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Copper-Catalyzed Regio- and Stereoselective Conjugate Allylation of Electron-Deficient Alkynes with Allylboronates under Mild Conditions

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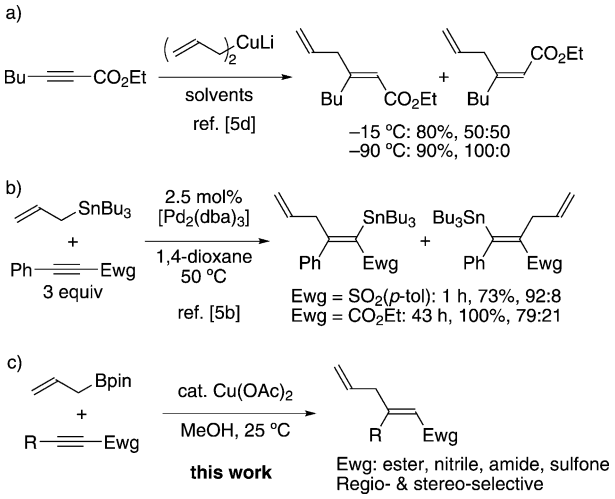
Conjugate allylation of alkenes activated by an electron-withdrawing group has been an important research subject in organic synthesis because carbon–carbon bonds formation occurs at the β-position to the activating group and the installed allyl moiety can be a versatile handle for further synthetic manipulations.[1] Therefore, various allylic metal reagents, with or without promoters, have been investigated to accomplish high 1,4 versus 1,2 selectivity,[2] and catalytic enantioselective conjugate allylations have been recently developed.[3,4]

In striking contrast, conjugate allylations of alkynic congeners have hardly been developed,[5] although they provide a powerful entry to functionalized skipped dienes.[6] Conjugate allylation of alkynoates with allyl and methallyl copper reagents was accomplished for the first time by Corey and co-workers.[5e] Later, the scope of allylic groups was carefully examined using both organocuprates and organocopper reagents.[5d] These investigations revealed that *syn* stereoselectivity can be achieved by performing the reaction at low temperature, typically at −90 °C (Scheme 1a). However, the scope of alkyne substrates has not been established yet. Nevertheless, the synthetic utility of this traditional method has been well demonstrated; it has been applied to the stereoselective synthesis of a functionalized allylboronate[7] and a dienoic acid building block for the total synthesis of natural products such as (+)-amphidinolide A and pectenotoxin 2.[8]

Apart from the copper chemistry, catalyzed or non-catalyzed allylmetalation of electron-deficient alkynes have been investigated. Shirakawa, Hiyama, and co-workers reported that the nickel- or palladium-catalyzed allylstannation of various alkynes activated by ester, cyano, or sulfonyl groups afforded 1,4-dienylstannanes (Scheme 1b),[5b,c] whereas Xie, Wang, and co-workers described the allylzincation of alkynyl sulfones.[5a] Although these methods have an advantage in that the 1,4-dienylmetal products can be used for subsequent cross-coupling reactions, successful results are limited to alkynyl sulfones. In fact, although palladium-catalyzed allylstannation of a phenylethynyl sulfone proceeded at 50 °C for 1 h to give the corresponding product in 73% yield with a high regioselectivity of 92:8, that of ethyl 3-phenylpropiolate was sluggish and the regioselectivity diminished to 79:21 (Scheme 1b).



Scheme 1. Conjugate allylation of electron-deficient alkynes.

Therefore, there is an unmet need for a practical synthesis method that has wide substrate scope and high regio- and stereoselectivity. It is also important for the newly developed protocol to proceed by using a bench-top stable, readily available, and less toxic allylating agent. Because it is highly important to develop a method for synthesizing multiply substituted alkenes, we have developed relevant copper-catalyzed syn hydroarylations of alkynoates and alkynic nitriles with arylboronic acids and applied these hydroarylations to the synthesis of biologically significant molecules.[9] As a continuation of these studies, we herein describe preliminary results obtained from the investigation of the copper-catalyzed conjugate allylation of electron-deficient alkynes with allylboronic acid pinacol (pin) esters (Scheme 1c). The newly established method has the following notable advantages:

1) A wide range of electron-deficient alkyne substrates are applicable.
2) Readily available allylboronic acid pinacol esters and inexpensive copper(II) acetate as a catalyst are used.

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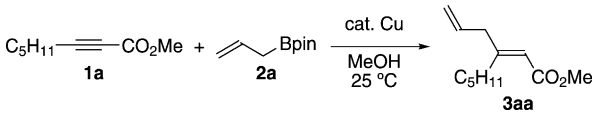
3) The reaction proceeds at room temperature to deliver 1,4-diene products with perfect regio- and stereoselectivity.

To the best of our knowledge, there is no example of a copper-catalyzed conjugate addition of alkylboron reagents to electron-deficient alkynes, although that to α,β-unsaturated imidazolyl ketones was recently reported by Sawamura and co-workers.[10]

At the outset, copper salts were screened using alkynoate **1a** and allylboronate **2a**, as outlined in Table 1. In a similar manner to our previous copper-catalyzed hydroarylation, **1a** and **2a** were treated with a copper salt in MeOH at 25 °C. Among the copper(I) halides examined, only CuCl exhibited catalytic activity (entries 1–3). The crude yield of **3aa** was, however, as low as 30 % with a 5 mol % catalyst loading after 24 h, as determined by ^{1}H NMR spectroscopy. In contrast, the reaction reached completion within 1 h when Cu(OAc) was used under the same conditions (entry 4). In this case, **3aa** was isolated in 91 % yield. The use of $Cu(OAc)_2$ in place of CuOAc led to a similar result (entry 5). Although $Cu(OAc)_2$ is presumably reduced to CuOAc under the reaction conditions, better reproducibility was obtained with $Cu(OAc)_2$ and loadings of both the catalyst and **2a** were successfully reduced to 3 mol % and 1.5 equivalents, respectively (entry 6). A further reduced loading of **2a** diminished the yield of **3aa** (entry 7). The copper catalyst is essential as no reaction occurred even in refluxing MeOH in the absence of the catalyst (entry 8). On the basis of these results, further explorations were carried out using $Cu(OAc)_2$ as the optimal copper source.

Table 1. Optimization of reaction conditions.

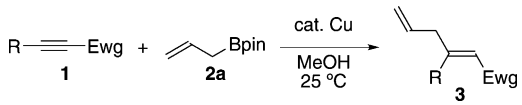


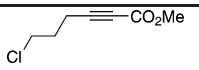
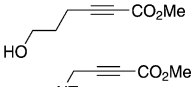
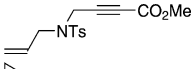
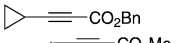
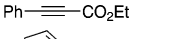
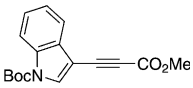
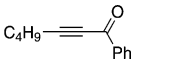
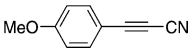
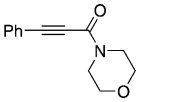
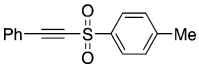
	Cu salt [mol %]	**2a** [equiv]	*t* [h]	Yield **3aa** [%]
1	CuCl (5)	2	24	29[a]
2	CuBr (5)	2	24	trace
3	CuI (5)	2	24	no reaction
4	Cu(OAc) (5)	2	1	91[b]
5	$Cu(OAc)_2$ (5)	2	1	93[b]
6	$Cu(OAc)_2$ (3)	1.5	3	92[b]
7	$Cu(OAc)_2$ (3)	1.2	4	84[a]
8[c]	none	1.5	24	no reaction

[a] Crude yields determined by ^{1}H NMR spectroscopy. [b] Isolated yields. [c] Reflux.

The substrate scope was investigated by performing allylations with various alkynes under optimized conditions (Table 2). Chloroalkyl, non-protected hydroxy, *N*-allyl tosylamide, and cyclopropyl groups were well tolerated (entries 1–4), and only a 1,4-addition was observed for the conjugated enyne substrate **1f** (entry 5). Aromatic and heteroaromatic alkynes **1g** and **1h** participated in the present conjugate allylation without any difficulty (entries 6 and 7). Notably, all these examples gave high isolated yields ranging from 88 to 99 % and excellent stereoselectivity, exclusively producing syn adducts. The reaction of **1g** was also performed on a 10 mmol (ca. 1.7 g) scale without erosion of the yield and selectivity. On the other hand, a bulky TBS-substituted propiolate failed to undergo conjugate allylation (Figure 1).

Table 2. Scope of alkyne substrates.[a]



	1		Cu [mol %]	*t* [h]	Yield [%]
1		**1b**	3	2	**3ba** 93
2		**1c**	3	3	**3ca** 91
3		**1d**	3	3	**3da** 88
4		**1e**	3	3	**3ea** 99
5		**1f**	3	3	**3fa** 92
6		**1g**	3	3	**3ga** 99 (96)[b]
7		**1h**	56	6	**3ha** 89
8		**1i**	3	24	**3ia** trace[c]
9		**1j**	33	3	**3ja** 94
10		**1k**	82	2	**3ka** quant
11		**1l**	3	3	**3la** 84

[a] Conditions: **1** (0.5 mmol or 0.3 mmol for entries 7 and 8), **2a** (1.5 equiv), MeOH solvent, 25 °C. [b] Yields of 10 mmol-scale reaction. [c] 1,2-adduct **4ia** was obtained in 61 % yield.

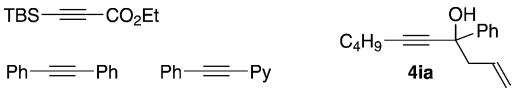


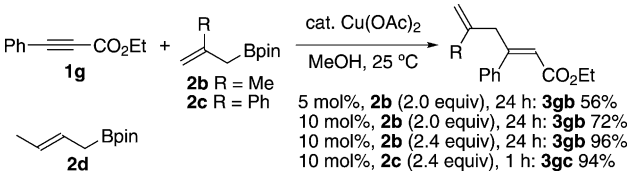
Figure 1. Inefficient alkynes and by-product.

The influence of activating groups was next examined. One limitation of the present method is its failure to obtain conjugate allylation product **3ia** from alkynyl ketone **1i** (Table 2, entry 8). In this case, 1,2-allylation product **4ia** was formed as the major product in 61 % yield (Figure 1).[11] In contrast, cyanoalkyne **1j** and propiolylamide **1k** underwent conjugate allylation to deliver **3ja** and **3ka**, respectively, in excellent yields (Table 2, entries 9 and 10). In the latter case, a catalyst loading of 8 mol % was necessary to ensure the complete conversion of **1k**, because the amide group has in-

ferior electron-withdrawing ability, rendering the reaction sluggish. Hydroallylation of alkynyl sulfone **1l** proceeded with a 3 mol% catalyst loading for 3 h to exclusively deliver syn adduct **3la** in 84% yield (entry 10). The syn selectivity of the present hydroallylation was supported by X-ray crystallographic analysis of **3la** (Supporting Information).

The effective electron-withdrawing group is imperative because diphenylacetylene and 2-(phenylethynyl)pyridine proved completely ineffective toward the present protocol (Figure 1). This is in contrast to the observation that the rhodium-catalyzed hydroarylation proceeded regio- and stereoselectively with 2-alkynylpyridines in water at 80°C.[12]

With an efficient hydroallylation method having been established with allylboronate **2a**, the scope of other allylboronate reagents was briefly examined (Scheme 2). The reaction of **1g** with methallylboronate **2b** (2.0 equiv) was carried

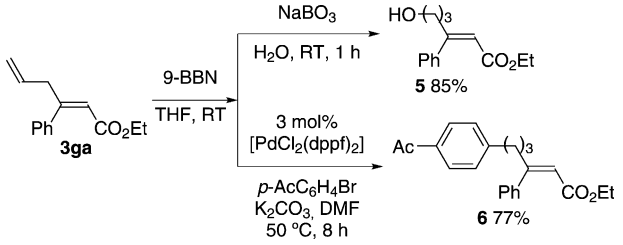


Scheme 2. Reactions of **1g** with substituted allylboronates **2b–d**.

out using 5 mol% $Cu(OAc)_2$ in MeOH at 25°C. In contrast to the case of parent **2a**, this reaction proceeded sluggishly and **1g** was not completely consumed within 24 h. To increase the reaction rate, a 10 mol% loading of $Cu(OAc)_2$ was used. Nevertheless, the ^1H NMR analysis of the crude products revealed that small amounts of **1g** remained intact, although **2b** completely disappeared. Thus, the loading of **2b** was increased to 2.4 equivalents to observe the full conversion of **1g**. Ultimately, the desired **3gb** was isolated in a high yield of 96%. Similarly, the use of 2-phenylallylboronate **2c** yielded **3gc** (94% yield) with a shorter reaction time. In contrast, further erosion of reactivity was observed for crotylboronate **2d**; the reaction was very sluggish under the same conditions and an inseparable mixture of several products was formed in a poor yield.

Although the installation of γ-substituted allyl groups is problematic at this stage, the parent allyl moiety can be easily functionalized in various ways. To demonstrate the synthetic utility of the developed method, we performed the derivatization of the conjugate allylation products. After hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN), subsequent oxidation with $NaBO_3$ or Suzuki–Miyaura coupling with *p*-acetylphenyl bromide transformed **3ga** into alcohol **5** and arylation product **6** in 85 and 77% yields, respectively (Scheme 3).[13]

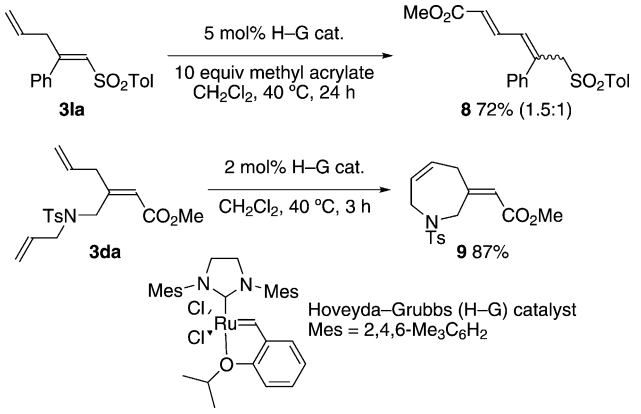
Olefin cross metathesis (CM) is also a powerful method for homologating terminal alkenes.[14] However, CM of skipped dienes such as **3ga** poses some selectivity issues.



Scheme 3. Derivatization of conjugate allylation product **3ga** by hydroboration.

1) It is desirable that the metathesis reaction occurs at the terminal alkene moiety rather than at the electron-deficient tri-substituted alkene moiety.
2) Skipped dienes might undergo isomerization, giving rise to conjugated 1,3-dienes under metathesis conditions.[15]

In fact, CM of **3ga** with methyl acrylate was carried out in refluxing CH_2Cl_2 for 24 h using the Hoveyda–Grubbs catalyst[16] to deliver the expected product with several inseparable minor by-products, which were presumably formed by alkene isomerization. The same reaction was performed with sulfone **3la**; in this reaction, the complete isomerization of the tri-substituted alkene moiety occurred to afford conjugated diene **8** as a mixture of *E* and *Z* isomers (Scheme 4). This result shows that the selective functionali-



Scheme 4. Derivatization of conjugate allylation products through metathesis.

zation of the introduced allyl group is possible using olefin metathesis. Olefin ring-closing metathesis (RCM) has been used for the construction of heterocyclic compounds.[17] In our study, RCM of **3da** proceeded effectively in a similar manner to obtain seven-membered nitrogen heterocycle **9** in 87% yield without isomerization of the *exo*-cyclic alkene (Scheme 4).

In summary, we successfully developed a copper-catalyzed conjugate allylation of electron-deficient alkynes with commercially available allylboronic acid pinacol esters and copper(II) acetate. This method can be applied to a variety of

functionalized alkynes bearing activating groups, such as ester, nitrile, amide, or sufone substituents, and hydroallylation products were obtained in high yields with perfect regio- and stereoselectivity. On the other hand, an alkynyl ketone underwent 1,2-addition to deliver a propargylic alcohol. It was demonstrated that the obtained products can be transformed into synthetically useful compounds using hydroboration or olefin metathesis of the introduced allyl moiety. Further studies of a superior catalytic system as well as synthetic applications of the present protocol are actively underway in our laboratory.

Experimental Section

Representative procedure—synthesis of 3aa: A solution of $Cu(OAc)_2$ (2.83 mg, 0.015 mmol), alkynoate **1a** (83 mL, 0.50 mmol) and allylboronate **2a** (142 mL, 0.75 mmol) in MeOH (1 mL) was degassed at −78 °C and then was stirred at 25 °C under Ar atmosphere for 3 h. The reaction mixture was diluted with Et_2O (3 mL) and was filtered through a plug of alumina. The residue was washed with Et_2O (20 mL), and the filtrate was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexane-AcOEt 100:1) to give dienoate **3aa** (90.6 mg, 92%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 7.2$ Hz, 3H), 1.26–1.52 (m, 6H), 2.61 (t, $J = 7.8$ Hz, 2H), 2.89 (dq, $J = 6.6$, 1.4 Hz, 2H), 3.69 (s, 3H), 5.07–5.15 (m, 2H), 5.65 (s, 1H), 5.77 ppm (ddt, $J = 16.8$, 10.5, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 22.6, 28.2, 32.0, 32.1, 42.5, 50.7, 115.4, 117.5, 134.1, 162.4, 166.3 ppm; IR ($CHCl_3$): $\tilde{\nu} = 1712$ cm^{-1} (C=O); HRMS (FAB): *m/z* calcd for $C_{12}H_{20}O_2$·H: 197.1542; found: 197.1549 $[M+H]^+$.

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Keywords: alkynes · copper · dienes · homogeneous catalysis · hydroallylation · organoboron

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