Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6208

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COMMUNICATION

Copper-catalyzed, aerobic oxidative cross-coupling of alkynes with arylboronic acids: remarkable selectivity in 2,6-lutidine media†‡

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Received 7th June 2011, Accepted 8th July 2011
DOI: 10.1039/c1ob05915g

Aerobic oxidative cross-coupling reactions between alkynes and boronic acids under mild conditions catalyzed by low loadings of a copper salt are reported. 2,6-Lutidine accelerated the reactions dramatically, and the desired coupling products were obtained in high yields with high selectivities.

While C–C bond-forming reactions catalyzed by noble metals (such as palladium) are among the most powerful tools for organic synthesis,[1] the development of reactions using abundant metals as a replacement for noble metals has been intensively studied recently,[2] reflecting supply shortages of several important elements.[3] Copper is an abundant and inexpensive metal, and is widely used in organic synthesis as a reagent or catalyst, thus attracting much attention for this purpose.[4]

Internal alkynes are useful compounds as intermediates for bioactive natural products[1b,5] as well as materials such as polymers and liquid crystals.[5b,6] Palladium- and/or copper-catalyzed Sonogashira-type cross-coupling reactions are well known as a traditional method for construction of C(sp)–C(sp^2) bonds between terminal alkynes and aryl halides.[5b,7] Palladium-catalyzed oxidative Sonogashira-type cross-coupling reactions between alkynes and arylboronic acids without using aryl halides have also been developed.[8] Although several groups have reported copper-mediated C–O, C–N, or C–S bond-forming reactions using boronic acids as aryl donors, there are few reports of C(sp)–C(sp^2) bond-formation reactions.[9] In addition, most of the reports required high temperature or a stoichiometric amount of a silver salt.[10] Recently, Fu's group has developed Cu_2O-catalyzed reactions using molecular oxygen as a green oxidant under mild conditions in pyridine-containing media.[11] However, even in this case, 10 mol% of Cu_2O was required and the scope of the alkynes was rather limited.

One of the significant difficulties of this reaction is how to suppress undesired homocoupling reactions of alkynes or aryl boronic acids, which readily occur in the presence of a copper catalyst, nitrogen base, and molecular oxygen.[12] Herein, we report oxidative cross-coupling reactions of alkynes with boronic acids catalyzed by relatively low loadings of copper catalysts (0.15–3.0 mol%) in the presence of 2,6-lutidine using molecular oxygen as an oxidant. The remarkable effect of 2,6-lutidine on the selectivity of the reactions is also described.

We began by investigating the cross-coupling reaction between phenyl acetylene and phenylboronic acid as a model reaction in methanol–pyridine media. To avoid undesired side reactions, we used only 0.75 mol% of CuBr as a catalyst because it was suggested that homocoupling reactions of alkynes proceeded *via* a dimerized copper–alkyne complex caused by a high concentration of the copper catalyst.[12a,13] However, in the presence of 0.75 mol% of CuBr, the reaction hardly proceeded (Table 1, entry 1). Amine solvents were then screened, and it was found that the yield was significantly improved to 57% in the presence of 2,6-lutidine (Table 1, entry 2).[14] It is noted that, although we also examined other pyridine derivatives, only 2,6-lutidine media could promote this reaction effectively (Table 1, entries 3–9). When *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was used, high conversion was observed; however, the major products were the homocoupled product, biphenyl, and methyl 2-phenylacetate, and the desired cross-coupled product was scarcely generated (Table 1, entry 10). Moreover, while 3,5-dimethylpiperidine media also promoted the cross-coupling reaction, 2,6-dimethylpiperidine did not gave good results (Table 1, entries 11, 12).

Several copper salts were examined in the presence of 2,6-lutidine (Table 2). It was shown that Cu(II) also catalyzed this reaction; however, the yield was lower than that using Cu(I) (Table 2, entries 1 *vs.* 2, 3 *vs.* 4, 8 *vs.* 9). Although Cu_2O did not dissolve completely, **3aa** was obtained in 35% yield (entry 7). From these results, CuBr and CuCN showed similar high activity, and based on solubility, we chose CuBr as the best catalyst (entries 1–11)[15] We also confirmed that the reaction did not proceed at all in the absence of any Cu salts (entry 12).

With CuBr, the ratio of methanol to 2,6-lutidine was examined (Table 3). When the amount of 2,6-lutidine was decreased, **3aa** was obtained in lower yield. In addition, the yield of **3aa** dropped in the presence of an excess amount of 2,6-lutidine (Table 3, entries 1–7). The ratio of methanol to 2,6-lutidine was optimized as 1 : 2 (Table 3, entry 4). The yield of **3aa** was improved to 83% at 45 °C in the presence of 1.5 mol% of CuBr (Table 3, entry 8). Using more than 1.5 mol% of copper salt and a higher concentration did not accelerate the reaction.[16] Reducing the equivalents of

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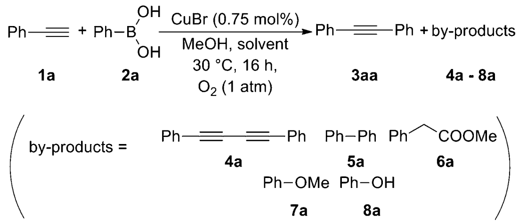
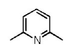
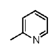
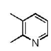
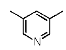
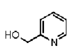
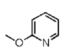
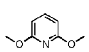
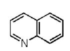
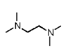
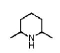
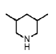
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05915g

‡ This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), Global COE Program, The University of Tokyo, MEXT, Japan, and NEDO. H. M. thanks the JSPS fellowship for Japanese Junior Scientist.

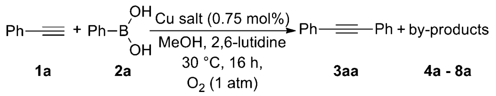
Table 1 Effect of nitrogen-containing solvents^{a}



Entry	Solvent	Conv. **1a** (%)^{b}	Yield (%)^{b}					
			3aa	**4a**	**5a**^{c}	**6a**	**7a**^{c}	**8a**^{c}
1		10	1	1	1	0	1	2
2		**64**	**57**	**4**	**1**	**1**	**9**	**9**
3		11	7	0	trace	0	2	2
4		25	16	2	1	0	4	6
5		16	1	1	1	0	2	3
6		7	0	0	0	0	0	0
7		11	6	1	trace	0	2	2
8		7	trace	1	0	0	0	trace
9		16	6	1	3	0	1	24
10		77	20	1	58	28	2	10
11		21	11	1	trace	0	1	6
12		68	49	2	5	0	8	9

^{a} Reaction conditions: 30 °C, alkyne (0.25 mmol), boronic acid (0.5 mmol), methanol (0.5 ml), amine solvent (0.5 ml). ^{b} Determined by GC analysis. ^{c} Yield was determined based on amount of **2a** used.

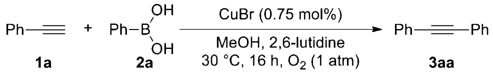
Table 2 Effect of copper salts^{a}



Entry	Cu	Conv. **1a** (%)^{b}	Yield (%)^{b}					
			3aa	**4a**	**5a**^{c}	**6a**	**7a**^{c}	**8a**^{c}
1	CuBr	64	57	4	1	1	9	9
2	$\mathrm{CuBr_2}$	55	46	2	1	0	7	7
3	Cu(OAc)	31	26	2	1	0	5	5
4	$\mathrm{Cu(OAc)_2\cdot H_2O}$	22	13	2	0	0	4	2
5	CuI	59	50	2	1	0	8	8
6	$\mathrm{Cu(PPh_3)_2NO_3}$	42	33	2	1	0	5	6
7	$\mathrm{Cu_2O}$	42	35	1	1	0	5	6
8	CuOTf·1/2PhMe	52	42	2	1	0	7	6
9	$\mathrm{Cu(OTf)_2}$	27	21	trace	trace	0	4	3
10^{d}	$\mathrm{CuSbF_6}$	50	41	3	2	0	7	9
11	CuCN	67	59	3	3	0	10	9
12	—	<1	0	0	0	0	0	0

^{a} Reaction conditions: 30 °C, alkyne (0.25 mmol), boronic acid (0.5 mmol), methanol (0.5 ml), 2,6-lutidine (0.5 ml). ^{b} Determined by GC analysis. ^{c} Yield was determined based on amount of **2a** used. ^{d} Cu salt was prepared from CuI and $\mathrm{AgSbF_6}$.

Table 3 Effect of solvent ratios^{a}



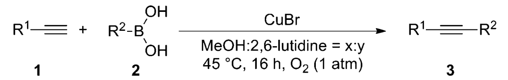
Entry	MeOH (ml)	2,6-Lutidine (ml)	Conv. **1a** (%)^{b}	Yield (%)^{b}
1	0.8	0.2	45	38
2	0.66	0.33	54	49
3	0.5	0.5	64	57
4	0.33	0.66	70	62
5	0.25	0.75	65	59
6	0.2	0.8	69	61
7	0.05	0.95	6	0
8^{c}	0.33	0.66	97	83
9^{c,d}	0.33	0.66	94	85

^{a} Reaction conditions: 30 °C, alkyne (0.25 mmol), boronic acid (0.5 mmol). ^{b} Determined by GC analysis. ^{c} Reaction temperature was 45 °C and 1.5 mol% of CuBr was used. ^{d} 1.9 equiv of boronic acid was used.

phenylboronic acid was also examined and **3aa** was obtained in 85% yield when 1.9 equivalents of phenylboronic acid were used (Table 3, entry 9).[17]

The substrate scope is summarized in Table 4 and Chart 1. *Ortho*- or *meta*-substituted phenylboronic acids gave good to high yields of **3ab** or **3ac** (Table 4, entries 2, 3). In the cases of phenylboronic acids with electron-withdrawing groups, the use of fewer equivalents of substrates improved the yields of **3ad** or **3ae**, presumably because the homocoupling reaction of boronic acids was suppressed (Table 4, entries 4, 5).[18] On the other hand, the reactions with phenylboronic acids bearing electron-donating groups proceeded slowly. The yield of **3af** was improved when the amount of the catalyst was increased (Table 4, entry 6). When 2-naphthylboronic acid was used, more diluted conditions (0.125 M and 0.75 mol% of CuBr) afforded a good yield of **3ag** (Table 4, entry 7). When an alkyne with an ester group was used, interestingly, diluted conditions and a significant decrease of 2,6-lutidine were effective in achieving better selectivity. In other cases, decomposition of the substrate was observed (Table 4, entries 8–12).[19] In addition, the amount of boronic acid could be decreased and the reaction temperature lowered while keeping high reactivity. Because the ease of formation of copper–acetylide species differs, the basicity of solvents may become the key to controlling the reaction. *Ortho*-, *meta*-, and *para*-substituted phenylacetylenes gave good yields of **3ca**, **3da**, or **3ea** (Table 4, entries 13–15). For phenylacetylene with a methoxy group, which has a lower acidity than the nonsubstituted phenylacetylene, more 2,6-lutidine was required to afford good yields of **3fa** or **3ga** (Table 4, entries 16, 17). Phenylacetylene with electron-withdrawing groups or biphenylacetylene gave good or moderate yields of **3ha**, **3ia**, or **3ja** (Table 4, entries 18–20). In the same way as for 2-naphthylboronic acid, diluted conditions improved the yield (Table 4, entries 18, 20).[18] 4-Pyridylacetylene is one of the most difficult substrates because of the possibility that the nitrogen on the pyridine ring will

Table 4 Substrate scope[a]



$$R^1\text{—≡} + R^2\text{-B(OH)}_2 \xrightarrow[\text{MeOH:2,6-lutidine = x:y; 45 °C, 16 h, O}_2\text{ (1 atm)}]{\text{CuBr}} R^1\text{—≡—}R^2$$

Entry	1	2 (equiv)	x : y	CuBr (mol%)	Conc.[b] (M)	Product	Yield (%)[c]
1	**1a**	**2a** (1.9)	1 : 2	1.5	0.25	**3aa**	85[d]
2	**1a**	**2b** (1.9)	1 : 2	1.5	0.25	**3ab**	85
3	**1a**	**2c** (1.9)	1 : 2	1.5	0.25	**3ac**	70
4	**1a**	**2d** (1.2)	1 : 2	1.5	0.25	**3ad**	62
5	**1a**	**2e** (1.3)	1 : 2	1.5	0.25	**3ae**	75
6	**1a**	**2f** (1.9)	1 : 2	3	0.25	**3af**	63
7[e]	**1a**	**2g** (1.9)	1 : 2	0.75	0.125	**3ag**	86
8[f]	**1b**	**2a** (1.5)	39 : 1	1.5	0.0625	**3ba**	82[d]
9[f]	**1b**	**2d** (1.1)	79 : 1	0.75	0.03125	**3bd**	71
10[f]	**1b**	**2e** (1.5)	79 : 1	0.75	0.0625	**3be**	77
11[f]	**1b**	**2b** (1.5)	39 : 1	1.5	0.0625	**3bb**	44
12[f]	**1b**	**2c** (1.5)	79 : 1	0.75	0.03125	**3bc**	66
13	**1c**	**2a** (1.9)	1 : 2	1.5	0.25	**3ca**	81
14	**1d**	**2a** (1.9)	1 : 2	1.5	0.25	**3da**	80
15	**1e**	**2a** (1.9)	1 : 2	1.5	0.25	**3ea**	83
16	**1f**	**2a** (1.9)	1 : 4	0.75	0.125	**3fa**	75
17	**1g**	**2a** (1.9)	1 : 4	0.75	0.125	**3ga**	76
18	**1h**	**2a** (1.9)	1 : 2	0.75	0.125	**3ha**	74
19	**1i**	**2a** (1.9)	1 : 2	1.5	0.25	**3ia**	51
20[e]	**1j**	**2a** (1.9)	1 : 2	0.75	0.125	**3ja**	71
21[g]	**1k**	**2a** (3.0)	1 : 4	0.15	0.125	**3ka**	44
22	**1l**	**2a** (1.9)	1 : 2	1.5	0.25	**3la**	56
23	**1m**	**2a** (1.9)	1 : 2	1.5	0.25	**3ma**	80
24[h]	**1n**	**2a** (1.9)	1 : 2	1.5	0.25	**3na**	66

[a] All reactions were conducted on a 0.125 mmol scale of alkynes. [b] Conc. means concentration. [c] Isolated yield. [d] Determined by GC analysis. [e] Reaction time was 30 h. [f] Reaction temperature was 30 °C. [g] Reaction temperature was 60 °C and reaction time was 36 h. [h] A mixture of diastereomers.

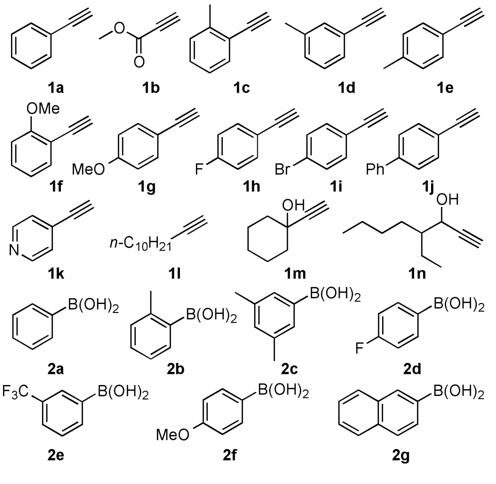


Chart 1 List of starting materials.

coordinate to copper in an unfavorable manner. As expected, 0.15 mol% of CuBr improved the reactivity and **3ka** was obtained with the highest turnover number (293) at 60 °C after 36 h (Table 4, entry 21).[18] Aliphatic alkynes were also examined and gave moderate or good yields of **3la**, **3ma**, or **3na** (Table 4, entries 22–24).

In conclusion, we have developed cross-coupling reactions between alkynes and boronic acids using a small amount of a copper salt in methanol and 2,6-lutidine media. This reaction proceeded smoothly with high selectivity, and undesired homocoupling reactions were suppressed. Wide substrate generality has been demonstrated. It is noted that lower amounts of the catalyst and lower concentration can improve the yields significantly for some substrates. Further investigations including mechanistic insights and more environmentally benign catalytic systems are currently underway in our laboratory.

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15 No contamination of palladium in CuBr was observed by ICP analysis (<2.7 ppm as a detection limit, see ESI† 2–7).

16 The effects of the amount of copper salt are shown in ESI† Table S-1.

17 The results of the reaction using varying amounts of the phenylboronic acids in various conditions are shown in ESI† Table S-3.

18 Using the optimized conditions for the formation of **3aa**, lower yields of these products and undissolved yellow solid were obtained (see ESI† Table S-6). This yellow solid was formed in the presence of phenylacetylene and 2,6-lutidine (see ESI† Scheme S-2). It might be an organocopper species formed from the copper catalyst and alkynes: (*a*) S. S. Y. Chui, M. F. Y. Ng and C.-M. Che, *Chem.–Eur. J.*, 2005, **11**, 1739; (*b*) B. R. Buckley, S. E. Dann and H. Heaney, *Chem.–Eur. J.*, 2010, **16**, 6278.

19 The ratios of solvent and concentrations were screened (see ESI† Tables S-4, S-5).