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Copper-Catalyzed *anti*-Selective Radical 1,2-Alkylarylation of Terminal Alkynes

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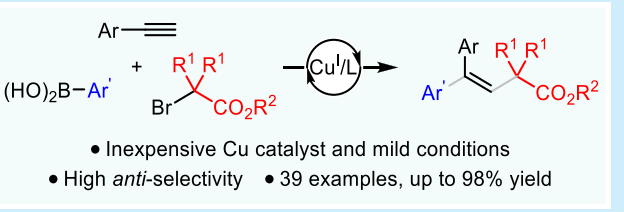
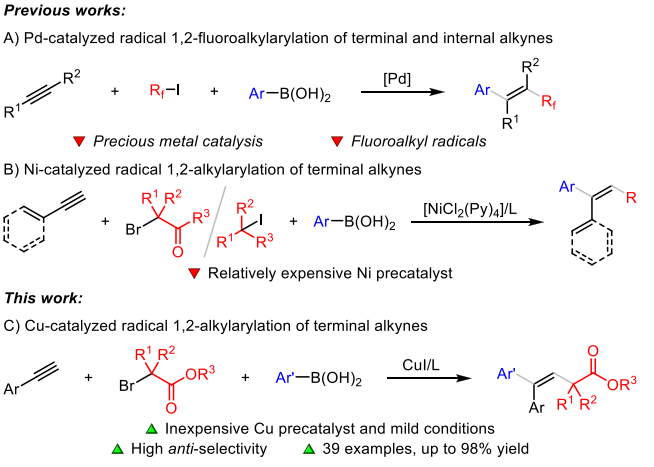
ABSTRACT: A copper-catalyzed highly *anti*-selective radical 1,2-alkylarylation of terminal alkynes with aryl boronic acids and alkyl bromides has been established. The reaction exhibits high compatibility with a wide range of terminal alkynes and diverse aryl boronic acids, thus providing facile access to various stereodefined trisubstituted alkenes in high yield under mild reaction conditions. Preliminary mechanistic investigations support the formation of alkyl radicals and their subsequent addition to alkynes in the reaction.



Transition-metal-catalyzed dicarbofunctionalization of alkynes[1] provides a powerful tool for preparing stereochemically defined multifunctional alkenes,[2] which are structural motifs commonly found in advanced materials[3] and bioactive compounds.[4] Despite remarkable progress, it is still urgently desirable and remains as a significant challenge to realize such transformations under mild conditions with high chemo-, regio-, and stereoselectivity. Recently, transition-metal-catalyzed radical addition to π bonds offers a novel robust platform for highly efficient and selective catalytic dicarbofunctionalization of unsaturated hydrocarbons.[5] On the other hand, organoboron reagents are among the most thoroughly studied and widely applied classes of reagents across organic synthesis and catalysis[6] given their characteristic stability and ready availability. Accordingly, much effort has been made in developing organoboron reagents as the nucleophilic coupling partners in transition-metal-catalyzed stereoselective radical dicarbofunctionalization of alkynes. Particularly, Nevado's[7] and Liang's[8] groups have pioneered in independently establishing Pd-catalyzed *anti*-selective 1,2-fluoroalkylarylation of terminal alkynes using various fluoroalkyl iodides as the radical precursors together with aryl boronic acid coupling partners (Scheme 1A). Later, Chaładaj,[9] Nevado,[10] and others[11] extended the reaction to internal alkynes and more fluoroalkyl iodides. Nonetheless, the reaction still requires expensive precious metal Pd for catalysis and is demonstrated to be compatible with only fluoroalkyl iodide radical precursors. In this regard, Nevado's group[12] has made a breakthrough by achieving the nickel-catalyzed *anti*-selective radical 1,2-alkylarylation of conjugated terminal alkynes (Scheme 1B),[13] which readily accommodates a panel of activated α-carbonyl alkyl bromides as well as unactivated tertiary alkyl iodides as radical precursors. Yet, the precatalyst

Scheme 1. Transition-Metal-Catalyzed Radical 1,2-Alkylarylation of Alkynes with Organoboron Reagents



$[NiCl_2(Py)_4]$ has a relatively high molecular weight and may not be readily commercially available.

Considering the usually low cost and ready commercial availability of common copper salts, our group has focused on copper-catalyzed radical functionalization of unsaturated hydrocarbons for generating complex and useful molecular

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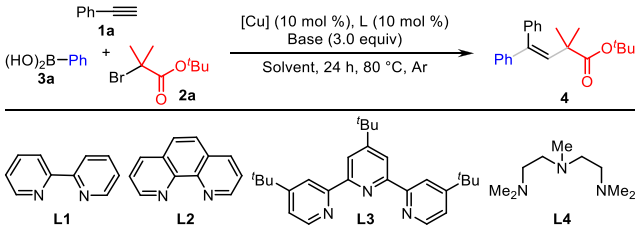
scaffolds.[14] Given the aforementioned challenges in transition-metal-catalyzed stereoselective radical 1,2-alkylarylation of alkynes and the great potential of corresponding products for applications in material sciences, we were intrigued to explore a copper-catalyzed version of this reaction that, if successfully realized, would favorably well complement those reported methods. Notably, to the best of our knowledge, such a reaction has so far remained unknown. Herein, we report our effort in achieving the copper-catalyzed *anti*-selective synthesis of trisubstituted alkenes (Scheme 1C) through a radical-mediated, three-component reaction of activated α-carbonyl alkyl bromides and aryl boronic acids with terminal aryl alkynes.

We began the condition optimization with the model reaction of ethynylbenzene **1a**, *tert*-butyl 2-bromo-2-methylpropanoate **2a**, and phenylboronic acid **3a** in the presence of CuBr and K_3PO_4 in THF by first screening ligands (Table 1).

Table 1. Screening of Reaction Conditions[a,b]



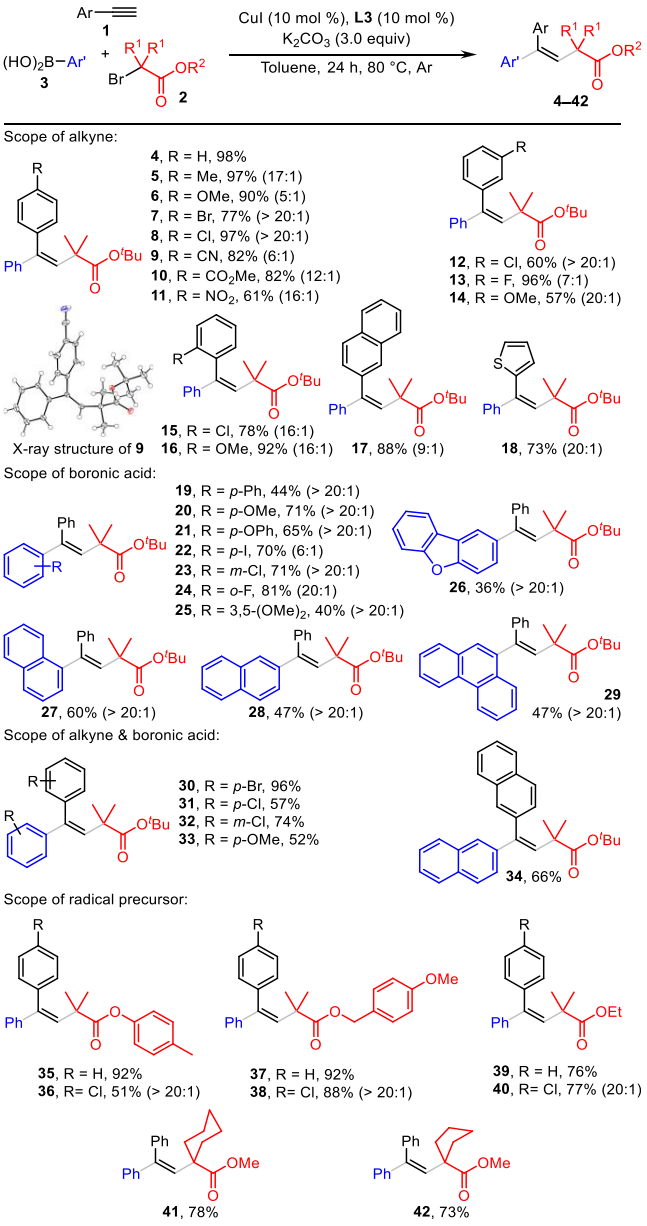
Entry	[Cu]	L	Base	Solvent	Yield (%)[b]
1	CuBr	**L1**	K_3PO_4	THF	trace
2	CuBr	**L2**	K_3PO_4	THF	10
3	CuBr	**L3**	K_3PO_4	THF	60
4	CuBr	**L4**	K_3PO_4	THF	N.D.
5	CuI	**L3**	K_3PO_4	THF	82
6	CuI	**L3**	K_3PO_4	DMF	N.D.
7	CuI	**L3**	K_3PO_4	DCE	62
8	CuI	**L3**	K_3PO_4	Toluene	96
9	CuI	**L3**	Na_3PO_4	Toluene	33
10	CuI	**L3**	Na_2CO_3	Toluene	7
11	CuI	**L3**	K_2CO_3	Toluene	98
12	CuI	**L3**	Cs_2CO_3	Toluene	60

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (2.0 equiv), **3a** (2.0 equiv), [Cu] (10 mol %), L (10 mol %), and base (3.0 equiv) in solvent (0.10 M) at 80 °C for 24 h under argon. [b]Isolated yield.

Tridentate terpyridine-type ligand **L3** provided the desired product **4** in moderate yield (entry 3) while bidentate ligands **L1** and **L2** afforded only marginal reactivity (entries 1 and 2). In contrast, the tridentate amine-type ligand **L4** failed to deliver any product (entry 4). These results emphasize the importance of ligand denticity and types of coordination motifs in attaining the desired reactivity. Switching the copper salt to CuI further enhanced the reaction efficiency (entry 5), and additional screening of different solvents (entries 6−8) and base additives (entries 8−12) led to the optimal reaction conditions as follows: the reaction of **1a** with 2.0 equiv of **2a** and 2.0 equiv of **3a** in the presence of 10 mol % CuI, 10 mol % **L3**, and 3.0 equiv of K_2CO_3 in toluene at 80 °C for 24 h gave rise to the trisubstituted alkene product **4** in 98% isolated yield (Table 1, entry 11 and Table 2).

With the optimal conditions established, we next investigated the scope of the reaction (Table 2). Generally, terminal aryl alkynes and aryl boronic acids bearing electron-donating

Table 2. Substrate Scope of Alkynes, Boronic Acids, and Radical Precursors[a,b,c]



[a]Reaction conditions: **1** (0.20 mmol), **2** (2.0 equiv), **3** (2.0 equiv), CuI (10 mol %), **L3** (10 mol %), and K_2CO_3 (3.0 equiv) in toluene (0.10 M) at 80 °C for 24 h under argon. [b]Isolated yield. [c]The ratios of *anti*- and *syn*-selective products are presented in parentheses.

or -withdrawing substituents at the *para*, *meta*, or *ortho* positions of the phenyl rings were all applicable to the reaction to provide **4**−**16** and **19**−**25** in moderate to high yield. In addition to monocyclic phenyl rings, bicyclic or polycyclic aryl or heteroaryl rings in alkyne or boronic acid substrates were also suitable for the reaction to generate **17**, **18**, and **26**−**29** in moderate to good yield. Importantly, the X-ray structures of products **9** (Table 2 and Figure S1) and **11** (Figure S2) indicated the reaction to be *anti*-selective, and we generally observed high stereoselectivity (*anti*/*syn* ≥ 10:1, 20 examples; 10:1 > *anti*/*syn* ≥ 5:1, 5 examples) among all the 25 products with potential stereoisomers. We further explored the substrate scope by simultaneously changing the aryl rings in both the

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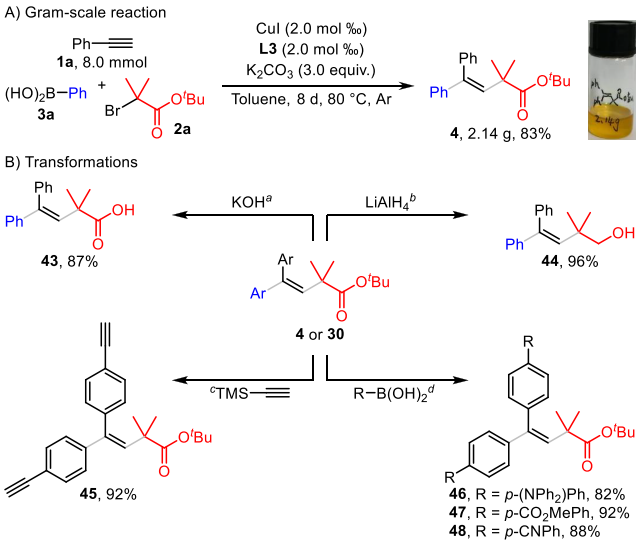
alkyne and boronic acid substrates, which was obviously well tolerated by the reaction to afford products **30**–**34**. Of particular note was the tolerance of potentially interfering functional groups such as aryl chloride (**8**, **12**, **15**, **23**, **31**, and **32**), bromide (**7** and **30**), iodide (**22**), nitrile (**9**), and nitro (**11**). It should be noted that alkyl alkynes are not suitable for the reaction, and no desired product was observed. In regard to the radical precursors, α,α-dimethyl-α-bromoesters derived from phenol as well as benzyl and ethyl alcohols all proved to be effective for the reaction to deliver the corresponding products **35**–**40** in high yield. Similarly, when extended to other precursors, the reaction could still obtain high *anti*-selectivity (*anti*/*syn* ≥ 20:1, **36**, **38**, and **40**). Furthermore, the cyclic α-bromoesters also readily participated in the reaction to efficiently produce **41** and **42**. Unfortunately, secondary alkyl bromides, such as(1-bromoethyl)benzene, 2-bromo-*N*-phenylpropanamide, and ethyl 2-bromopropanoate as well as unactivated 2-iodo-2-methylpropane, are not suitable for the reactions.

As for the synthetic practicality of this methodology, we were pleased to find that the reaction of 8.0 mmol **1a** proceeded smoothly to give **4** in 83% yield at a much lower catalyst loading of 2.0 mol ‰ (Scheme 2A). In order to

Scheme 2. Scale-up and Product Transformations

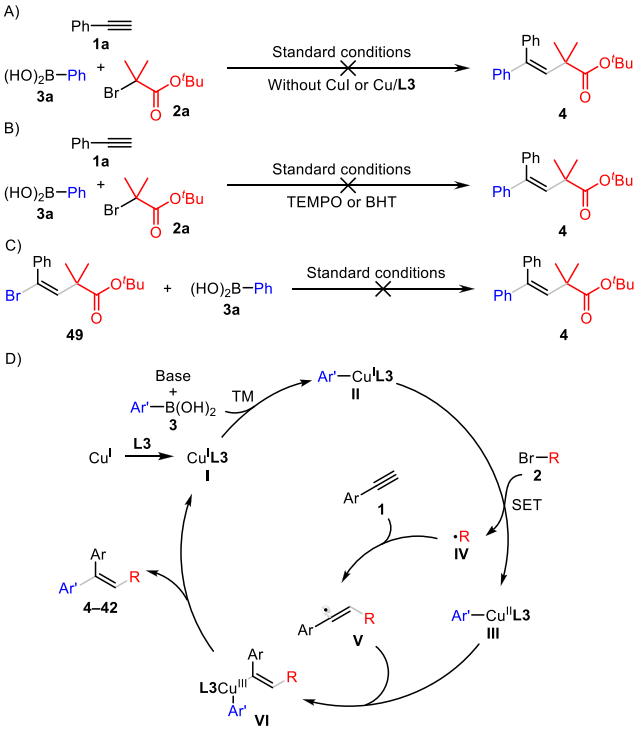


[a]KOH (10 equiv), EtOH, 100 °C, 24 h. [b]$LiAlH_4$ (3.0 equiv), Et_2O, 0 °C, 4 h. [c]$Pd(PPh_3)_2Cl_2$ (5.0 mol %), CuI (10 mol %), $^iPr_2NH$, 100 °C, 24 h; then K_2CO_3 (2.0 equiv), MeOH, rt, 2 h. [d]$Pd(PPh_3)_4$ (10 mol %), K_2CO_3 (6.0 equiv), THF/H_2O (3/1), 80 °C, 24 h.

demonstrate the synthetic utility, we readily hydrolyzed the ester group in **4** to free carboxylic acid (**43**) and chemoselectively reduced **4** to alcohol **44** (Scheme 2B, top). More importantly, we took advantage of the excellent compatibility of our reaction with aryl bromide by successfully implementing double Sonogashira or Suzuki–Miyaura coupling reactions with **30**, forging the products **45** or **46**–**48**, respectively, in moderate to high overall yields (Scheme 2B, bottom). Taken together, these results highlight the great synthetic potential of our methodology for future applications in related areas.

Control experiments in the absence of CuI or CuI/**L3** did not provide the product **4** (Scheme 3A), confirming the indispensable role of copper catalysis. Further radical

Scheme 3. Control Experiments and Proposed Reaction Mechanism



inhibition experiments with TEMPO (2,2,6,6-tetramethylpiperidinyloxy) or BHT (butylated hydroxytoluene) revealed complete reaction inhibition (Scheme 3B), likely suggesting the involvement of radical species in the reaction. An additional control experiment with alkenyl bromide **49** failed to produce any product **4** under the otherwise standard conditions (Scheme 3C). Accordingly, a tandem atom-transfer radical addition/cross-coupling reaction pathway[15] is unlikely. Based on these results as well as previous reports,[14] we proposed a plausible reaction mechanism, as shown in Scheme 3D. Copper(I) salt first coordinates with **L3** to form the catalytically active species **I** (Cu^I**L3**), entering the catalytic cycle. Next it undergoes transmetalation (TM) with boronic acid **3** to produce the Ar′–Cu^I**L3** intermediate **II**,[16] which subsequently reduces alkyl bromide **2** via SET (single-electron transfer)[17] to concomitantly deliver the Ar′–Cu^{II}**L3** complex **III** and alkyl radical **IV**. The following intermolecular addition of **IV** to the triple bond of alkyne **1** affords the vinyl radical **V**, which would probably combine with **III** to provide the Cu^{III} complex **VI**. Finally, the reductive elimination of **VI** leads to the trisubstituted alkenes **4**–**42** and regenerates the Cu^I**L3** complex **I** for the next catalytic cycle. The high *anti*-stereoselectivity of the reaction is likely depending on the relative stability of the intermediate **VI**, where the sterically demanding alkyl group is *anti* to the large Ar′Cu^{III}**L3** group.[18]

In summary, we have developed a convenient Cu-catalyzed three-component reaction of terminal alkynes with boronic acids and alkyl bromides. This method features inexpensive copper catalyst, high *anti*-stereoselectivity, and a broad substrate scope as well as excellent functional group tolerance. In addition, the reaction can be readily scaled up and the obtained products are readily transformable. Preliminary experimental results support a tandem radical addition to the alkyne/C–C bond formation reaction mechanism. All these

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characteristics make this methodology an outstanding complementary approach toward other known strategies that will ultimately benefit research based on trisubstituted alkene molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00692.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2142776−2142777 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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