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Original article

Copper-catalyzed decarboxylative hydroboration of phenylpropiolic acids under ligand-free or both ligand- and base-free conditions

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ABSTRACT

An efficient copper-catalyzed decarboxylative hydroboration of phenylpropiolic acids with bis(pinacolato)diboron was developed, affording β-vinylboronates as the only products in high yields. Extra hydrogen sources such as methanol are not needed in this catalytic system. This reaction could be performed successfully under ligand- and base-free conditions. It demonstrated that phenylpropiolic acids can be employed as alkyne synthons in the hydroboration reaction and exhibited good reactivity and higher selectivity than terminal alkynes.

1. Introduction

Alkenylboron compounds are especially versatile building blocks that are widely employed as vinyl anionic or cationic synthons in a myriad of coupling reactions [1], as well as they can be readily transformed into various vinylic derivatives [2]. Over the past years, the transition-metal-catalyzed addition of boron to carbon–carbon triple bonds presents a convenient and important strategy for alkenylboron synthesis [3]. Among them, copper-catalyzed hydroboration of alkynes has attracted much attention due to the readily availability, low cost, and low toxicity of copper salts. Great progress has been made by Miyaura [4], Yun [5], Li [6], Haveyda [7], and others [8]. However, some limitations still exist, such as the requirement of ligand, base, and special hydrogen source, thus the development of more efficient method with much wide applicability to prepare vinylboronates via copper-catalyzed regioselective hydroboration of aryl alkynes is still a challenge for synthetic organic chemistry. On the other hand, alkynyl carboxylic acids are regarded as ideal substitutions for terminal alkynes and have been widely applied in the transition-metal-catalyzed construction of C–C and C-heteroatoms bonds via decarboxylation [9]. In particular, alkynyl carboxylic acids exhibit superiority to terminal alkynes in the reactions: they are often more reactive, and they can efficiently suppress the Glaser coupling reaction that frequently occurs in the Sonogashira reactions. As part of our ongoing research into the development of highly efficient and versatile copper-catalyzed decarboxylative reactions [10], and in conjunction with our work on oxidative decarboxylative coupling of arylpropiolic acids with dialkyl H-phosphonates [11], we decided to expand this strategy in the copper-catalyzed hydroborations. Recently, we have achieved the synthesis of bis-deuterated β-borylated α,β-styrene derivatives from the reaction of alkynyl acids with bis(pinacolato)diboron under base-free conditions [12]. Herein, we report our results on the general hydroboration using alkynyl acids as the substrates under ligand-free or both ligand- and base-free conditions.

2. Experimental

All experiments were conducted with a Schlenk tube. Flash column chromatography was performed over silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a Bruker AVIII-400M or AVIII-500M spectrometers. Chemical shifts (in ppm) were referenced to $CDCl_3$ (δ 7.26) as an internal standard. ^{13}C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ (δ 77.0). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Anhydrous dioxane was obtained by refluxing for at least 12 h over sodium and freshly distilled prior to use.

General procedure for the synthesis of (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (**3a**): A Schlenk tube with a magnetic stirring bar was charged with 3-phenylpropiolic acid (**1a**, 68 mg,

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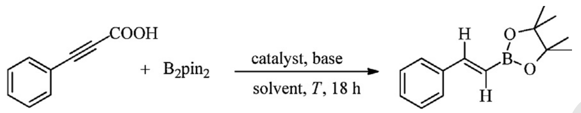
0.5 mmol), bis(pinacolato)diboron (**2a**, 152 mg, 0.6 mmol), $Cu(TFA)_2$ (29 mg, 10 mol%), Na_2CO_3 (127 mg, 1.2 mmol), and 1,4-dioxane (2 mL) under N_2. The reaction mixture was stirred at 80 °C for 18 h (monitored by TLC and GC). Upon completion of the reaction, the reaction mixture was then cooled to ambient temperature, diluted with ethyl acetate (20 mL), filtered through a plug of silica gel, and washed with ethyl acetate (20 mL). The organic layer was washed with saturated brine (20 mL × 2) and dried over anhydrous Na_2SO_4. The solvents were removed via rotary evaporator and the residue was purified by flash chromatography (silica gel, ethyl acetate: petroleum ether = 1:30) to give 89.7 mg of desired product **3a** in 78% yield as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.50 (*m*, 2H), 7.41 (*d*, 1H, *J* = 18.5 Hz), 7.29–7.32 (*m*, 3H), 6.18 (*d*, 1H, *J* = 18.4 Hz), 1.32 (*s*, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 136.4, 127.9, 127.5, 126.0, 82.3, 23.8.

3. Results and discussion

We chose 3-phenylpropiolic acid (**1a**) and bis(pinacolato)diboron (**2a**) as the model substrates. Initially, the reaction was conducted in the presence of 10 mol% of $Cu(OTf)_2$ and 1.2 equiv. of Na_2CO_3 in benzene at 80 °C under N_2 atmosphere and no extra ligand and hydrogen source were used. To our delight, β-borylated α,β-styrene with *E*-configuration (**3aa**) was formed in 55% yield as the single product (Table 1, entry 1). When the reaction temperature was raised to 90 °C, a slight decrease on the product yield was observed and no reaction occurred at room temperature (Table 1, entries 2 and 3). Further screening of the solvents showed that acetonitrile and 1,4-dioxane are good choice for this reaction (Table 1, entries 5–9). We also employed other copper catalysts and copper trifluoroacetate ($Cu(TFA)_2$) exhibited the best activity (Table 1, entry 12). The yield of **3aa** could be further enhanced to 83% when 2.2 equiv. of Na_2CO_3 was employed. To our surprise, in the absence of the base Na_2CO_3, also 37% yield could be obtained (Table 1, entry 14). Then we screened the copper catalyst again under base-free condition and found out that Cu_2O could lead to satisfied result, probably because of its potential basicity (Table 1, entry 18). Considering that actually a double amount of [Cu] was involved for Cu_2O, a loading of 5 mol% was used and a little lower yield was obtained (Table 1, entry 20). Further increasing the reaction temperature to 100 °C made the product being formed nearly quantitatively (Table 1, entry 21). Finally, this reaction performed smoothly at room temperature if a phosphorous ligand was added (Table 1, entry 22). It is noteworthy that the solvents we used were actually wet. When the reaction under the conditions as in entry 19 was performed in anhydrous dioxane, only 7% of **3aa** was obtained. If extra 0.25 mmol of water (0.5 equiv.) was added to anhydrous dioxane, the yield was 31%. Only when more than 1 equiv. of water was used, acceptable around 60% yield could be achieved, indicating that water content in the wet dioxane we used was higher than 0.4%.

After establishing the optimized reaction conditions of the different catalytic systems, a variety of alkynyl carboxylic acids and diboron reagents were subjected (Table 1, entries 13 and 21) to evaluate the scope of the copper-catalyzed decarboxylative regioselective hydroboration reaction. As shown in Scheme 1, phenylpropiolic acids with both electron-rich and electron-deficient substituents on the aromatic ring could be smoothly converted into the desired products. The position of the substitutes on the aromatic rings had some influence on yields (**3b-3c**, **3d-3e**, **3m-3o**, **3p-3q**), with *ortho*-substitutions usually giving lower

Table 1
Optimization of the reaction conditions.[a]



1a **2a** **3aa**

Entry	Cu catalyst	Base	Solvent	T (°C)	Yield (%)[b]
1	$Cu(OTf)_2$	Na_2CO_3	Benzene	80	55
2	$Cu(OTf)_2$	Na_2CO_3	Benzene	90	46
3	$Cu(OTf)_2$	Na_2CO_3	Benzene	R.T.	0
4	$Cu(OTf)_2$	Na_2CO_3	Benzene	50	Trace
5	$Cu(OTf)_2$	Na_2CO_3	DMSO	80	26
6	$Cu(OTf)_2$	Na_2CO_3	DMF	80	0
7	$Cu(OTf)_2$	Na_2CO_3	CH_3CN	80	63
8	$Cu(OTf)_2$	Na_2CO_3	DMA	80	8
9	$Cu(OTf)_2$	Na_2CO_3	1,4-dioxane	80	65
10	$Cu(OAc)_2$	Na_2CO_3	benzene	80	45
11	$Cu(TFA)_2$	Na_2CO_3	Benzene	80	73
12	$Cu(TFA)_2$	Na_2CO_3	1,4-dioxane	80	75
13	$Cu(TFA)_2$	Na_2CO_3[c]	1,4-dioxane	80	83
14	$Cu(TFA)_2$	–	1,4-dioxane	80	37
15	$Cu(OAc)_2$	–	1,4-dioxane	80	42
16	$Cu(OTf)_2$	–	1,4-dioxane	80	Trace
17	$CuSO_4$	–	1,4-dioxane	80	19
18	CuO	–	1,4-dioxane	80	61
19	Cu_2O	–	1,4-dioxane	80	76
20[d]	Cu_2O	–	1,4-dioxane	80	58
21	Cu_2O	–	1,4-dioxane	100	96
22[e]	Cu_2O	–	1,4-dioxane	R.T.	77

[a] Reaction conditions: (**1**) (0.5 mmol), (**2**) (1.2 equiv., 0.6 mmol), copper catalyst (0.05 mmol), base (0.6 mmol), solvent (2 mL), under N_2 atmosphere.
[b] Yields are based on GC analysis with *n*-dodecane as the internal standard.
[c] 1.1 mmol (2.2 equiv.) of Na_2CO_3 was used.
[d] 0.025 mmol of Cu_2O was used.
[e] 0.05 mmol of Xantphos was added.

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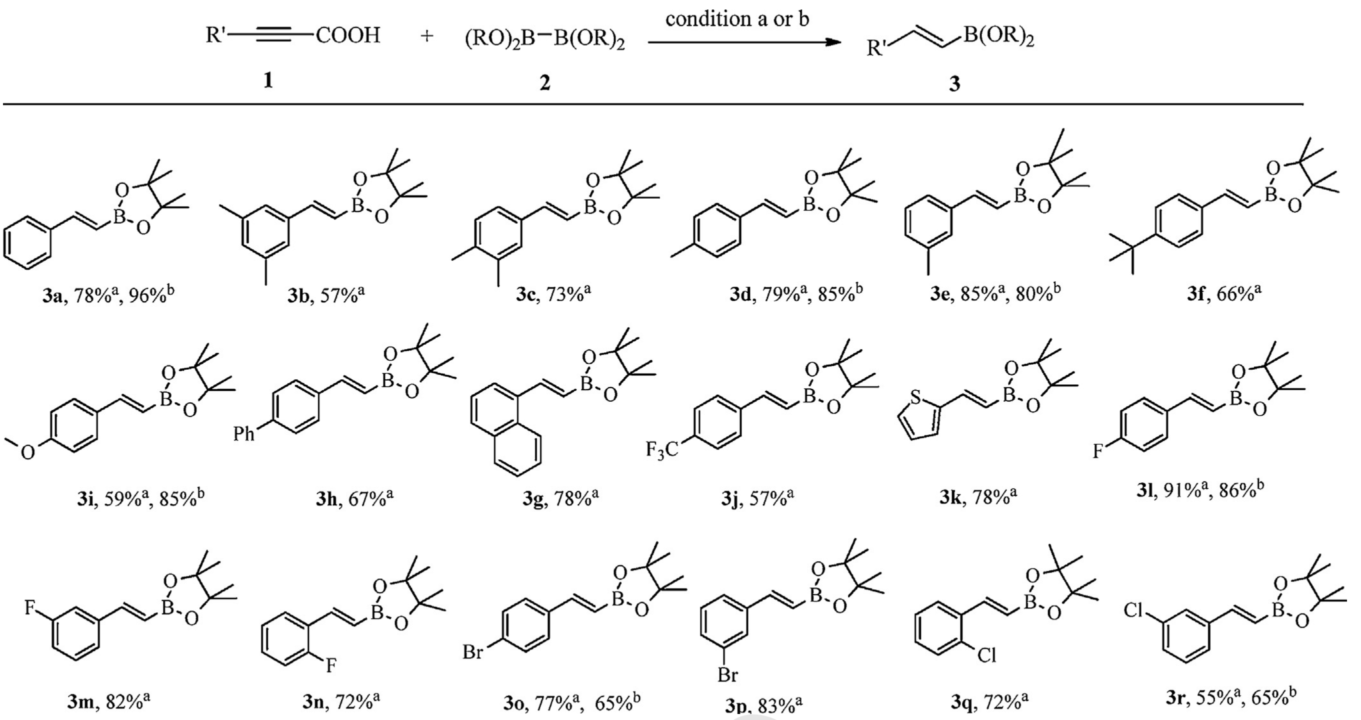
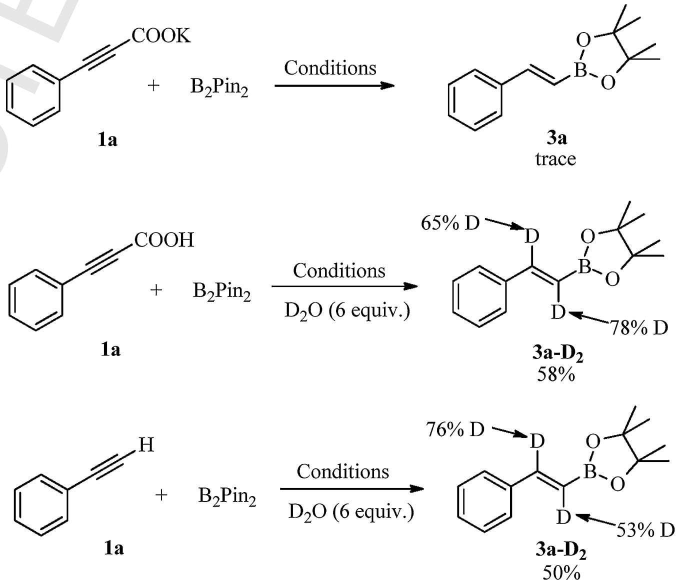


Scheme 1. Substrate scope. Reaction conditions: (a) 1 (0.5 mmol), 2 (1.2 equiv., 0.6 mmol), Cu(TFA)$_2$ (10 mol%), Na_2CO_3 (2.2 equiv., 1.1 mmol), 1,4-dioxane (2 mL) under N_2, 80 °C, 18 h, isolated yield; (b) 1 (0.5 mmol), 2 (1.2 equiv., 0.6 mmol), Cu_2O (10 mol%), 1,4-dioxane (2 mL) under N_2, 100 °C, 18 h, isolated yield.

yields of β-borylated α,β-styrene when compared to *meta*- and *para*-substitutions, probably because of steric hindrance. It is noteworthy that most halo-substituted aryl groups survived well, leading to halo-substituted aromatic β-borylated α,β-styrene in good yields which could be used for further transformations (**3m**-**3r**). In addition, 4-phenyl, 1-naphthyl, 4-trifluoromethyl, 4-cyano substituted 3-phenylpropiolic acid and 3-(thiophen-2-yl)propiolic acid were transformed into corresponding β-borylated α,β-styrenes smoothly as well (**3h**-**3l**).

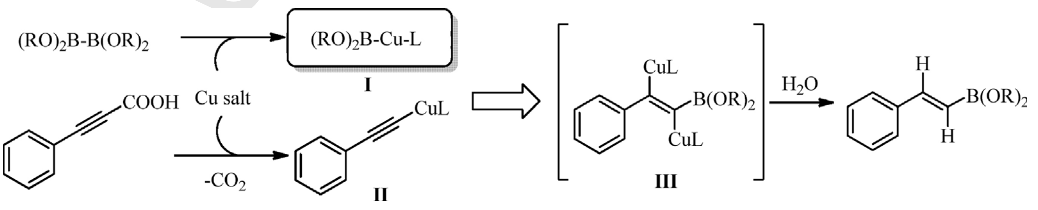
In order to understand the reaction mechanism, some control experiments were performed. When potassium 3-phenylpropiolate was performed as starting material in anhydrous solvent (Scheme 2, eq. 1), only trace of hydroboration product was formed. This result indicates that the hydrogen of alkynyl carboxylic acids and water in the solvent under “standard condition” offers the protons as the electrophilic source. When D_2O was added to the standard reaction system, high deuterium incorporation for both olefinic protons in **3a-D$_2$** was obtained (Scheme 2, eq. 2). Utilizing phenylacetylene instead of 3-phenylpropiolic acid as the substrate to perform the reactions with D_2O under the standard conditions resulted in a slight lower reactivity and poorer deuterium incorporation than alkynyl carboxylic acids (Scheme 2, eq. 3) Q2 (Scheme 3).

Based on previous copper-catalyzed hydroboration reactions and our own work, we suggested that the reaction may be



*Reaction conditions are that shown in entry 20, Table 1

Scheme 2. Control experiments.



Scheme 3. Proposed mechanism.

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performed through the addition of copper-boron species (**I**) to the C–C triple bond of (phenylethynyl) copper intermediate (**II**) which is generated via decarboxylation of phenylpropiolic acid under base-free condition, followed by the formation of (*E*)-alkenyl-bis-copper reactive intermediate (**III**) which has two reactive positions with two copper atoms on. Finally, it can be trapped by protons to afford the (*E*)-β-borylated α,β-styrene.

4. Conclusion

In conclusion, we have developed efficient catalytic systems to synthesize alkenylboronates via copper-catalyzed decarboxylative regioselective hydroboration of alkynyl carboxylic acids under ligand-free or both ligand and base-free conditions. The application of alkynyl carboxylic acids instead of terminal alkynes can lead to a highly active and selective hydroboration reaction. Mechanic investigations supported the formation of an alkenyl-bis-copper reactive intermediate. This novel strategy has great potential in the development of bis-functionalization of carbon–carbon triple bond. Further studies on exploration of the reaction scope, mechanistic elucidation, and synthetic application of this protocol are ongoing in our laboratory.

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