Cu-catalyzed stereoselective conjugate addition of arylboronic acids to alkynoates $\ensuremath{^\dagger}$

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Received (in Cambridge, UK) 8th February 2008, Accepted 5th March 2008 First published as an Advance Article on the web 25th March 2008 DOI: 10.1039/b802231c

The CuOAc-catalyzed reaction of internal alkynoates with arylboronic acids proceeded under mild conditions to yield trisubstituted cinnamates stereoselectively.

The conjugate addition of organometallic reagents to alkynoates is one of the most efficient methods to obtain synthetically valuable multiply substituted acrylates. For this purpose, organocopper reagents have been typically used,¹ since the first report of Corey's group^{2a} and others.^{2b,c} Organocopperbased methods, however, have several limitations: (a) they usually require stoichiometric amounts of the copper source, (b) the stereochemistry of the resulting alkene depends on both the reaction conditions and nature of the organocopper reagents,¹ and (c) they are incompatible with highly reactive functional groups such as aldehydes. Therefore, other methods using catalytic amounts of transition-metal complexes as promoters were developed. Hayashi and co-workers have reported the rhodium-catalyzed hydroarylation of alkynes.³ In their study, they obtained conjugate addition products from two internal alkynoates with phenylboronic acid in high yields. Later, Oh and co-workers also carried out the palladiumcatalyzed conjugate addition of arylboronic acids to alkynoates with a good substrate scope.⁴ Although these catalytic protocols enable the use of commercially available bench-top stable boronic acids and yield trisubstituted α , β -unsaturated esters with moderate to excellent regio- and stereoselectivity. the development of a new method using an inexpensive nonprecious metal catalyst would be beneficial. In this regard, the copper-catalyzed addition of Grignard reagents to alkynoates has been reported by Jennings and co-workers.⁵ It should be noted that they have succeeded in obtaining both syn- and anti-hydroarylation products with moderate to good stereoselectivities by selecting appropriate trialkylsilyl mediators and quenching methods. However, substrate scope in terms of both the organometallic reagent and alkynoate has not been addressed in this copper-catalyzed method. In this communication, we report the copper-catalyzed conjugate addition of differently functionalized arylboronic acids to alkynoates that proceeds under mild reaction conditions to yield syn-hydroarylation products in good yields.







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[†] Electronic supplementary information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/b802231c

Table 1 Cu-catalyzed reaction of 1a and 2a

Run	Cu salt, mol%	Time/h	Yield (%)
1	Cu(OAc) ₂ , 10 mol%	2.5	96
2	$Cu(OAc)_2$, 1 mol%	8	95
3	CuOAc. 10 mol%	1	95^a
4	CuOAc, 1 mol%	5	94^a
5	CuOAc, 1 mol $\%^b$	6	95^a
6	CuCl. 10 mol%	14	93
7	CuBr. 10 mol%	9	92^a
8	Cu(OAc) ₂ (bipy), 5 mol%	2	95 ^a
9	CuCl(SI ^P Pr). 5 mol%	24	80^a
10	CuCl(IMes), 5 mol%	24	61 ^{<i>a</i>}
a Trace	amounts of A were detected in	¹ H NMP sp	ectra of crude

" Trace amounts of 4 were detected in 'H NMR spectra of crude samples. b 1.5 equiv. of **2a** was used.

IMes]⁷ did not show any positive effect (runs 8–10). Accordingly, CuOAc was employed for further study.

The scope and limitations of the arylboronic acid are summarised in Table 2.8 To ensure complete consumption of the alkynoates, 3 equiv. of arylboronic acid were employed. In the presence of 1-3 mol% CuOAc, o-, m-, and p-tolylboronic acids, 3,5-xylylboronic acid, and 2-naphthylboronic acid gave the corresponding adducts **3ab–3af** in high yields (runs 1–5). Similarly, *p*-halophenylboronic acids 2g-i can be used without the loss of the reactive $C(sp^2)$ -halogen bonds that are useful synthetic handles for carrying out further functionalization (runs 6-8). Moreover, carbonyl groups reactive towards Grignard or organolithium reagents are compatible with the present Cu-catalyzed conjugate addition of arylboronic acids (runs 9-11). Consequently, (E)-cinnamates 3aj-3al, whose phenyl rings have a formyl, acetyl, or ethoxycarbonyl group, were obtained in 82-93% yields. Although a catalyst loading of 10 mol% was required, m-nitro derivative 3am was also obtained in 94% yield (run 12). However, the use of electronrich *p*-methoxyphenylboronic acid **2n** was problematic, leading to an inseparable mixture of the desired compound 3an, 4,4'-dimethoxybiphenyl, and 1,4-dimethoxybenzene (run 13). The latter side products were formed probably by the Cucatalyzed homo coupling of 2n and its Ullmann-type coupling with the methanol solvent. In contrast to phenylboronic acids,

Table 2CuOAc-catalyzed addition of various arylboronic acids 2to $1a^a$

Run	2 , Ar	Cu (mol%)	Time/h	3, yield (%)
1	2b , p -MeC ₆ H ₄	1	4	3ab , 94
2	$2c, m-MeC_6H_4$	1	10	3ac , 94
3	2d, o -MeC ₆ H ₄	3	6	3ad, 91
4	2e , $3,5-Me_2C_6H_3$	3	2	3ae , 88
5	2f , 2-naphthyl	1	24	3af , 90
6	$2g, p-ClC_6H_4$	3	4	3ag , 94
7	2h , p -BrC ₆ H ₄	5	24	3ah , 94
8	$2i, p-IC_6H_4$	5	3	3ai , 91
9	$2\mathbf{j}, p$ -OHCC ₆ H ₄	3	10	3aj , 88
10	$2\mathbf{k}$, p-AcC ₆ H ₄	3	5	3ak , 93
11	2l , p -EtO ₂ CC ₆ H ₄	3	24	3al , 82
12	2m, m -O ₂ NC ₆ H ₄	10	5	3am, 94
13	2n p-MeOC/H	1	24	3an 60 ^b

^{*a*} Methyl 2-octynoate (**1a**) was reacted with 3 equiv. of the arylboronic acid in MeOH (0.5 M) at 28 °C. ^{*b*} Yield determined by ¹H NMR analysis of a mixture with 4,4'-dimethoxybiphenyl and 1,4-dimethoxybenzene.



Fig. 1 Reagents which failed to give conjugate addition products.

heteroaryl-, ferrocenyl-, 2-(*p*-chlorophenyl)ethenyl-, and *n*-pentylboronic acids did not undergo conjugate addition to alkynoate **1a** under the optimal reaction conditions (Fig. 1).

Then, we examined the catalytic conjugate addition of arylboronic acids to various alkynoates 1b-1g (Scheme 2 and Table 3). Alkynoates **1b**,**c** whose alkyl chains have methoxy or chloro substituents were allowed to react with phenylboronic acid (2a), affording the corresponding cinnamates 3ba and 3ca in excellent yields (runs 1 and 2). It is noteworthy that protectionfree propargyl alcohol derivative 1d can be directly used in our Cu-catalyzed conjugate addition. In this case, the conjugate addition of 2a was followed by in situ lactonization to yield the known 3-phenylbutenolide 5, albeit in a moderate yield of 61% (run 3). We then focused on the synthesis of 3,3-diarylacrylates that are difficult to prepare with precise control of stereochemistry via the conventional Horner-Wittig and Wadsworth-Emmons methods. In the presence of 1-3 mol% CuOAc, phenylboronic acids bearing methyl, chloro, and methoxy substituents at the *para*-position were allowed to react with ethyl phenylpropiolate 1e, affording the corresponding diarylacrylates 3eb, 3eg, and 3en in high yields as single stereoisomers (runs 4-6). It is noteworthy that electron-rich 2n reacted with 1e uneventfully to yield (E)-3en in 91% yield. On the other hand, its stereoisomer (Z)-3fa was selectively obtained by the addition of phenylboronic acid to (p-methoxyphenyl)propiolate 1f (run 7). The present method enabled the stereoselective preparation of **3gn** possessing *o*- and *p*-methoxyphenyl groups (run 8).



Scheme 2 Reaction of various alkynoates 1b-1g.

Table 3 Conjugate addition of arylboronic acids to alkynoates 1b-1g

Run	1, R^1/R^2	2 , Ar	Conditions ^a	3, yield (%)
1	1b, MeO(CH ₂) ₃ /Me	2a , Ph	2 mol%, 3 h	3ba , 92
2	1c, $Cl(CH_2)_3/Me$	2a, Ph	1 mol%, 2 h	3ca, 97
3	1d, HOCH ₂ /Me	2a, Ph	2 mol%, 2 h	5, 61
4	1e, Ph/Et	2b , p -MeC ₆ H ₄	1 mol%, 4 h	3eb, 90
5	1e, Ph/Et	$2g, p-ClC_6H_4$	3 mol%, 12 h	3eg, 89
6	1e, Ph/Et	$2n, p-MeOC_6H_4$	1 mol%, 4 h	3en (E), 91
7	1f, p-MeOC ₆ H ₄ /Et	2a, C ₆ H ₅	1 mol%, 24 h	3fa (Z), 97
8	1g, o -MeOC ₆ H ₄ /Me	2n , p -MeOC ₆ H ₄	3 mol%, 1 h	3gn , 88

^a All reactions were carried out with CuOAc in 0.5 M MeOH solution at 28 °C.



Scheme 3 Cu-catalyzed conjugate addition of 2a to alkynyl ketone 6.



Scheme 4 Reactions in MeOD.



Similar to other alkynyl ester substrates, methyl propiolate and its trimethylsilyl and bromo analogues were also tested, but none of them gave the desired product (Fig. 1). This result is in contrast to that of alkynyl ketone **6** that underwent conjugate addition to yield the corresponding adduct **7** in a high yield with a moderate stereoselectivity of E : Z = 86 : 14(Scheme 3). The minor stereoisomer (*Z*)-**7** was considered to be formed due to the isomerization of the initially formed vinylcopper species (*E*)-**8** to (*Z*)-**8** via transient allenolate **9**, as previously reported for the related conjugate additions of organocopper reagents to alkynoates.^{1,5,9}

To obtain further insight into the reaction mechanism, we carried out the reaction of **1a** and **2a** (1.5 equiv.) in MeOD (Scheme 4). As a result, mono-deuterated (*E*)-**3aa**-*d* was obtained with 74% D content, indicating that the hydroxy group of methanol behaved as a proton donor. Insufficient deuteration might be attributed to the H–D exchange between MeOD and **2a** or direct proton transfer from **2a** to an alkenylcopper intermediate (see below). Thus, the use of 2-phenyl-5,5-dimethyl-1,3,2-dioxaborinane **10** instead of **2a** gave (*E*)-**3aa**-*d* with a D content of more than 98%.

Scheme 5 outlines a plausible mechanism of the Cu-catalyzed conjugate addition of arylboronic acids to alkynoates. Transmetallation from the arylboronic acids to copper methoxide (or acetate) proceeds *via* a four-centered transition state to yield reactive arylcopper species.⁶ Subsequent carbocupration of the alkynoates produces vinylcopper intermediates, which then undergo protonolysis by methanol to yield the final cinnamates with the concomitant restoration of copper methoxide. In previous cuprate-based methods, a low reaction temperature was required to prevent the isomerization of the initially formed *syn*-carbocupration adducts to *anti*-isomers *via* allenolate intermediates.^{1,5,9} Because our protocol employs methanol as a solvent, the vinylcopper intermediates undergo facile protonolysis before isomerization, resulting in the stereoselective formation of the *syn*-hydroarylation products even at ambient temperature.

In conclusion, we succeeded in carrying out the catalytic conjugate addition of arylboronates to alkynoates.¹⁰ The reaction proceeded in MeOH under mild conditions to yield trisubstituted cinnamates with precise *syn*-selectivity. This protocol is compatible with phenylboronic acids bearing carbon–halogen bonds as well as carbonyl functional groups.

This research was partially supported by the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for Young Scientists (A), 17685008, and the Global COE program (Tokyo Instituted of Technology). We thank Prof. H. Suzuki (Tokyo Institute of Technology) for use of the GC mass spectrometer, and Prof. K. Tomooka (Kyushu University) for use of the NMR spectrometer.

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