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COMMUNICATION

Copper-Catalyzed Electrophilic Amination Using *N*-Methoxyamines

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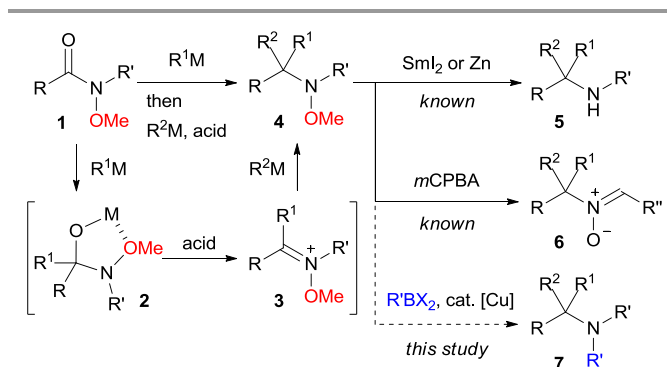
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Copper-catalyzed electrophilic amination of a triarylboroxin using an *N*-methoxyamine to give quick access to a variety of anilines was reported. The reaction was especially useful for syntheses of functionalized anilines when combined with our previously reported nucleophilic addition to *N*-methoxyamides.

Our research group has been exploring nucleophilic additions to *N*-methoxyamides **1** as a practical synthetic tool for complex alkaloids and pharmaceuticals (Scheme 1, **1**→**4**).^{1–3} In contrast to the well-known Weinreb ketone synthesis,⁴ our nucleophilic addition to *N*-methoxyamides **1** enabled installation of two different organometallic reagents in the presence of an acid, producing multi-substituted *N*-methoxyamines **4** in high yields. The developed reaction proceeded under mild reaction conditions in the presence of a variety of functional groups, and was applied to the concise total synthesis of gephyrotoxin.^{2e} We envisioned that, if we could develop new transformations of the generated *N*-methoxyamines **4**, those reactions would render our nucleophilic additions more useful. Indeed, transformations of *N*-methoxyamines **4** are much less explored than their construction.⁵ One representative reaction is reductive cleavage with SmI_2 or zinc via single electron transfer to give secondary amines **5**. Oxidation of **4** to nitrone **6** is another practical transformation. However, to the best of our knowledge, no direct carbon-nitrogen bond formation has been reported from *N*-methoxyamines **4**. In this communication, we disclose a copper-catalyzed electrophilic amination with an *N*-methoxyamine and a triarylboroxin under acidic conditions, giving access to functionalized tertiary anilines **7**.



Scheme 1 Nucleophilic addition to *N*-methoxyamide **1** and further transformations of *N*-methoxyamine **4**.

Transition-metal-catalyzed electrophilic amination⁶ has been extensively studied as a useful alternative to the Buchwald-Hartwig coupling⁷ and the Chan-Lam-Evans coupling⁸ (Scheme 2A, **8**→**9**). Most of the reported examples employ *N*-benzoyloxyamine **8** as an electrophilic aminating reagent due to the good leaving ability of the benzoyloxy group. The research group of Johnson opened up the copper-catalyzed electrophilic amination of diorganozinc reagents or Grignard reagents using *N*-benzoyloxyamines.^{9a,b} After their reports, Hirano/Miura^{9c} and Lalic^{9d,e} independently disclosed landmark reports on the copper-catalyzed electrophilic amination of organoborane reagents. Electrophilic amination using *N*-benzoyloxyamines is now one of the hot topics in current organic chemistry.⁹ On the other hand, *N*-methoxyamine **10** could be another practical electrophilic aminating reagent due to the easy availability of highly functionalized **10** through multi-step synthesis including our nucleophilic addition. Unfortunately, the poor leaving ability of the methoxy group has prevented development of this electrophilic amination.¹⁰ To overcome the poor reactivity, we envisioned copper-catalyzed electrophilic amination under acidic conditions (Scheme 2B). Both a copper catalyst and an organoborane reagent show high Lewis acidity by installation of electron withdrawing groups. The resulting Lewis acidic

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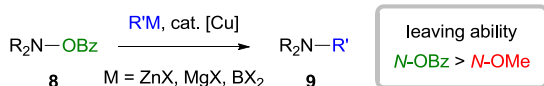
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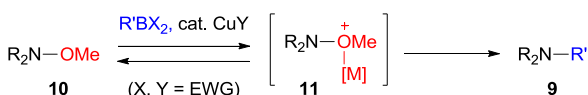
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reagents could activate the leaving ability of the methoxy group by formation of cationic intermediate **11**,¹¹ which would then undergo the copper-catalyzed electrophilic amination with the organoborane reagent to give **9**.

(A) Previous approaches



(B) This study: Acid-mediated electrophilic amination



Scheme 2 Working hypothesis: electrophilic amination using *N*-methoxyamine **10** under acidic conditions.

The present investigation commenced by examining the reaction of *N,N*-dibenzyl-*N*-methoxyamine **12** (Table 1). A solution of **12** in DME was treated with various organoborane reagents in the presence of 10 mol % $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ at 85 °C. The reaction with phenylboronic acid **14** resulted in recovery of the starting material **12**, along with *N,N*-dibenzylamine **13** in 16% yield (entry 1). Use of boron ester **15** or trifluoroborate **16**¹² did not promote the reaction (entries 2 and 3). Gratifyingly, the reaction with phenyl difluoroborane **17**¹³ provided phenylaniline **9a** in 42% yield, together with secondary amine **13** in 33% yield (entry 4). The best result was obtained when using triphenylboroxin **18**, to give phenylaniline **9a** in 70% yield (entry 5). The acidity of the reaction media was proved to be crucial in this electrophilic amination, in contrast to most electrophilic aminations that are known to take place under basic conditions. The reaction required assistance of the highly acidic copper catalyst, $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ (entry 5), while the reaction without the copper catalysts or with other copper catalysts resulted in recovery of **12** (entries 6–9). Addition of triethylamine completely inhibited the reaction, probably because it neutralized the requisite acidic media (entry 10). Interestingly, extra addition of Lewis or Brønsted acids provided none of the desired product **9a**, but generated reduced secondary amine **13** exclusively (entries 11 and 12). Although a detailed mechanism has not yet been elucidated, we succeeded in the copper-catalyzed electrophilic amination using *N*-methoxyamines.

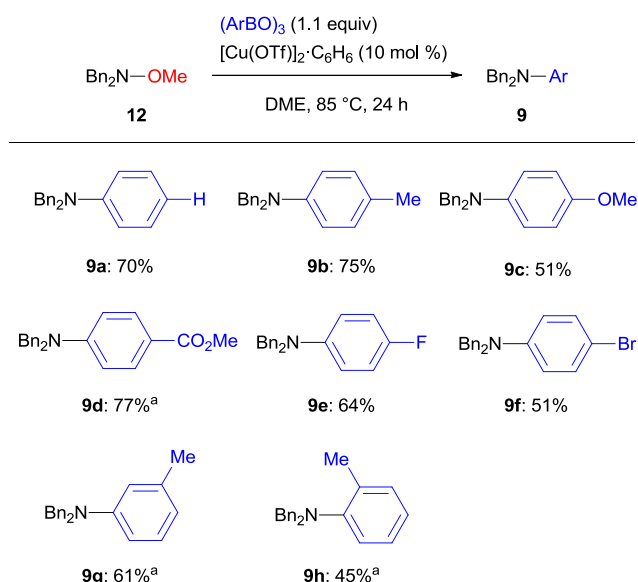
With the optimized conditions in hand, we surveyed the scope of the triarylboroxins (Scheme 3). The reaction proceeded in the presence of electron donating groups such as 4-methyl and 4-methoxy groups (**9b**: 75%; **9c**: 51%). Substituents including 4-methyl ester and 4-fluoro groups were well tolerated (**9d**: 77%; **9e**: 64%). Although the yield was moderate with tris(4-bromophenyl)boroxin, the resulting **9f** with the arylbromide moiety was synthetically useful upon further transformation using other transition metal-catalyzed reactions such as Suzuki-Miyaura coupling (**9f**: 51%). This electrophilic amination was sensitive to the steric factors of the boroxins. While the reaction with the tris(4-tolyl)boroxin provided **9b** in

75% yield, the 3-tolyl and the 2-tolyl derivatives gave **9g** and **9h** in 61% and 45% yields, respectively. DOI: 10.1039/C5OB02167G

Table 1 Optimization of electrophilic amination using *N*-methoxyamine **12**^a

| | | PhBX_2 (1.1 equiv) CuY (20 mol %) additive (1.1 equiv) DME, 85 °C, 24 h | | $\text{Bn}_2\text{N}-\text{OMe}$ | | $\text{Bn}_2\text{N}-\text{Ph}$ + Bn_2NH |
|-----------------|-----------|--|---------------------------|----------------------------------|-----------|--|
| | | | | 12 | | 9a + 13 |
| | | | | 14 | 15 | 16 |
| | | | | 17 | 18 | |
| Entry | [B] | [Cu] | additive | yields (%) ^b | | |
| | | | | 9a | 13 | 12 |
| 1 ^c | 14 | $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ | none | 0 | 16 | 60 |
| 2 ^c | 15 | $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ | none | 0 | 0 | 84 |
| 3 ^c | 16 | $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ | none | 0 | 0 | 91 |
| 4 ^c | 17 | $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ | none | 42 | 33 | 0 |
| 5 ^c | 18 | $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ | none | 70 | 14 | 0 |
| 6 | 18 | none | none | 0 | 0 | 87 |
| 7 | 18 | $\text{Cu}(\text{OAc})$ | none | 0 | 0 | 81 |
| 8 | 18 | CuCN | none | 0 | 0 | 90 |
| 9 | 18 | CuCl | none | 0 | 0 | 88 |
| 10 ^c | 18 | $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ | Et_3N | 0 | 0 | 88 |
| 11 ^c | 18 | $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ | $\text{Sc}(\text{OTf})_3$ | 0 | 71 | 0 |
| 12 ^c | 18 | $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ | CSA | 0 | 57 | 0 |

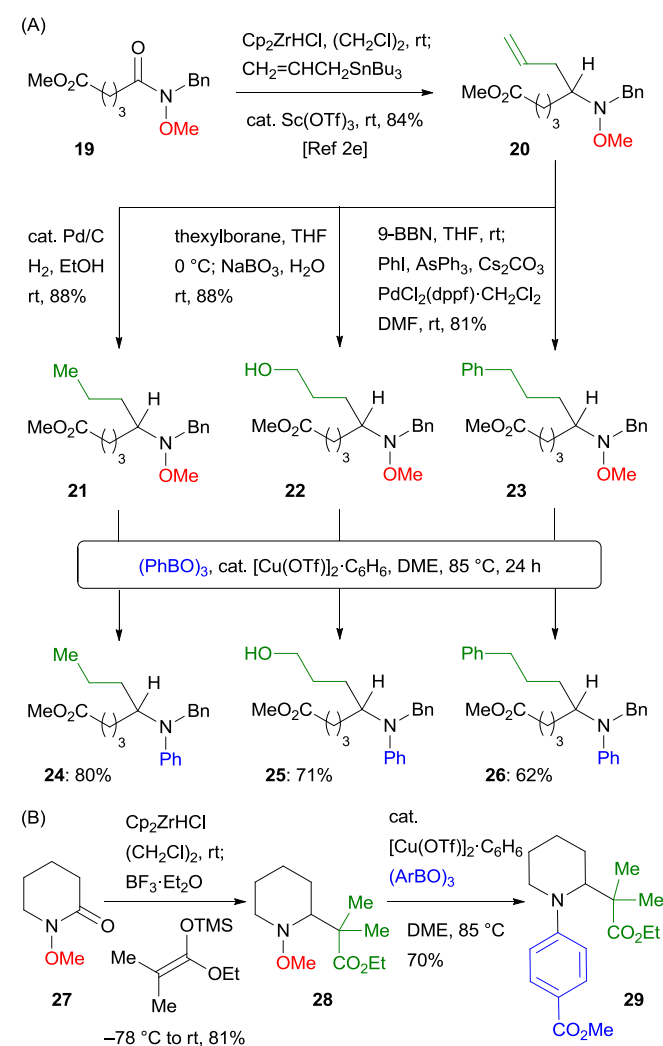
^a Reaction conditions: **5** (1.0 equiv), PhBX_2 (1.1 equiv), CuY (20 mol %), additive (1.1 equiv), DME (0.4 M), 85 °C, 24 h. ^b Yields of isolated product after purification by column chromatography are given. ^c $[\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6]$ (10 mol %) was used.



Scheme 3 Scope for triarylboroxins in the electrophilic amination. ^a $(\text{ArBO})_3$ (1.5 equiv) was used.

The most conspicuous advantage of our electrophilic amination is the quick preparation of a variety of *N*-methoxyamines via nucleophilic addition to *N*-methoxyamides

(Scheme 4A). Previously, we reported amide-selective reductive allylation of *N*-methoxyamide **19** using the Schwartz reagent [Cp₂ZrHCl]^{14,15} to provide *N*-methoxyamine **20** in 84% yield.^{2c,e} The resulting *N*-methoxyamino group is chemically stable, and enables quick diversification of **20** due to its high compatibility with various reaction conditions. For example, the terminal olefin in **20** was selectively functionalized without affecting the *N*-methoxyamine in subsequent hydrogenation, hydroboration and Suzuki-Miyaura coupling reactions.¹⁶ These three products **21–23** were then exposed to the optimized electrophilic amination conditions, affording functionalized aniline derivatives **24–26** in good yields. Cyclic *N*-methoxyamines were also useful electrophilic aminating reagents (Scheme 4B). Reductive Mukaiyama-Mannich reaction of *N*-methoxylactam **27** provided *N*-methoxyamine **28** in 81% yield. The next electrophilic amination was relatively insensitive to the steric factors. The reaction smoothly took place in spite of the steric congestion of **28**, giving multi-substituted aniline **29** in 70% yield.



Scheme 4 Synthesis of functionalized anilines via the electrophilic amination.

Conclusions

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DOI: 10.1039/C5OB02167G

We have demonstrated copper-catalyzed electrophilic amination using an *N*-methoxyamine and a triarylboroxin. The reaction allows direct carbon-nitrogen bond formation from the stable *N*-methoxyamines under acidic conditions to provide tertiary anilines. Our method proved to be especially powerful when combined with our nucleophilic addition to *N*-methoxyamides. We believe that the developed electrophilic amination has broadened the utility of our nucleophilic addition, and *N*-methoxyamines will become the new choice as an electrophilic aminating reagent.

Acknowledgement

This research was supported by a Grant-in-Aid for Scientific Research (C) from MEXT (15K05436). Synthetic assistance from Ms. Minami Nakajima and Mr. Seiya Katahara is gratefully acknowledged.

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