

Expanding the oxidative chemistry of organocopper reagents: facile oxidative cross-coupling of copper acetylides with arylboronic acids

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Abstract We have developed an efficient procedure for oxidative cross-coupling between arylboronic acids and alkynylcopper reagents. Upon simple addition of 1,10-phenanthroline in the presence of oxygen, these highly stable, readily available polymeric reagents are easily activated and transfer their alkynyl group after subsequent transmetalation with the boronic acid. These results further expand the oxidative chemistry of organocopper compounds together with providing a user-friendly entry to diaryl acetylenes.

Keywords Organocopper reagents · Copper acetylides · Oxidative coupling · Boronic acids · Alkynes · Transmetalation

Introduction

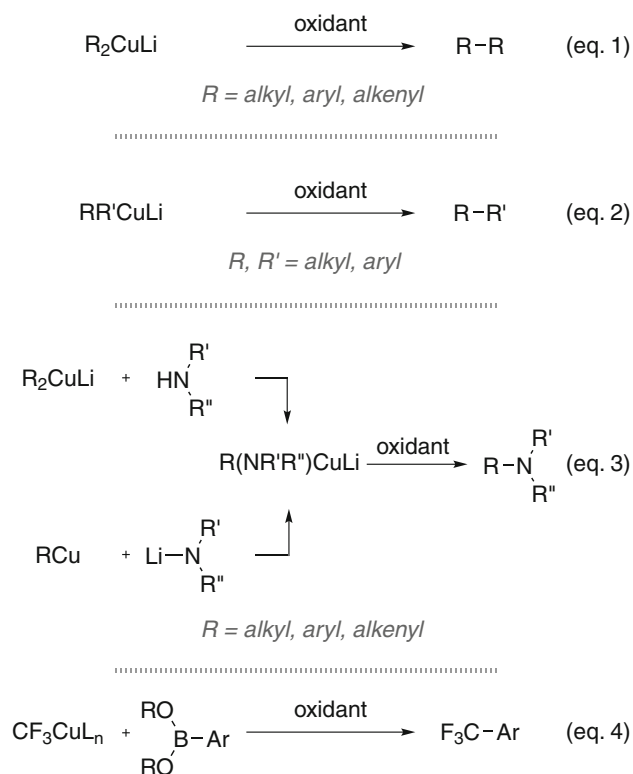
Although organocopper reagents have found numerous applications in organic synthesis such as in conjugate additions, S_N2/S_N2' reactions, and carbocuprations, their behavior in the presence of oxidants has long been a synonym for serious side reactions leading to the formation of undesired dimerization products, even though most useful procedures based on this concept such as the Glaser-Hay coupling [1–3] have been known for more than a century.

Despite remarkable systematic studies by Whitesides on the oxidative dimerization of organocuprates and cross-coupling from mixed cuprates in the 1960s and 1970s

[4–6], the synthetic potential of the oxidative chemistry of organocopper reagents was realized only later on [7, 8]. Remarkable work by Lipshutz [9], Knochel [10], and Spring [11–13] demonstrated the efficiency of such procedures, notably for the formation of carbon–carbon bonds in biaryls, dienes, and aromatic alkynes, all these reactions being based on the formation of an organocuprate followed by its oxidation (Scheme 1, Eqs. 1 and 2). Besides the development of efficient procedures for the formation of a wide range of C–C bonds based on the oxidation of organocopper reagents, this chemistry has been recently extended to the formation of C–N bonds with remarkable efficiency. This resulted in noteworthy studies by Yamamoto [14], Snieckus [15], Ricci [16, 17], and Knochel [18–21], who demonstrated the full potential of the oxidative coupling of amidocuprates and developed especially efficient and mild amination procedures based on this chemistry (Scheme 1, Eq. 3). The oxidation chemistry of trifluoromethyl/perfluoroalkyl organocopper has in addition been extensively studied in the last couple of years, as evidenced with the development of most efficient oxidative trifluoromethylation/perfluoroalkylation of arylboronic acids/boronates using stable, pre-formed trifluoromethyl/perfluoroalkyl copper complexes (Scheme 1, Eq. 4) [22–24].

Although the oxidative cross-coupling of aryl, alkenyl-, alkyl-, and perfluoroalkyl-copper/cuprate reagents have therefore been extensively studied recently, copper acetylides **2** have for some reasons been left aside from those studies, despite the high potential of their oxidation chemistry for the development of mild alkynylation reactions. Stimulated by the potential of strategies based on the oxidation of alkynylcopper reagents and motivated by our experience in copper-catalyzed alkynylation of heteronucleophiles [25–30], we started investigating this area in 2011 and reported efficient processes for the aerobic

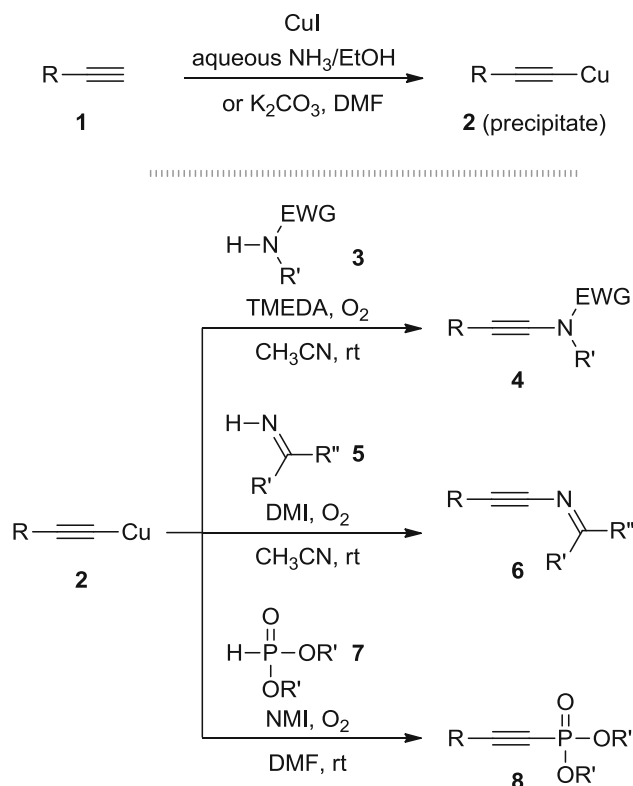
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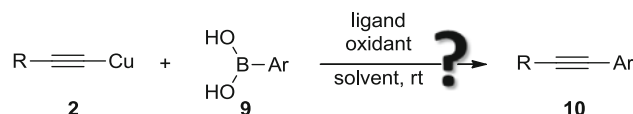
Scheme 1

alkynylation of N- and P- nucleophiles with copper acetylides (Scheme 2) [31, 32]. Indeed, by simply stirring these bench-stable polymeric reagents **2** (except for the copper derivatives of acetylene and *p*-diethynylbenzene, alkynylcopper reagents are stable to shock and heat [33]), which are readily prepared by reaction of the corresponding alkynes **1** and cuprous iodide in a mixture of aqueous ammonia and ethanol or in DMF in the presence of potassium carbonate, with the desired heteronucleophiles (lactams and oxazolidinones **3**, imines **5**, or dialkylphosphites **7**) in the presence of simple activating ligands under an atmosphere of oxygen, the corresponding ynamides **4** [31], ynimines **6** [32], and alkynylphosphonates **8** [31] are smoothly obtained at room temperature under especially mild and practical conditions.

The success met during the development of these efficient procedures based on the oxidative cross-coupling with copper acetylides, which are thought to proceed by oxidation of the alkynylcopper(I) and coordination of the nucleophile to the electrophilic copper center followed by reductive elimination, prompted us to further explore their chemistry. We therefore decided to check if we could replace the heteronucleophiles used in these processes by organometallic reagents such as organoboron derivatives to investigate whether an oxidation/transmetallation/reductive elimination pathway would still be operative (Scheme 3).



Scheme 2



Scheme 3

In this article, we report results based on this hypothesis, which enabled the development of a facile oxidative cross-coupling of copper acetylides with arylboronic acids (for copper-catalyzed oxidative cross-coupling of terminal alkynes with arylboronic acids, see [34–36]; for palladium-catalyzed oxidative cross-coupling of terminal alkynes with arylboronic acids, see [37–40]; for gold-catalyzed oxidative cross-coupling of terminal alkynes with arylboronic acids, see [41]; for iron-catalyzed oxidative cross-coupling of terminal alkynes with arylboronic acids, see [42]; for palladium-catalyzed cross-coupling involving electrogenerated silver acetylides, see [43]).

Results and discussion

Optimization of the oxidative cross-coupling

To test this hypothesis, we decided to investigate the cross-coupling between (4-methoxyphenylethynyl)copper (**11**)

and 4-tolylboronic acid (**12**), the latter being used in excess (two equivalents) to minimize the homocoupling of the former. As in our oxidative cross-coupling with heteronucleophiles, oxygen was chosen as the oxidant for practical reasons (abundance, low cost, lack of toxic byproducts), DMF as the solvent, and the efficiency of different additives (pyridine, TMEDA, 1,10-phenanthroline, 2-2'-bipyridine, triphenylphosphine, *N*-methylimidazole, and 1,2-dimethylimidazole) susceptible to trigger the reaction at room temperature was evaluated (Fig. 1). Among all these ligands, pyridine and triphenylphosphine were found to be totally inefficient and did not promote the reaction, both starting materials being recovered after 3 days. Full conversion was observed with all other ligands and in all cases, mixtures of the desired aromatic alkyne **13** and diyne byproduct **14** were obtained, the ratio being determined by GC analysis of crude reaction mixtures. Among all ligands evaluated, 1,10-phenanthroline was the most efficient, a one-to-one mixture of **13** and **14** being formed with this promoter.

Further screening of the reaction conditions involved examination of various solvents using 1,10-phenanthroline as the ligand to evaluate the solvent effect on the ratio of products resulting from cross-coupling and dimerization. The influence of solvent was therefore next examined using

solvent or solvent mixtures in which the boronic acid was fully soluble and with various polarities: THF, 1,4-dioxane, CH₂Cl₂/DMF (90/10), toluene/DMF (95/5), acetonitrile/DMF (80/20), and DMF (Fig. 2). Among all the solvents/solvent systems screened, 1,4-dioxane turned out to be by far the best and allowed minimizing the amount of homodimer **14** formed. While we could not completely suppress the formation of the latter, the use of 1,4-dioxane considerably reduced its formation, the optimized ratio **13**:**14** being 9:1 with this solvent, which allowed for the isolation of the desired cross-coupled product **13** in 75 % yield after column chromatography. Importantly, a control experiment performed under nitrogen showed that no coupling occurred at all, the starting copper acetylide being unchanged in the absence of oxygen after 3 days at room temperature.

Scope of the oxidative cross-coupling

Having the optimized conditions in hand, we next examined the scope and limitations of this procedure by looking at the reactivity of a set of representative alkynylcopper reagents and arylboronic acids (Fig. 3). As shown by these results, aromatic-substituted copper acetylides performed well in the oxidative cross-coupling and provided the

Fig. 1 Compared efficiency of ligands for the alkylation of 4-tolylboronic acid. Standard conditions: 0.25 mmol **11**, 0.5 mmol **12**, 0.25 mmol (if bidentate) or 0.5 mmol (if monodentate) ligand, 1 atm O₂, 1 cm³ DMF, rt, 72 h

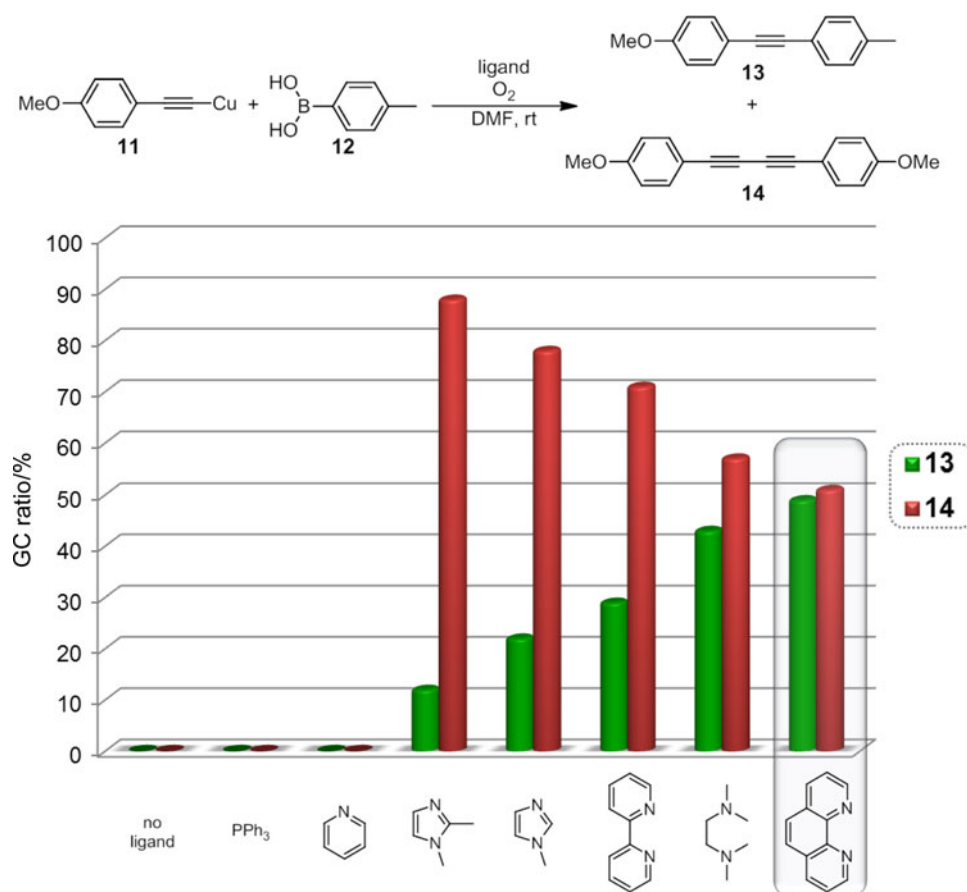
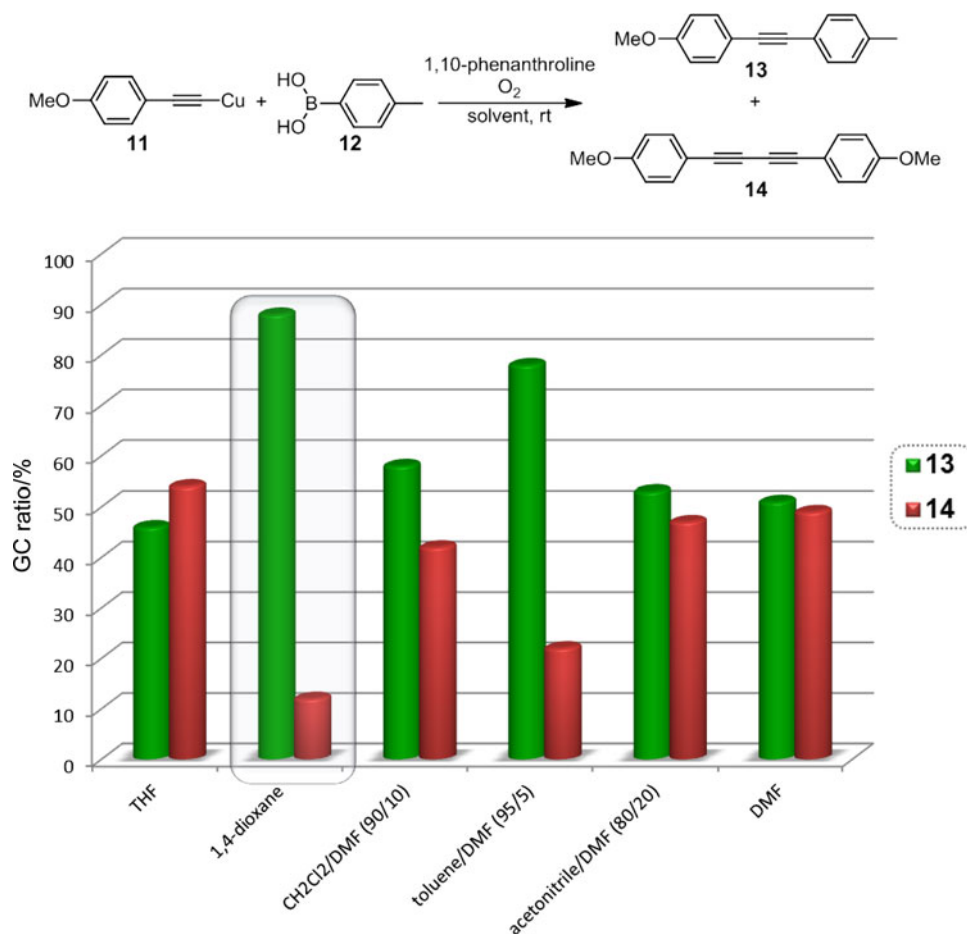


Fig. 2 Compared efficiency of solvents for the alkylation of 4-tolylboronic acid. Standard conditions: 0.25 mmol **11**, 0.5 mmol **12**, 0.25 mmol 1, 10-phenanthroline, 1 atm O₂, 1 cm³ solvent, rt, 72 h



corresponding aromatic alkynes in moderate to good yields regardless of the electronic properties of the aromatic rings that can be substituted with electron donating (e.g., **13** obtained in 75 % yield) or withdrawing (e.g., **15** obtained in 58 % yield) substituents. In contrast, alkyl-substituted alkynylcopper reagents such as undec-1-yn-1-ylcopper were found to be poor reaction partners, only traces of the corresponding cross-coupled product **20** being detected in the reaction mixture. The electronic properties of the starting arylboronic acids were also found to have a strong influence on the outcome of the reaction, electron-rich boronic acids being by far superior to electron-poor ones (compare for example the yields of **17** and **19** with those of **21** and **22**), the competitive homodimerization of the starting copper acetylide being the major side reaction in the last case, which might be attributed to a faster transmetalation in the case of electron-donating substituents on the arylboronic acid. Interestingly, the reaction is compatible with various substituents such as aromatic nitrile or aldehyde, and even the presence of an additional ferrocene on the starting copper acetylide did not interfere with the oxidative cross-coupling.

In all cases, the attractiveness of this procedure lies in its simplicity since the desired aromatic alkynes are readily

obtained by simply stirring a combination of the starting arylboronic acid, the alkynylcopper reagent, and phenanthroline in reagent-grade 1,4-dioxane under oxygen at room temperature. From a practical point of view, it ought to be mentioned that the endpoint of the reaction is remarkably easy to detect since the reaction mixture turns from a heterogeneous yellow suspension to a brownish homogeneous solution upon completion, which can then be concentrated and directly loaded onto silica gel to eliminate the excess of boronic acid and the copper(II) complexes formed in the process.

Oxidative cross-coupling in 2,6-lutidine media

To further expand the scope of this oxidative cross-coupling, we next looked at the reactivity of heteroarylboronic acids and chose 3-quinolinylboronic acid (**25**) as a test substrate. Using our standard conditions for the cross-coupling with phenylethynylcopper (**24**), the corresponding 3-(phenylethynyl)quinoline (**26**) was however obtained in 11 % yield only (conditions A), dimerization of both the starting copper acetylide and boronic acid being serious side reactions in this case (Scheme 4). Capitalizing on the

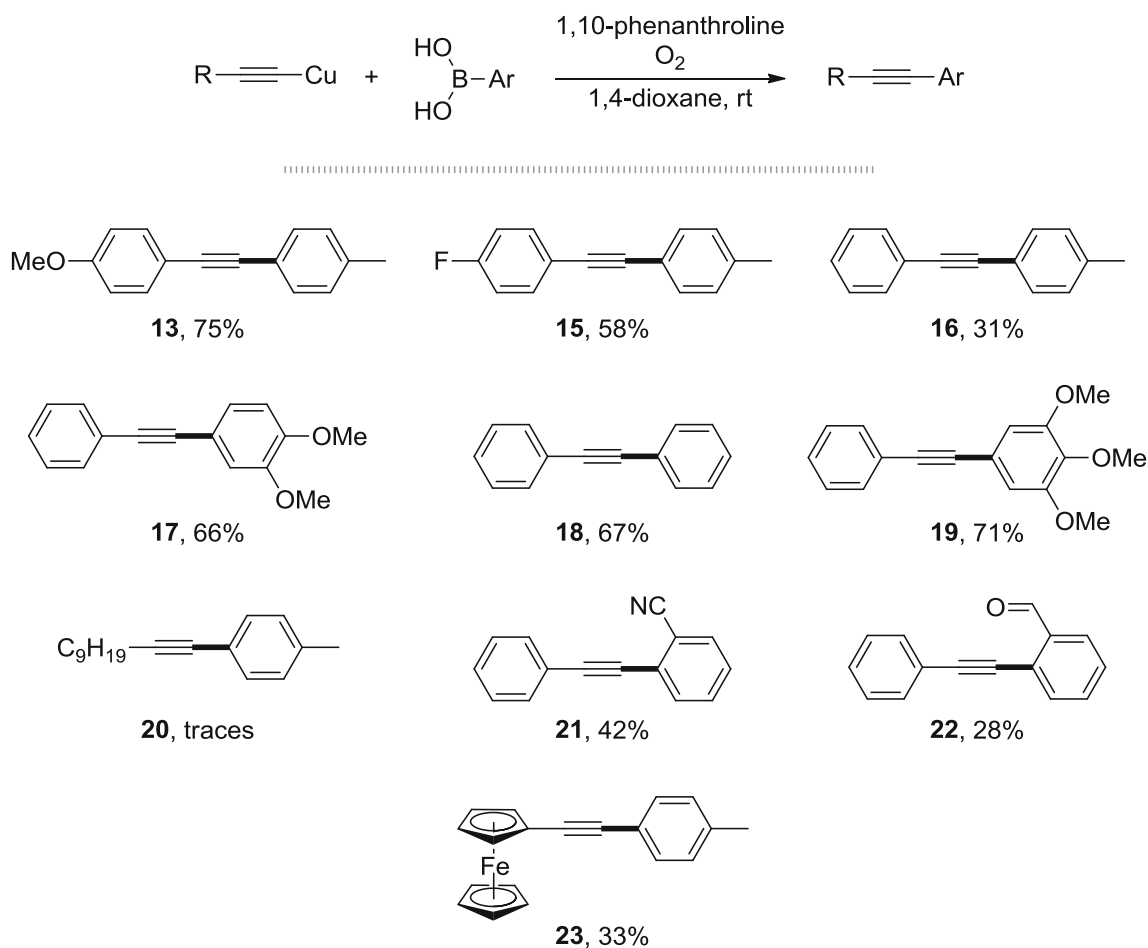
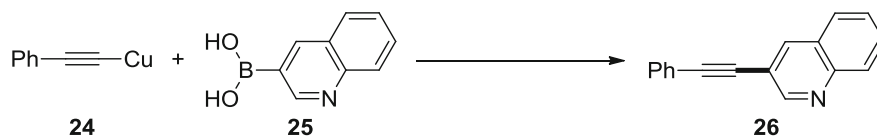


Fig. 3 Scope of the oxidative cross-coupling of copper acetylides and arylboronic acids (bonds formed shown in *bold*)

Scheme 4



Conditions A: 1,10-phenanthroline (1 equiv)
1,4-dioxane, O₂, rt 11%

Conditions B: 1,10-phenanthroline (0.5 equiv,
portionwise addition) 50%
MeOH/2,6-lutidine (1:1), O₂, rt

remarkable selectivity obtained by the Kobayashi group for the aerobic copper-catalyzed oxidative cross-coupling of alkynes with arylboronic acids in 2,6-lutidine at 45 °C [36], we evaluated the use of this co-solvent in combination with methanol and were delighted to note that the dimerization could be reduced, the desired substituted quinoline **26** being obtained in 50 % yield provided that the phenanthroline was added portion-wise to further slow down the competitive dimerization processes (conditions B). Interestingly, 1,10-phenanthroline is still required with this solvent system, 2,6-lutidine alone being inefficient to promote the oxidative cross-coupling.

The efficiency of this alternative modified procedure was briefly evaluated with a couple of substrates (Fig. 4), and if the yields could be improved in some cases, this improvement was not systematic, and this other system was therefore complimentary to the first one.

Conclusion

In conclusion, we have developed an efficient procedure for the oxidative cross-coupling between arylboronic acids and alkynylcopper reagents. Upon simple addition of 1,10-

Fig. 4 Oxidative cross-coupling of copper acetylides and arylboronic acids in 2,6-lutidine/methanol (bonds formed shown in *bold*, yield obtained in 1,4-dioxane indicated in *parentheses* for comparison)

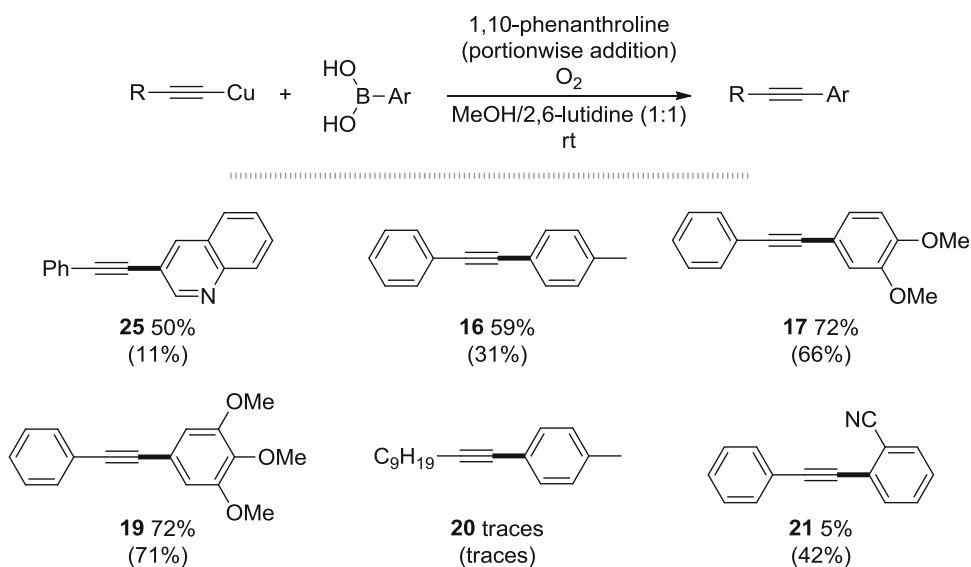


Table 1 Product yields and references reporting $^1\text{H}/^{13}\text{C}$ NMR spectra

Product	Yield/% (conditions A)	Yield/% (conditions B)	References
13	75	–	[44]
15	58	–	[45]
16	31	59	[45]
17	66	72	[44]
18	67	–	[45]
19	71	72	[46]
21	42	5	[47]
22	58	–	[35]
23	33	–	[48]
26	11	50	[49]

phenanthroline in the presence of oxygen, these highly stable, readily available polymeric reagents are readily activated and transfer their alkynyl group after subsequent transmetalation with the boronic acid. These results further expand the oxidative chemistry of organocopper compounds together with providing a user-friendly entry to diaryl acetylenes.

Experimental

All solvents were reagent grade. Pyridine, N,N,N',N' -tetramethylethylenediamine, and 2,6-lutidine were distilled from calcium hydride. Copper acetylides were prepared from the corresponding alkynes using our previously reported procedures [31]. All other reagents were used as supplied. Reactions were magnetically stirred. Yields

refer to chromatographically and spectroscopically pure compounds.

General procedure (conditions A for reactions in 1,4 dioxane)

A 5-cm³ round bottom flask was successively charged with the boronic acid (1.0 mmol), 90 mg 1,10-phenanthroline (0.5 mmol), and 2 cm³ 1,4-dioxane. When the starting boronic acid was not fully dissolved, additional N,N -dimethylformamide was slowly added until complete dissolution (typically 0.5–1.5 cm³). The alkynylcopper reagent (0.5 mmol) was next added to the reaction mixture, which was then vigorously stirred at room temperature and under atmosphere of oxygen (balloon) until complete disappearance of the alkynylcopper reagent (complete dissolution to a brownish homogeneous solution; typically 48–72 h). When the reaction was run in 1,4-dioxane only, the crude reaction mixture was filtered over a plug of silica gel (washed with EtOAc) and concentrated. When additional DMF was required, the reaction was diluted with an aqueous mixture of saturated ammonium chloride and 28 % ammonium hydroxide (1:1 solution) and extracted with ethyl acetate. Combined organic layers were washed with brine, dried over MgSO_4 , and concentrated. The crude residue was in both cases purified by flash chromatography over silica gel to give the desired aromatic alkynes (see Table 1 for yields and references reporting $^1\text{H}/^{13}\text{C}$ NMR spectra).

General procedure (conditions B for reactions in 2,6-lutidine/methanol)

In a 5-cm³ round bottom flask, the boronic acid (1.0 mmol) was dissolved in 1 cm³ methanol and 1 cm³ 2,6-lutidine.

The alkynylcopper reagent (0.5 mmol) was next added to the reaction mixture, which was then vigorously stirred at room temperature and under atmosphere of oxygen (balloon). 1,10-Phenanthroline was next added portion-wise (5×9 mg, 5×0.05 mmol) every 2 h, and the reaction mixture was kept under vigorous stirring at room temperature and under atmosphere of oxygen until complete disappearance of the alkynylcopper reagent (complete dissolution to a brownish homogeneous solution; typically 48–72 h). The crude reaction mixture was next filtered over a plug of silica gel (washed with EtOAc) and concentrated. The crude residue was then purified by flash chromatography over silica gel to give the desired aromatic alkynes (see Table 1 for yields and references reporting $^1\text{H}/^{13}\text{C}$ NMR spectra).

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