl and fused aromatic substrates (Table 3, entries 11 and 12).

Table 3. Cross-coupling of various boronic esters with $TMSN_3$ under optimized conditions.[a]



| Entry | ArBPinacol | $t$ [h] | $ArN_3$ | Yield [%][b] |
|---|---|---|---|---|
| 1 |  | 11 |  | 79[c] |
| 2 |  | 9.5 |  | 91 |
| 3 |  | 8 |  | 95 |
| 4 |  | 8 |  | 86 |
| 5 |  | 4.5 |  | 77 |
| 6 |  | 9 |  | 67 |
| 7 |  | 7.5 |  | 86 |
| 8 |  | 10 |  | 78 |
| 9 |  | 7 |  | 84 |
| 10 |  | 7.5 |  | 75 |
| 11 |  | 8 |  | 96 |
| 12 |  | 6.5 |  | 95 |

[a] Reaction conditions: Arylboronic ester (1 mmol), $TMSN_3$ (1.2 mmol), CuCl (10 mol %), TBAF (1.2 mmol, 1 mol $L^{-1}$ solution in THF), MeOH (4 mL) under reflux. [b] Isolated yields. [c] Part of the product was lost during evaporation and drying under reduced pressure owing to the rather volatile property of the product.

In summary, we have developed a reliable and highly efficient methodology for the diverse synthesis of aryl azides through copper-catalyzed coupling reactions of aryl boronic acids or esters with $TMSN_3$. This procedure offers several advantages over the available methods that include an increased safeness and a broadened functional group compatibility. These points are of crucial importance for large-scale azide production. Most importantly, we demonstrated that boronic esters are also viable substrates, providing a more practical pathway to access a rich range of aryl azides. Consequently, the method presented in this work would provide an important advance in the synthetic chemistry of aryl azides, and thereby serve as a more powerful tool to offer structurally more abundant materials for the downstream fields related to organic azides. Further efforts towards the clarification of the solvent effect on this transformation, and the applications of our azides to the diverse construction of biologically important compounds that contain tetrazole skeletons such as valsartan and olmesartan derivatives are currently underway.

## Experimental Section

**Typical procedure for copper-catalyzed coupling of aryl boronic acids (or esters) with TMSN$_3$**: TBAF (1.2 mmol), TMSN$_3$ (1.2 mmol), and CuCl (10 mol%) were sequentially added to a solution of the boronic acid (or ester; 1 mmol) in MeOH (4 mL). The resulting solution was then stirred under reflux until the starting material had disappeared as monitored by TLC. The reaction mixture was concentrated under reduced pressure and the crude product was purified by silica-gel chromatography to give the desired products (a mixture of EtOAc and petroleum ether was used as the eluent, and the ratio of EtOAc to petroleum ether was adjusted based on the solubility and polarity of the products).

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**Keywords:** aryl azides · boronic acids · boronic esters · copper · cross-coupling

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