



Ligand-free copper(I)-catalyzed Sonogashira-type coupling of arylboronic acids with terminal alkynes

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ARTICLE INFO

Article history:

Received 27 March 2009

Revised 13 June 2009

Accepted 19 June 2009

Available online 23 June 2009

ABSTRACT

An efficient ligand-free CuI-catalyzed Sonogashira-type coupling reaction of arylboronic acids with terminal alkynes under air is described. The electron-deficient alkynes gave the desired cross-coupling products in good yields. Thus, it represents a simple and alternative method for the traditional Sonogashira reaction.

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The Sonogashira reaction of terminal alkynes with aryl or alkenyl halides is the most straightforward and powerful method for constructing C(sp)–C(sp²) bonds,¹ and has been widely applied to the synthesis of natural products,² pharmaceuticals,³ and molecular organic materials.⁴ Although various modifications have been reported on this reaction,⁵ some limitations still remain. For example, when electron-deficient alkynes were subjected to the Sonogashira reaction conditions, there were not the coupling products but the Michael addition products that were formed.^{1b,5a,6}

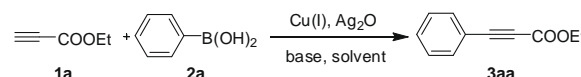
To overcome this limitation, the Sonogashira-type coupling reactions of terminal alkynes with arylboronic acids or aryl trimethoxysilanes have been reported recently. In 2003, Zou and co-workers firstly reported a new procedure for constructing aryl alkynes through cross-coupling of terminal alkynes with arylboronic acids catalyzed by a palladium–silver system under mild conditions.⁷ In 2007, Wu and co-workers also described the cross-coupling reaction of arylboronic reagents with terminal alkynes catalyzed by cyclopalladated ferrocenylimine/silver(I) oxide at room temperature.⁸ Very recently, we reported the mild coupling reaction of aryl trimethoxysilanes with terminal alkynes catalyzed by a palladium–silver system.⁹ All the aforementioned Sonogashira-type catalytic systems were efficient for electron-deficient alkynes. However, palladium and phosphine ligand complex employed as catalyst is often expensive. From a synthetic point of view, the development of an improved, facile procedure using less expensive and more sustainable catalysts has remained a highly desirable goal. Herein, we wish to report a ligand-free copper-catalyzed coupling reaction of arylboronic acids with terminal alkynes including electron-deficient and common aromatic analogues under air.

Initial studies were performed by using ethyl propiolate **1a** and phenylboronic acid **2a** as model substrates, employing copper(I)

iodide as catalyst (Table 1). Silver(I) oxide, which was reported to activate C–B bond, was applied as the promoter.¹⁰ Gratifyingly, in the presence of K₂CO₃, this reaction proceeded smoothly in

Table 1

Effects of copper sources, bases, and solvents on the reaction of phenylboronic acid with ethyl propiolate^a



Entry	Cu(I)	Base	Solvent	Yield ^b (%)
1	CuI	K ₂ CO ₃	DCE	52
2	CuI	Na ₂ CO ₃	DCE	30
3	CuI	Cs₂CO₃	DCE	80 (46)^c
4	CuI	NaHCO ₃	DCE	48
5	CuI	K ₃ PO ₄ ·3H ₂ O	DCE	23
6	CuI	KF·2H ₂ O	DCE	37
7	CuI	CsF	DCE	44
8	CuI	—	DCE	25
9	CuI	Cs ₂ CO ₃	Toluene	44
10	CuI	Cs ₂ CO ₃	CH ₃ CN	25
11	CuI	Cs ₂ CO ₃	1,4-Dioxane	57
12	CuI	Cs ₂ CO ₃	DMF	<5
13	CuBr	Cs ₂ CO ₃	DCE	22
14	CuCl	Cs ₂ CO ₃	DCE	<5
15	—	Cs ₂ CO ₃	DCE	0
16	Cu(OAc) ₂	Cs ₂ CO ₃	DCE	<5
17	CuI	Cs ₂ CO ₃	DCE	0 ^d
18	CuI	Cs ₂ CO ₃	DCE	45 ^e

^a Reaction condition: **1a** (0.375 mmol), **2a** (0.25 mmol), Cu source (15 mol %), base (2.0 equiv), Ag₂O (2.0 equiv), solvent (2 mL), 80 °C, 36 h.

^b Isolated yield.

^c Under N₂.

^d In the absence of Ag₂O.

^e Ag₂O (1.0 equiv).

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1,2-dichloroethane (DCE) to afford the coupling product **3aa** in 52% yield (Table 1, entry 1). Further investigation revealed that the base used had played a significant role in this reaction. Cs₂CO₃ was the most effective among the tested bases and the yield of **3aa** was sharply increased to 80% (Table 1, entry 3), while 25% of the product was isolated in the absence of any base. The yield dramatically decreased to 46% when the reaction was conducted under N₂. However, replacing N₂ with O₂ did not increase the yield significantly. A profound solvent effect on the reaction was also observed. DCE was the best choice in the procedure. Several copper(I) sources were also examined, and CuI turned out to be the best among others. No product was formed in the absence of Cu(I) (Table 1, entry 15) or Ag₂O (Table 1, entry 17), and Cu(II) provided only trace amount of the coupling product (Table 1, entry 16). In addition, when the quantity of Ag₂O was decreased to 1.0 equiv, the yield decreased to 45% (Table 1, entry 18).

Finally, the optimized reaction condition was to use CuI (15 mol %), Ag₂O (2 equiv), and Cs₂CO₃ (2 equiv) in DCE (2 mL). With the optimized reaction conditions in hand, a series of arylboronic acids and electron-deficient terminal alkynes were tested under these conditions. The results are summarized in Table 2.

Table 2
Coupling reaction of arylboronic acids with electron-deficient terminal alkynes^a

$\text{R-C}\equiv\text{C-H} + \text{ArB(OH)}_2 \xrightarrow[\text{Cs}_2\text{CO}_3, \text{DCE}]{\text{CuI, Ag}_2\text{O}} \text{R-C}\equiv\text{C-Ar}$				
Entry	1	2	3	Yield ^b (%)
1			3aa	80
2			3ab	74
3			3ac	45
4			3ad	57
5			3ae	67
6			3af	88
7			3ag	72
8			3ah	75
9			3ai	64
10			3ba	49
11			3bf	50

^a Reaction condition: **1** (0.375 mmol), **2** (0.25 mmol), CuI (15 mol %), Ag₂O (0.5 mmol), Cs₂CO₃ (0.5 mmol), DCE (2 mL), 80 °C, 36 h.

^b Isolated yield.

As expected, electron-rich, as well as electron-deficient arylboronic acids worked well under the reaction conditions. However, the steric hindrance of the arylboronic acids had significant effect on the reaction, and the yields were sharply decreased to 45% for *o*-tolylboronic acid **2c** and 57% for *m*-tolylboronic acid **2d**, respectively (Table 2, entries 3–4). The catalytic system tolerated some functional groups, such as F, CF₃, and COOMe. Particularly, the chloro of **2f** survived under these conditions and could be valuable for further manipulation (Table 2, entry 6). 1-(Piperidin-1-yl)prop-2-yn-1-one **1b** was subjected to the procedure and provided the coupling products in moderate yields (Table 2, entries 10–11). It is worth noting that the dimerized byproducts of **1a** and **1b** were not detected by GC–MS. The formed conjugated acetylenic carboxylates are important intermediates that have been used to synthesize a variety of cyclic compounds and pharmaceutical agents.¹¹ In our procedure, the ethyl 3-aryl propiolates were prepared in moderate to good yields from commercially available materials in a simple and facile method.¹²

Having demonstrated the utility of this coupling reaction condition on electron-deficient alkynes, we then focused on the scope of the substrates. As shown in Table 3, the aromatic alkynes also worked well under these conditions, accompanied with 10% of dimerized byproduct of the terminal alkynes (based on aromatic alkyne) and little lower but acceptable yields were obtained.

The rigorous exclusion of air/moisture was not required in any of these transformations, and comparable results were obtained in freshly distilled versus commercial solvents. As such, this represents an exceedingly practical method for the arylation of electron-deficient terminal alkynes and offers an attractive alternative to the traditional Sonogashira reaction.

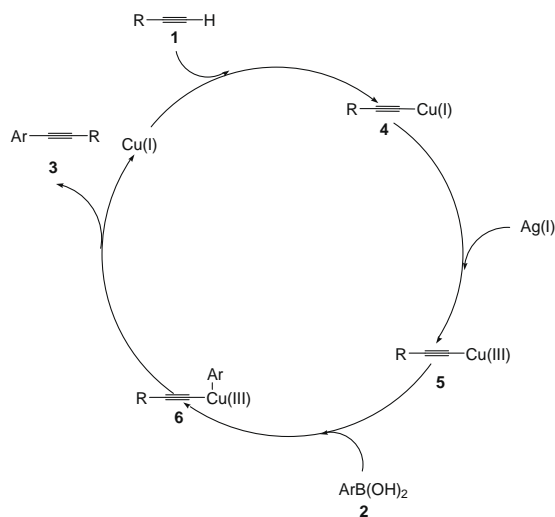
A working mechanism was proposed as outlined in Scheme 1 based on the previously reported mechanism.^{13,4c,5f} First step could involve the formation of alkynylcopper(I) species **4**. Alkynylcopper(I) species **4** could undergo oxidation to yield copper(III) complex **5**. Then transmetalation of intermediate **5** with arylboronic acid could occur to form intermediate **6**, followed by a reduc-

Table 3
Coupling reaction of arylboronic acids with aromatic terminal alkynes^a

$\text{Ar}^1\text{-C}\equiv\text{C-H} + \text{Ar}^2\text{B(OH)}_2 \xrightarrow[\text{Cs}_2\text{CO}_3, \text{DCE}]{\text{CuI, Ag}_2\text{O}} \text{Ar}^1\text{-C}\equiv\text{C-Ar}^2$				
Entry	1	2	3	Yield ^b (%)
1			3ca	63
2	1c		3ce	63
3			3cf	36
4			3da	53
5	1d		3db	43
6			3de	61

^a Reaction condition: **1** (0.375 mmol), **2** (0.25 mmol), CuI (15 mol %), Ag₂O (0.5 mmol), Cs₂CO₃ (0.5 mmol), DCE (2 mL), 80 °C, 36 h.

^b Isolated yield.



Scheme 1. Possible mechanism.

tive elimination of intermediate **6**, giving the coupled product **3** and regenerating the active copper(I).

In summary, we have successfully developed a copper-catalyzed cross-coupling reaction of arylboronic acids with terminal alkynes, especially electron-poor analogue in moderate to good yields.¹⁴ It represents a practical alternative for the Sonogashira reaction. Compared with other transition-metal catalyst systems, this protocol is simple and avoids the use of air-sensitive and/or expensive catalysts.

Acknowledgment

We thank the National Natural Science Foundation of China (No. 20504023) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.093.

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- General procedure*: Under air atmosphere, a reaction tube was charged with arylboronic acid (0.25 mmol), alkyne (0.375 mmol), CuI (7.2 mg, 15 mol %), Ag₂O (115 mg, 0.5 mmol), Cs₂CO₃ (163 mg, 0.5 mmol), and DCE (2 mL). After the mixture was heated at 80 °C for 36 h, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on a silica gel to give the product.