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Copper-catalyzed 1,1-arylalkylation of terminal alkynes with diazo esters and organoboronic acids†

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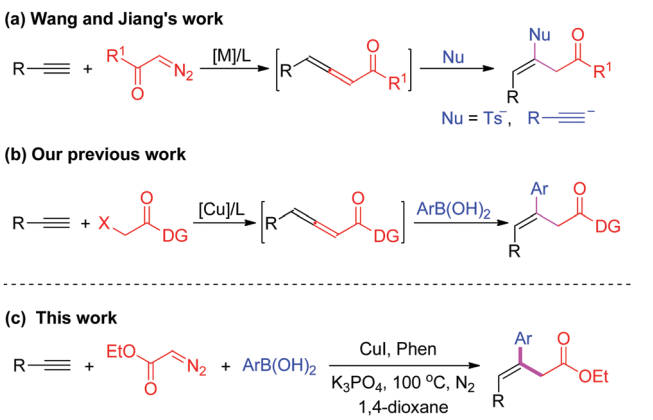
A novel copper-catalyzed 1,1-arylalkylation of terminal alkynes with diazo esters and organoboronic acids is described. With this methodology, (*E*)-β-aryl-β,γ-unsaturated esters can be easily constructed in good to excellent yields directly from readily available and inexpensive traditional coupling reagents.

β,γ-Unsaturated esters are important structural motifs in natural products,[1] and they are also useful intermediates in organic synthesis.[2] The methods generally used to synthesize these key compounds include carbonylation reactions with allylic substrates,[3] cross-couplings of potassium alkenyltrifluoroborates or alkenyl-9-BBN with 2-chloroacetate esters,[4] or decarboxylative alkylcarboxylation of α,β-unsaturated acids.[5] Despite these significant achievements, the difunctionalization of alkynes for the synthesis of β,γ-unsaturated esters has not yet been reported. Therefore, the development of new, versatile and reliable methods is still of great importance.

Difunctionalizations of alkynes have received significant interest for the synthesis of multisubstituted olefins in organic synthesis.[6] In this context, classical methods for the difunctionalization of alkynes almost exclusively involve the addition of two functional groups to the two carbons of the alkyne, namely, 1,2-difunctionalizations (vicinal). Compared to classical difunctionalization reactions, 1,1-difunctionalizations of alkynes are underexplored. In the past few decades, Iwasawa, Takai, Zhu, Chirik, Sawamura, Yin, Wang and Jiang have independently reported 1,1-dicarbofunctionalizations, 1,1-aminoacylations, 1,1-diborations and 1,1-carbosulfonylations of terminal alkynes.[7] Among which, strategies through allenes provided a new perspective for the 1,1-difunctionalization of alkynes. Diazo compounds are becoming very popular as synthons for the preparation of allenes through Cu(I)-catalyzed cross-couplings of terminal alkynes,[8] and they have been used in 1,1-difunctionalizations of alkynes (Scheme 1a).[7g,i] Recently, we realized a regio- and stereoselective copper-catalyzed three-component 1,1-arylalkylation of alkynes with α-chloroacetamides and organoboronic acids with a cleavable bidentate 8-aminoquinoline auxiliary (Scheme 1b).[9] An allene is also generated as an intermediate in this transformation. Although it undergoes highly selective *syn*-carbocupration and protonolysis to afford the product, to the best of our knowledge, copper-catalyzed regioselective hydroarylations of allenes with arylboronic acids have not been explored.[10] Therefore, we envisioned that an allene, generated *in situ* from a terminal alkyne and a diazo compound in the presence of a copper catalyst, could undergo hydroarylation to realize the 1,1-arylalkylation of a terminal alkyne given suitable conditions for the above two processes. Herein, as part of our ongoing interest in the 1,1-difunctionalization of alkynes, we report a novel, copper-catalyzed 1,1-arylalkylation of terminal alkynes with diazo esters and organoboronic acids for the synthesis of (*E*)-β-aryl-β,γ-unsaturated esters (Scheme 1c).

Inspired by our previous research on copper-catalyzed 1,1-arylalkylations of alkynes, we commenced our study by testing



Scheme 1 Strategies for the 1,1-difunctionalization of alkynes through allenes.

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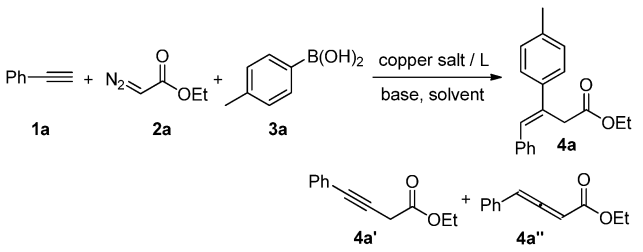
the coupling of ethynylbenzene (**1a**) with ethyl 2-diazoacetate (**2a**) and *p*-tolylboronic acid (**3a**) in the presence of a catalytic amount of CuI (10 mol%), 1,10-phenanthroline (10 mol%) and Cs_2CO_3 (2.0 equiv.) in dioxane at 100 °C. To our delight, the desired 1,1-arylalkylation product **4a** was smoothly obtained in 40% yield along with 14% of ethyl 4-phenylbut-3-ynoate (**4a′**) and trace ethyl 4-phenylbuta-2,3-dienoate (**4a″**) (Table 1, entry 1). To improve the utility of this 1,1-arylalkylation reaction, various conditions were then optimized. The choice of base has a significant effect on these transformations, and K_3PO_4 afforded the best results (Table 1, entries 2–5). Bipy was also an effective ligand for this transformation (Table 1, entry 6), and other ligands, such as PPh_3 and DPPE, were examined but did not lead to any significant improvement (Table 1, entries 7 and 8). Further investigations of different solvents (*e.g.*, CH_3CN, EtOAc, acetone and DMSO) revealed that dioxane gave the best reaction outcome (Table 1, entries 9–12). In addition, other catalysts, such as CuCl and CuBr, were not as effective as CuI (Table 1, entries 13 and 14). Finally, control reactions demonstrated that the catalyst, ligand and base were essential for the reaction (Table 1, entries 15–17).

With the optimal reaction conditions in hand, we examined the substrate scope of this methodology employing a series of alkynes, and the results are presented in Table 2. In general, ethynylbenzenes **1b–1n** bearing different substituents were viable substrates and smoothly reacted with ethyl 2-diazoacetate (**2a**) and *p*-tolylboronic acid (**3a**) to give 1,1-arylalkylation products **4b–4n** in moderate to good yields. Sterically bulky groups on the substrates did not have an obvious effect on the reaction, and the *para*-, *meta*-, and *ortho*-fluoro and chloro ethynylbenzenes afforded the corresponding products **4h**, **4i**, and **4k–4n** in similar yields. *N*-Propargyl amides, such as *tert*-butyl prop-2-yn-1-ylcarbamate (**1o**), also provided the desired product (**4o**) in 90% yield. Alkyl propargyl ethers **1p–1r** underwent the 1,1-arylalkylation reaction to give the corresponding products **4p–4r** in good yields. Importantly, an aliphatic alkyne (ethynylcyclopropane, **1s**) was a suitable substrate and gave **4s** in 90% yield. Meanwhile, pent-1-yne and hex-1-yne proceeded smoothly to afford **4t** and **4u** in 55% and 56% yields, respectively. However, methyl propiolate and propiolamide were not effective for this 1,1-arylalkylation reaction. Notably, a broad range of synthetically crucial functional groups, such as F, Cl, Br, OH, oxirane and cyclopropyl, were well tolerated in the transformation and remained intact.

We then evaluated the scope of arylboronic acids, and the results are summarized in Table 3. Arylboronic acids bearing alkyl, vinyl, Cl, and Br substituents at the *para* position of the aromatic ring all worked well with **1a** and **2a** producing desired products **5b–5h** in moderate to good yields. Electron-donating and electron-withdrawing groups, including alkyl (**3i**), alkoxyl (**3j**), formyl (**3k**), and halide (**3l–3n**) moieties, were tolerated. Disubstituted arylboronic acids were found to be compatible with this coupling and produced **5o–5r**. In addition, 2-diazo-*N*-phenylacetamide (**2b**) and ethyl 2-diazo-2-phenylacetate (**2c**) provided desired products **5s** and **5t** in 34% and 42% yields,

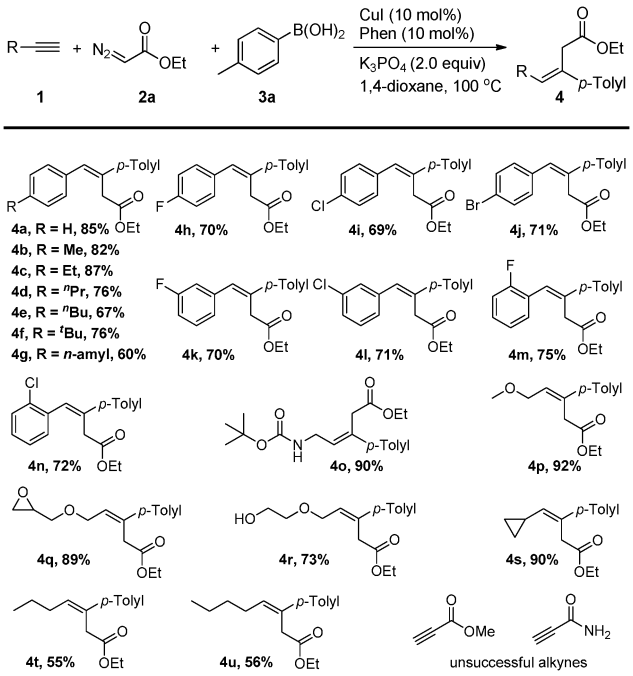
Table 1 Optimization of the reaction conditions[a]



Entry	Metal	Ligand	Base	Solvent	Yield[b] (%) 4a	4a′	4a″
1	CuI	Phen	Cs_2CO_3	Dioxane	40	14	Trace
2	CuI	Phen	K_2CO_3	Dioxane	32	26	10
3	CuI	Phen	K_3PO_4	Dioxane	85	Trace	Trace
4	CuI	Phen	Et_3N	Dioxane	Trace	Trace	Trace
5	CuI	Phen	DBU	Dioxane	0	0	0
6	CuI	Bipy	K_3PO_4	Dioxane	83	Trace	Trace
7	CuI	PPh_3	K_3PO_4	Dioxane	Trace	<5	<5
8	CuI	Dppe	K_3PO_4	Dioxane	<5	<5	<5
9	CuI	Phen	K_3PO_4	CH_3CN	40	20	0
10	CuI	Phen	K_3PO_4	EtOAc	48	12	0
11	CuI	Phen	K_3PO_4	Acetone	28	21	0
12	CuI	Phen	K_3PO_4	DMSO	0	0	0
13	CuBr	Phen	K_3PO_4	Dioxane	36	Trace	Trace
14	CuCl	Phen	K_3PO_4	Dioxane	<5	Trace	Trace
15	None	Phen	K_3PO_4	Dioxane	0	0	0
16	CuI	None	K_3PO_4	Dioxane	<5	10	0
17	CuI	Phen	None	Dioxane	Trace	<5	<5

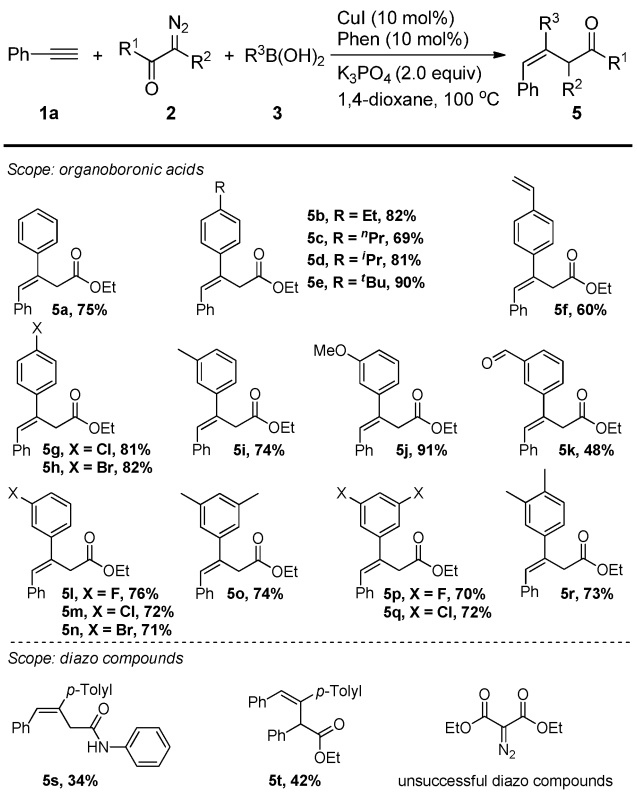
[a] Reactions were carried out with **1a** (0.36 mmol), **2a** (0.3 mmol), **3a** (0.9 mmol), metal (10 mol%), ligand (10 mol%) and base (2.0 equiv.) in 1.0 mL of solvent under a N_2 atmosphere at 100 °C for 1.5 h unless otherwise noted. [b] Yield of the isolated product.

Table 2 The scope of alkynes in the 1,1-arylalkylation[a]



[a] Reactions were carried out with **1** (0.36 mmol), **2a** (0.3 mmol), **3a** (0.90 mmol), CuI (10 mol%), Phen (10 mol%) and K_3PO_4 (0.6 mmol) in dioxane (1.0 mL) under a N_2 atmosphere at 100 °C for 1.5 h. Yield of the isolated product.

Table 3 The scope of organoboronic acids and diazo compounds in the 1,1-arylalkylation[a]

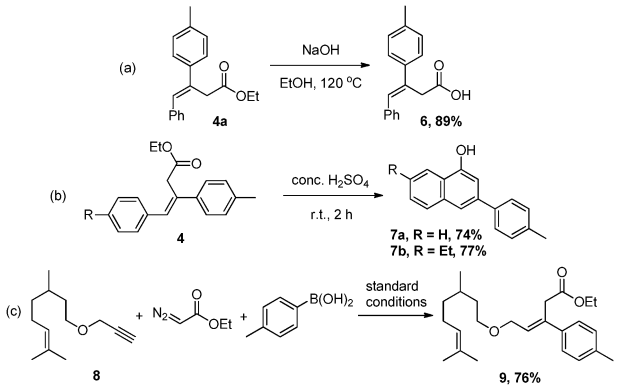


[a] Reactions were carried out with **1a** (0.36 mmol), **2a** (0.3 mmol), **3** (0.90 mmol), CuI (10 mol%), Phen (10 mol%) and K_3PO_4 (0.6 mmol) in dioxane (2.0 mL) under a N_2 atmosphere at 100 °C for 1.5 h. Yield of the isolated product.

respectively. However, the reaction of diethyl 2-diazomalonate (**2d**) did not give the desired product.

Further transformations of the 1,1-arylalkylation products were surveyed to illustrate the value of this method (Scheme 2). Treatment of **4a** with NaOH in EtOH afforded (*E*)-4-phenyl-3-(*p*-tolyl)-but-3-enoic acid (**6**) in 89% yield (Scheme 2a). The absolute configuration of product **6** (CCDC 1943644†), as determined by X-ray diffraction, further confirmed the regioselectivity of dicarbofunctionalization of the alkyne. Under concentrated H_2SO_4, **4a** and **4c** could be transformed into 3-aryl-1-naphthols (Scheme 2b), which are important motifs in pharmaceuticals and photoelectric materials.[11] This novel transformation was also applied to the late-stage modification of biologically relevant compounds containing alkyne groups. Citronellol-derived alkyne **8** smoothly underwent the developed 1,1-arylalkylation to afford desired products **9** in 76% yield (Scheme 2c).

Control experiments were performed to elucidate the mechanism of the reaction (Scheme 3). In the absence of **3a** and K_3PO_4, the reaction of **1a** and **2a** generated a mixture of cross-coupling products **4a′** and **4a″** in nearly a 5 : 1 ratio, albeit in 42% yield.[12] Subsequently, compounds **4a′** and **4a″** could be reacted with **3a** to give product **4a** in 45% and 73% yields, respectively (Scheme 3a and b). Therefore, compounds **4a′** and **4a″** are likely intermediates in this reaction. In addition, radical

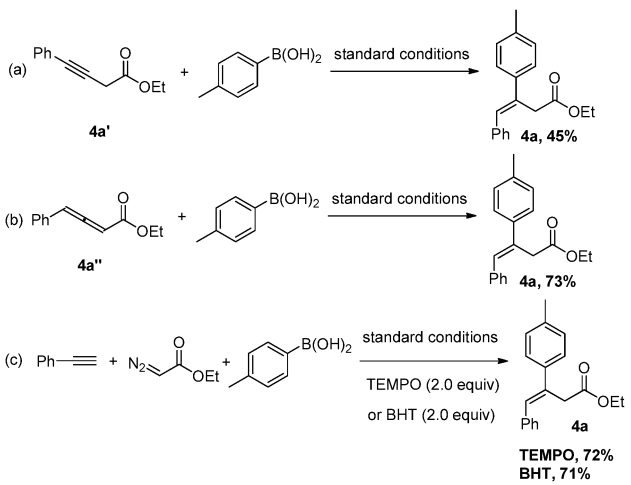


Scheme 2 Transformation of a product and synthetic applications of this reaction.

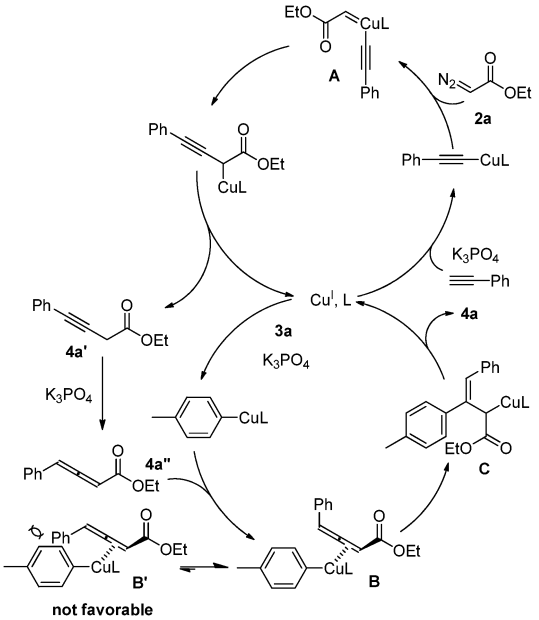
scavengers, such as 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO, 2.0 equiv.) and 2,6-di-*tert*butyl-4-methylphenol (BHT, 2.0 equiv.), were added to reactions conducted under the standard conditions, and product **4a** was isolated in 72% and 71% yields, respectively (Scheme 3c). This result excludes the involvement of a radical process in this reaction.

On the basis of the previous studies and the abovementioned experiments, a possible mechanism was proposed (Scheme 4). Initially, the copper-catalyzed cross coupling of **1a** with **2a** generated intermediate **4a′** though an alkynyl migratory insertion of Cu(I) carbene **A**,[13] and **4a′** then undergoes facile rearrangement to afford intermediate **4a″**. Then, the arylcopper species readily generated *via* transmetalation of **3a**, *via* regeneration of the Cu(I) species in the presence of Phen,[14] reacted with **4a″** to form intermediates **B** and **B′**. The carbonyl-substituted double bond selectively coordinates to the arylcopper species on the side opposite the phenyl group to avoid steric interactions. Intermediate **B** then undergoes *syn*-carbocupration to afford intermediate **C**, which gives the product and regenerates the Cu(I) catalyst through protonolysis.

In conclusion, a novel, copper-catalyzed 1,1-arylalkylation of terminal alkynes with diazo esters and organoboronic acids has



Scheme 3 Control experiments.



Scheme 4 Plausible mechanistic pathway.

been described. This transformation is a powerful approach for the construction of (*E*)-β-aryl-β,γ-unsaturated esters. Further mechanistic investigations and explorations of the *gem*-difunctionalization of other types of alkynes are currently underway in our laboratory.

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Conflicts of interest

The authors declare no conflicts of interest.

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