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# Highly Efficient Copper-Catalyzed Synthesis of Internal Alkynes *via* Aerobic Oxidative Arylation of Terminal Alkynes

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**Abstract:** We have developed a novel and highly efficient, copper-catalyzed synthesis of internal alkynes *via* oxidative couplings of aromatic boronic acids with terminal alkynes at room temperature. The protocol uses inexpensive copper(I) oxide [$Cu_2O$] as the catalyst, oxygen in the air as the stoichiometric oxidant; no ligand and sealed reaction vessels are required, and remarkable functional group tolerability is observed with coupling occurring.

**Keywords:** C–H activation; copper; internal alkynes; oxidative coupling; synthetic methods

## Introduction

The development of methods for forming C–C bonds plays a central role in synthesis design,[1] and the metal-catalyzed cross-coupling reactions are the most powerful.[2] Internal alkyne intermediates are widely used in the synthesis of many antimycotics,[3] antibiotics,[4] liquid crystals, polymers, and optical or electronic materials.[5] The traditional palladium/copper co-catalyzed Sonogashira-type coupling[6] is a popular strategy for the construction of C($sp^2$)–C($sp$) bonds,[7] and the protocol shows high efficiency and tolerance of functional groups under mild conditions (even at room temperature). A palladium-free, copper-catalyzed Sonogashira reaction was also reported under CuBr/*rac*-BINOL catalysis at 130 °C.[8] Oxidative coupling reactions, particularly methods that enable the direct functionalization of C–H bonds, have been the focus of significant recent interest.[9] Unfortunately, some methods often require stoichiometric special oxidants and this reduces their appeal relative to classical cross-coupling reactions. Obviously, it is economical and environmentally benign to employ molecular oxygen in air as the stoichiometric oxidant.[10] Recently, copper- or palladium-catalyzed Sonogashira-type couplings of terminal alkynes with arylboronic acids/esters,[11] or aryltrimethoxysilanes[12] have been investigated in the presence of 1–3 equivalents of Ag(I) salts as the additives. Very recently, we have developed an efficient, copper-catalyzed approach to primary aromatic amines by couplings of aromatic boronic acids with aqueous ammonia[13] *via* the Chan–Lam amination strategy.[14] Herein, we report a novel and highly efficient, copper-catalyzed synthesis of internal alkynes *via* aerobic oxidative arylation of terminal alkynes at room temperature.

## Results and Discussion

Initially, 2-formylphenylboronic acid and phenylacetylene were chosen as the model substrates to optimize the reaction conditions [Eq. (A) in Table 1]. As shown in Table 1, the effect of additives was tested by using $Cu_2O$ as the catalyst, methanol as the solvent, and the target product was not observed in the absence of additive (entry 1) or in the presence of $Et_3N$ (entry 2). When pyridine was used as the additive, the desired target product (**3a**) was obtained in 40% yield while a 40% yield of the by-product – 2-methoxybenzaldehyde from the coupling of 2-formylphenylboronic acid with methanol – was observed (entry 3). However, the coupling reaction did not work when pyridine was used as the solvent instead of methanol (entry 4). Inspiringly, a high-yield of product was obtained by using $CHCl_3$ as the solvent and pyridine as the additive (entry 5). The target product was also obtained in the presence of 0.5 equivalents of pyridine


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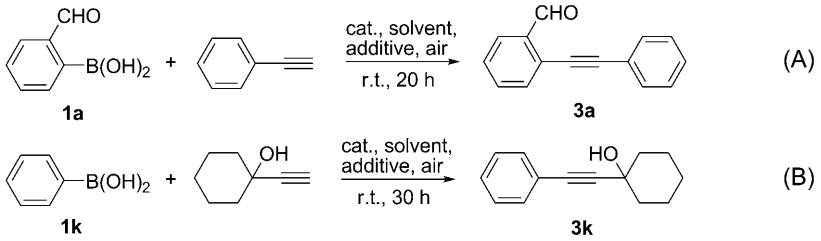
**Table 1.** Copper-catalyzed oxidative coupling of 2-formylphenylboronic acid with phenylacetylene [Eq. (A)] or phenylboronic acid with 1-ethynyl-1-cyclohexanol [Eq. (B)]: optimization of conditions.[a]




| Entry | Catalyst | Solvent | Additive(s) [mL] | Yield [%][b] |
|---|---|---|---|---|
| 1[f] | $Cu_2O$ | MeOH | – | trace |
| 2[f] | $Cu_2O$ | MeOH | $Et_3N$ (0.4) | trace |
| 3[f] | $Cu_2O$ | MeOH | Pyridine (0.4) | 40[c] |
| 4[f] | $Cu_2O$ | – | Pyridine (2) | 0[d] |
| **5[f]** | **$Cu_2O$** | **$CHCl_3$** | **Pyridine (0.2)** | **72** |
| 6[f] | $Cu_2O$ | $CHCl_3$ | Pyridine (0.5 equiv.) | 59 |
| 7[f] | $Cu_2O$ | $CHCl_3$ | DMAP (1.0 equiv.) | 30 |
| 8[f] | $Cu_2O$ | $CH_2Cl_2$ | Pyridine (0.4) | 60 |
| 9[f] | $Cu_2O$ | $CH_3CN$ | Pyridine (0.4) | 18 |
| 10[f] | $Cu(OAc)_2$ | $CHCl_3$ | Pyridine (0.2) | 50 |
| 11[f] | $CuSO_4$ | $CHCl_3$ | Pyridine (0.2) | 40 |
| 12[f] | CuI | $CHCl_3$ | Pyridine (0.2) | 35 |
| 13[f] | Cu | $CHCl_3$ | Pyridine (0.2) | 40 |
| 14[g] | $Cu_2O$ | $CHCl_3$ | Pyridine (0.2) | 30 |
| 15[g] | **$Cu_2O$** | **$CHCl_3$** | **Pyridine (0.2) + MeOH (0.2)** | **70** |
| 16[g] | $Cu_2O$ | $CHCl_3$ | Pyridine (0.2) + MeOH (0.1) | 55 |
| 17[g] | $Cu_2O$ | $CHCl_3$ | Pyridine (0.2) + MeOH (0.4) | 55 |
| 18[g] | $Cu_2O$ | $CHCl_3$ | Pyridine (0.2) + EtOH (0.2) | 30 |
| 19[g] | $Cu_2O$ | $CHCl_3$ | Pyridine (0.2) + *i*-PrOH (0.2) | 20 |
| 20[g] | $Cu_2O$ | $CHCl_3$ | Pyridine (0.2) + MeOH (0.2) | Trace[e] |

[a] *Reaction conditions:* room temperature (~25 °C), catalyst (0.05 mmol), arylboronic acid (0.5 mmol), alkyne (1 mmol), solvent (2 mL).
[b] Isolated yield.
[c] 2-Methoxybenzaldehyde was obtained in 40% yield.
[d] Pyridine (2 mL) as the solvent.
[e] Under nitrogen atmosphere.
[f] Eq. (A).
[g] Eq. (B).

(entry 6) or one equivalent of DMAP (entry 7), and the yield gradually increased as reaction time was elongated, the result showed that pyridine or DMAP acted as catalyst together with $Cu_2O$. Some other solvents were investigated, and $CHCl_3$ was the best solvent (compare entries 5, 8 and 9). Several copper catalysts were tested, and $Cu_2O$ was proved to be most effective (compare entries 5, 10–13). Unexpectedly, the desired target product was observed in only 30% yield (entry 14) when phenylboronic acid and 1-ethynyl-1-cyclohexanol [Eq. (B) in Table 1] were used as the model substrates under the optimized condition above, so we had to continue our optimization process. Coupling of phenylboronic acid with 1-ethynyl-1-cyclohexanol provided the target product (**3k**) in 70% yield when pyridine and methanol (volume ratio 1:1) were used as the additives (entry 15). The yield decreased as the amount of methanol was changed (entries 16 and 17). The coupling reaction provided lower yields when ethanol (entry 18) or isopropyl alcohol (entry 19) replaced methanol in entry 15 as the additive. Only trace amounts of product appeared if air was excluded by introducing a nitrogen atmosphere to the reaction system (entry 20), and this result showed that oxygen participated in the coupling reaction, so the reaction underwent an oxygen-involving oxidation process like the Chan–Lam amination.[14]

After the optimization process above, copper-catalyzed oxidative couplings of aromatic boronic acids with terminal alkynes were carried under the following conditions: 10 mol% $Cu_2O$ (relative to the aromatic boronic acid) as the catalyst, $CHCl_3$ as the solvent, pyridine (conditions **A**) or pyridine and methanol (volume ratio 1:1) (conditions **B**) as the addi-

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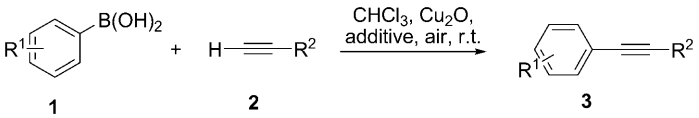
tive(s) under an atmosphere of air at room temperature (~25 °C). As shown in Table 2, all the substrates examined provided good to excellent yields at room temperature. The electronic effect of substituent groups on the aromatic boronic acids did not show any evident difference of reactivity. The choice of catalysis conditions (conditions **A** and **B** in Table 2) and reaction rates mainly depended on the structural specialty of the terminal alkynes. For alkynes containing hydroxy (entries 11–13) or imino groups (entry 14), a small amount of methanol as extra additive was required. The coupling reactions could tolerate various

**Table 2.** Copper-catalyzed oxidative couplings of aromatic boronic acids with terminal alkynes.[a]




1 2 3

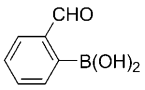
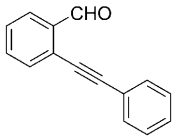
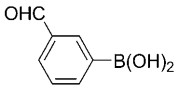
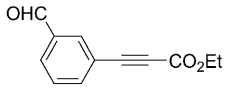
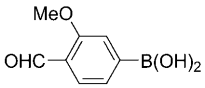
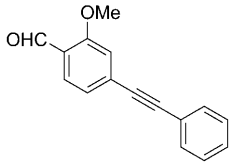
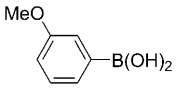
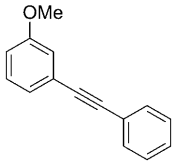
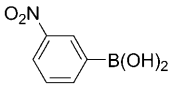
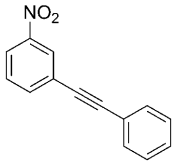
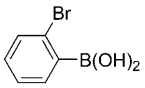
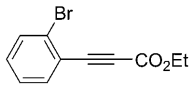
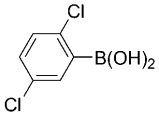
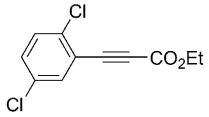
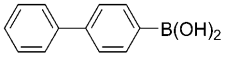
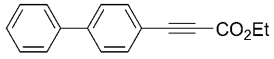
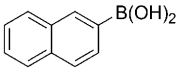
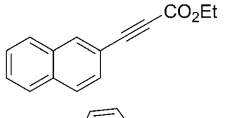
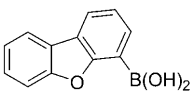
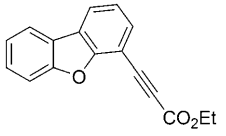
| Entry | Substrate **1** | Conditions/Time [h] | Product **3** | Yield [%][b] |
|---|---|---|---|---|
| 1 | **1a**  | **A**/24 | **3a**  | 79 |
| 2 | **1b**  | **A**/28 | **3b**  | 77 |
| 3 | **1c**  | **A**/24 | **3c**  | 82 |
| 4 | **1d**  | **A**/24 | **3d**  | 69 |
| 5 | **1e**  | **A**/24 | **3e**  | 73 |
| 6 | **1f**  | **A**/29 | **3f**  | 82 |
| 7 | **1g**  | **A**/28 | **3g**  | 71 |
| 8 | **1h**  | **A**/29 | **3h**  | 70 |
| 9 | **1i**  | **A**/26 | **3i**  | 67 |
| 10 | **1j**  | **A**/26 | **3j**  | 71 |

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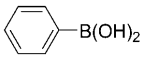
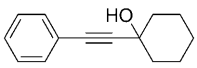
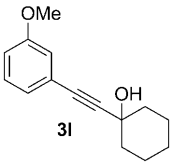
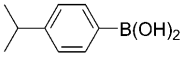
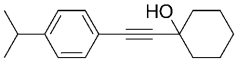
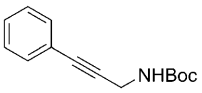
**Table 2.** (Continued)

| Entry | Substrate **1** | Conditions/Time [h] | Product **3** | Yield [%][b] |
|---|---|---|---|---|
| 11 | **1k**  | **B**/36 | **3k**  | 76 |
| 12 | **1d** | **B**/36 | **3l**  | 75 |
| 13 | **1l**  | **B**/33 | **3m**  | 76 |
| 14 | **1k** | **B**/36 | **3n**  | 83 |

[a] *Reaction conditions:* arylboronic acid (0.5 mmol), alkyne (1.0 mmol), $Cu_2O$ (0.05 mmol), $CHCl_3$ (2 mL), room temperature (~25 °C). Conditions **A**: pyridine (0.2 mL) as the additive; conditions **B**: pyridine (0.2 mL) and methanol (0.2 mL) as the additives.

[b] Isolated yield.

functional groups including aldehyde (entries 1–3), ether (entries 3, 4 and 10), nitro (entry 5), carbon-halogen bonds (entries 6 and 7) in the aromatic boronic acids, as well as ester (entries 2, 6–10), hydroxy (entries 11–13) and amino groups (entry 14) in the terminal alkynes.

## Conclusions

We have developed a novel and highly efficient method for copper-catalyzed synthesis of internal alkynes by oxidative couplings of aromatic boronic acids with terminal alkynes at room temperature, and the target products were obtained in good to excellent yields by using inexpensive $Cu_2O$ as the catalyst, $O_2$ in the air as the stoichiometric oxidant and, moreover, no ligand and sealed reaction vessels were required. The method is of high tolerance towards various functional groups in the substrates, and the syntheses of these compounds will attract much attention in industrial and academic research because of their biological and pharmaceutical properties. Further mechanistic investigations are now in progress.

## Experimental Section

### General Procedure for Synthesis of Internal Alkynes 3a–n

A round-bottom flask was charged with a magnetic stirrer and $CHCl_3$ (2 mL), and the substituted aromatic boronic acid (0.5 mmol), the terminal alkyne (1 mmol), $Cu_2O$ (0.05 mmol, 8 mg) and pyridine (0.2 mL) were added to the flask (*Note*: *extra methanol (0.2 mL) was added to the solution for entries 11–14 in* Table 2). The flask was not sealed so that air was allowed to enter the flask, and the mixture was stirred for a time shown in Table 2 under an atmosphere of air at room temperature (~25 °C). After completion of the reaction (the reaction progress was monitored by TLC), the mixture was filtered, and the solvent of the filtrate was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel to provide the desired product.

## Acknowledgements

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