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Copper-catalyzed 1,4-protosilylation and 1,4-protoborylation of enynic orthoesters for synthesis of functionalized 2,3-allenoates

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ABSTRACT

Herein, copper-catalyzed 1,4-protosilylation and 1,4-protoborylation of enynic orthoesters have been developed. The enynic orthoesters as precursors of unstable enynic esters were applied to produce the functionalized 2,3-allenoate products. Meanwhile, the asymmetric 1,4-protosilylation of enynic orthoesters with $PhMe_2Si$-Bpin was also studied. The chiral monopyridine imidazoline ligand was efficient to provide the asymmetric 1,4-protosilylation products with high enantioselectivity.

Allenyl fragments are often observed in natural products and medically active compounds, which are increasingly used as building blocks for construction of complex organic molecules [1–6]. Therefore, the synthesis of allenes has attracted continuous attention [7–12]. Among the available methods, the catalytic 1,4-addition of nucleophiles to the electron-deficient conjugated enynes has been recognized as an ideal pathway to access the allenes due to their high reactivity [13,14]. However, the precise control of regioselective 1,4-addition [15–17,20–28] to avoid the competitive 1,2-addition [15–19] and produce the valuable allene products is usually challenging (Scheme 1A). So far, the electron-biased 1,3-enynes including enynic ketones, 2-trifluoromethyl-1,3-enynes, enynic amides, enynic esters, *etc.*, have been applied to synthesize the corresponding functionalized allene derivatives *via* nucleophilic 1,4-additions (Scheme 1A) [15–17,20–28]. Despite the distinguished advances have been made in this area, the limited substrate scopes of conjugated enynes and nucleophiles in reactions still remain a large space to be expanded for synthesis of multi-functionalized compounds.

It is worth noting that the 2,3-allenoates as building blocks have been widely applied in a broad array of organic reactions including Morita-Baylis-Hillman reactions [29–31], nucleophilic addition reactions [32–34], rearrangements [35], electrophilic addition reactions [3,36] and cycloadditions [37–39]. Therefore, so far, some efficient catalytic methodologies have been reported to prepare this kind of compounds [40–45]. Among them, regioselective 1,4-addition to enynic esters is undoubtedly the most direct way for synthesis of allenoates. Notably, in 2008, a base-catalyzed racemic preparation of allenoates from enynic esters was reported by Zhang, but the asymmetric catalytic version has not been explored [20]. Subsequently, in 2013, Sun and Zhang *et al.* developed an elegant work on cinchona based thiourea-catalyzed asymmetric nitroethylation of enynic esters. There only three aryl-substituted enynic esters were investigated due to their poor stability [23]. The relatively limited substrate scopes and poor stability of enynic esters motivated us to develop a new protocol to address these issues. It is well known that orthoester group can act as a good ester group precursor because it is easily hydrolyzed under acidic conditions. Combined our previous studies [46], we envisioned that protosilylation-hydrolyzation reaction of enynic orthoesters in one-pot would tackle this problem efficiently. Herein, we described the results of copper-catalyzed 1,4-protosilylation-hydrolyzation [47–50] and 1,4-protoborylation-hydrolyzation [51–54] of enynic orthoesters in one-pot to synthesize the ester-substituted homoallenylsilane and homoallenylboronate derivatives. Besides, the optically pure ester-substituted homoallenylsilanes were obtained in high yields with good enantioselectivity by using newly designed chiral monopyridine imidazoline ligand.

Initially, the 1,4-protosilylation reaction was tested with using enynic orthoester **1a** and $PhMe_2Si$-Bpin **2a** as model substrates (Table 1). The choice of base had a significant impact on yield. The organic base such as Et_3N or DMAP, only afforded trace amount of product **3a** with using 5 mol% CuBr as catalyst (entries 1 and 2). It is worth noting that the yield of **3a** could be enhanced to 40%

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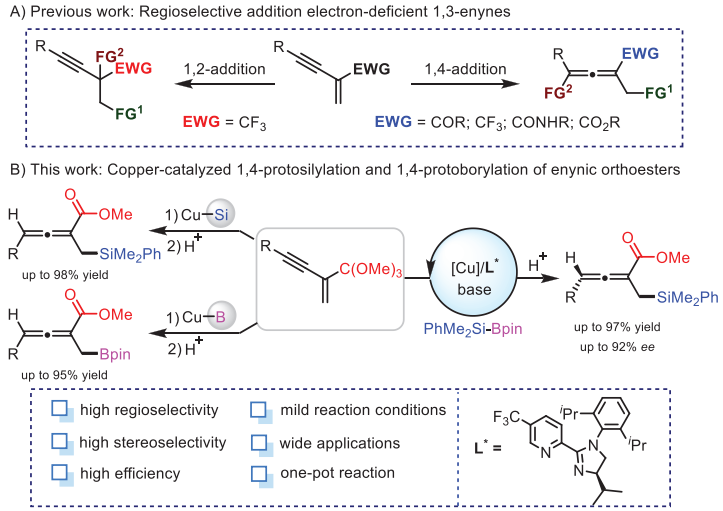
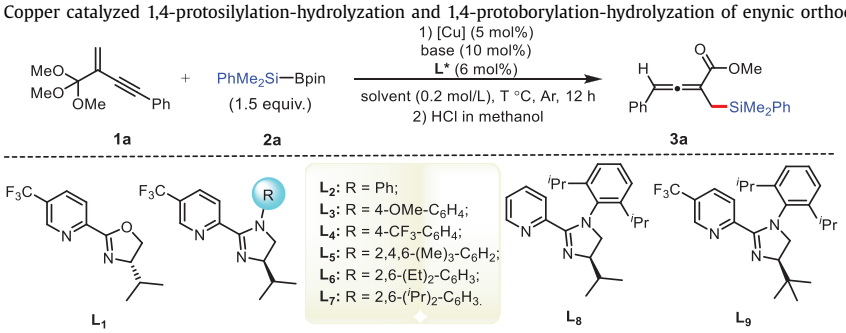


Scheme 1. Regioselective addition of electron-deficient 1,3-enynes.

Table 1
Copper catalyzed 1,4-protosilylation-hydrolyzation and 1,4-protoborylation-hydrolyzation of enynic orthoesters.[a]



Entry	[Cu]	Base	L*	Solvent	T (°C)	Yield (%)[b]	*ee* (%)[c]
1	CuBr	Et_3N	/	MeOH	25	trace	/
2	CuBr	DMAP	/	MeOH	25	10	/
3	CuBr	Cs_2CO_3	/	MeOH	25	40	/
4	CuI	Cs_2CO_3	/	MeOH	25	63	/
5	CuCN	Cs_2CO_3	/	MeOH	25	98/97[d]	/
6[e]	CuCN	Cs_2CO_3	/	MeOH	25	92/95[d]	/
7	CuI	Cs_2CO_3	**L_1**	MeOH	25	98	55
8	CuI	Cs_2CO_3	**L_2**	MeOH	25	98	66
9	CuI	Cs_2CO_3	**L_3**	MeOH	25	93	66
10	CuI	Cs_2CO_3	**L_4**	MeOH	25	91	60
11	CuI	Cs_2CO_3	**L_5**	MeOH	25	93	74
12	CuI	Cs_2CO_3	**L_6**	MeOH	25	94	74
13	CuI	Cs_2CO_3	**L_7**	MeOH	25	98	81
14	CuI	Cs_2CO_3	**L_8**	MeOH	25	79	74
15	CuI	Cs_2CO_3	**L_9**	MeOH	25	39	53
16	CuI	Cs_2CO_3	**L_7**	MeOH	−10	98	84
17	CuI	Et_3N	**L_7**	MeOH	−10	76	83
18	CuI	MeOK	**L_7**	MeOH	−10	83	85
19	CuI	Na_2CO_3	**L_7**	MeOH	−10	99	86
20	CuBr	Na_2CO_3	**L_7**	MeOH	−10	99	85
21	Cu_2O	Na_2CO_3	**L_7**	MeOH	−10	99	87
22[f]	Cu_2O	Na_2CO_3	**L_7**	CH_3CN/MeOH (9:1)	−10	99	89
23[f]	Cu_2O	Na_2CO_3	**L_7**	CH_3CN/MeOH (9:1)	−15	98/95[d]	90
24[f]	Cu_2O	Na_2CO_3	**L_7**	CH_3CN/MeOH (9:1)	−20	98	89
25[f]	Cu_2O	Na_2CO_3	**L_7**	CH_3CN/MeOH (9:1)	−30	92	85

[a] Unless otherwise noted, the reaction was run under the following conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Cu] (5 mol%), base (10 mol%), ligand (6 mol%) in 1.0 mL anhydrous solvent were stirred for 12 h at indicated temperature under argon atmosphere.
[b] Yield was determined by ^1H NMR.
[c] The *ee* was determined by HPLC.
[d] Isolated yield.
[e] **2b** (0.22 mmol).
[f] 25 mg 4 Å molecular sieves was added to the reaction.

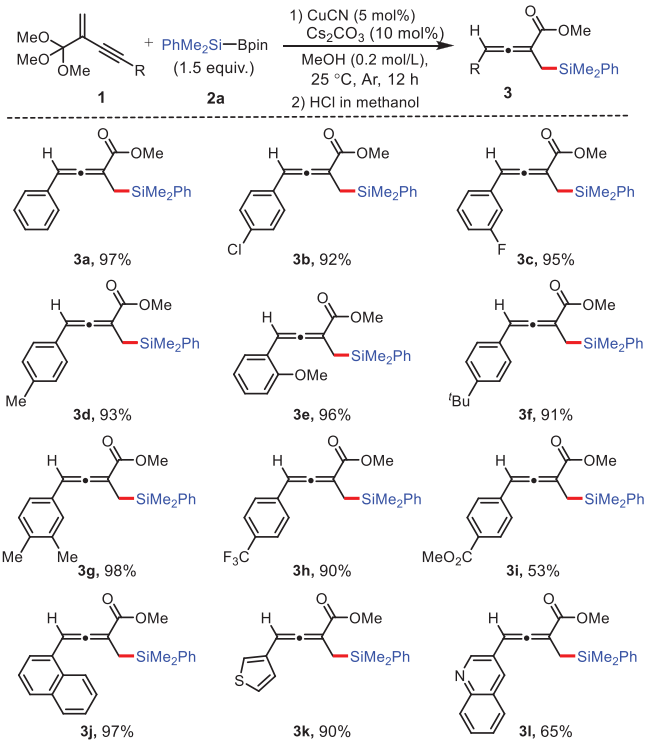
when the reaction was performed in the presence of Cs_2CO_3 (entry 3). After screening different copper catalysts, it was found that the yield of **3a** could be increased to 97% when the 1,4-protosilylation reaction was catalyzed by CuCN (entries 3–5). These results indicates that good acid-base ion pair matching of CuCN may be the reason for its high catalytic activity in this reaction [55]. To our delight, under above-mentioned optimal conditions (entry 5), the corresponding homoallenylboronate **4a** was obtained in 95% isolated yield (entry 6).

Subsequently, we investigated the synthesis of chiral ester-substituted homoallenylsilanes. Inspired by our previous studies on asymmetric protosilylation reaction [56,57], we embarked on screening different chiral oxazoline ligands such as Box ligands, Py-box ligands, *etc.* Fortunately, when $\mathbf{L_1}$ was used, the desired product **5a** was obtained in 98% yield with 55% *ee* value (entry 7). To avoid the strong background reaction, we attempted to improve the coordination capacity of the ligand. Because the nitrogen atom is a better π electron donor than oxygen atom, we replaced the oxazoline moiety with imidazole fragment [58–59]. As expected, when $\mathbf{L_2}$ was applied as ligand, the *ee* value of **5a** was enhanced to 66% (entry 8). Next, we adjusted the electronic and steric effect by modifying the substituent (R) on the nitrogen atom of imidazole fragment. It was found that $\mathbf{L_3}$ with an electron-donating group (4-OMe) on the phenyl ring had little effect on the reaction (entry 9), but the introduction of -CF_3 group on the phenyl ring lowered the *ee* value to 60% (entry 10). We also found that increasing the steric hindrance of R group could improve the product's enantioselectivity significantly (entries 11–13). The ligand $\mathbf{L_7}$ with larger steric hindrance could increase the *ee* value of product to 81%. However, removing the trifluoromethyl group from the pyridine ring resulted in decreased yield and enantioselectivity (entry 14). More bulky *tert*–butyl substituted monopyridine imidazoline ligand ($\mathbf{L_9}$) also afforded lower enantioselectivity possibly due to its inhibition for the coordination between ligand and copper atom (entry 15).

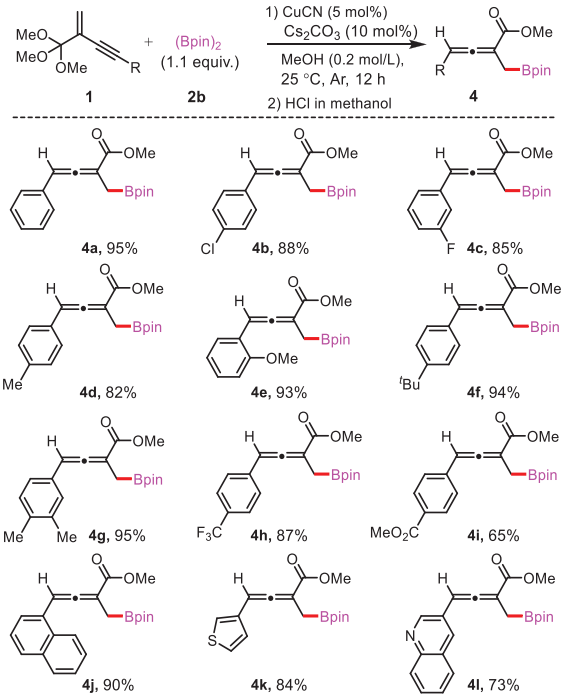
After screening different bases and copper catalysts, the results showed that Na_2CO_3 and Cu_2O were the optimal choice for this reaction (entries 16–21). Gratifyingly, the desired chiral allene compound **5a** was obtained in 95% yield with 90% *ee* when the reaction was performed in CH_3CN/MeOH (9:1) at −15 °C (entry 23). Further elevating or lowering the reaction temperature resulted in a lower *ee* value (entries 22–25). Unfortunately, when the reaction was performed with bis(pinacolato)diboron **2b** under the optimal conditions, the corresponding chiral product was obtained only in 49% yield and with poor enantioselectivity (26% *ee*).

Having established the conditions for the racemic 1,4-protosilylation of enynic orthoesters, the substrate scope of enynic orthoesters was investigated (Scheme 2). Generally, different aryl-substituted substrates were compatible in this reaction. The results indicated that the substrates with electron-donating or electron-withdrawing group on phenyl ring all could provide the desired products in good yields. Additionally, other enynic orthoesters bearing naphthyl (**1j**), thienyl (**1k**) or halogen-substituted phenyl ring (**1b**, **1c**) also could be well tolerated in this reaction. When the quinolone-substituted substrate **1l** was applied to the reaction, the product **3l** was formed only in moderate yield. Furthermore, we tried the racemic 1,4-protoborylation and hydrolyzation of different enynic orthoesters with bis(pinacolato)diboron **2b** (Scheme 3). Similarly, the enynic orthoesters above could afford the corresponding 1,4-protoborylation products in moderate to high yields under the optimized reaction conditions.

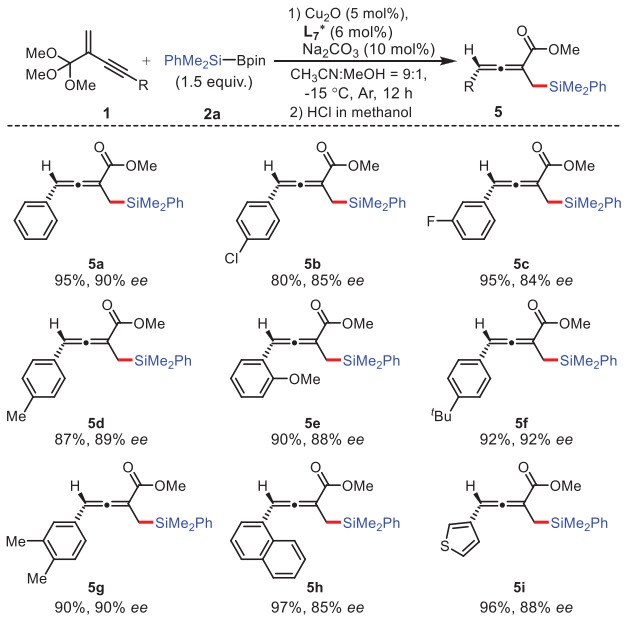
Subsequently, we examined the substrate compatibility of the asymmetric 1,4-protosilylation-hydrolyzation of enynic orthoesters (Scheme 4). In general, the enynic orthoesters with electron-donating goups (Me, OMe, ^{t}Bu, 3,4–Me_2) on the phenyl ring were suitable substrates and gave the corresponding products in high



Scheme 2. Substrate scope of 1,4-protosilylation-hydrolyzation of enynic orthoesters. Unless otherwise noted, reaction was run under the following reaction condition: **1a** (0.2 mmol), **2a** (0.3 mmol), CuCN (5 mol%), Cs_2CO_3 (10 mol%) in 1.0 mL anhydrous MeOH at 25 °C for 12 h under argon atmosphere, isolated yield.



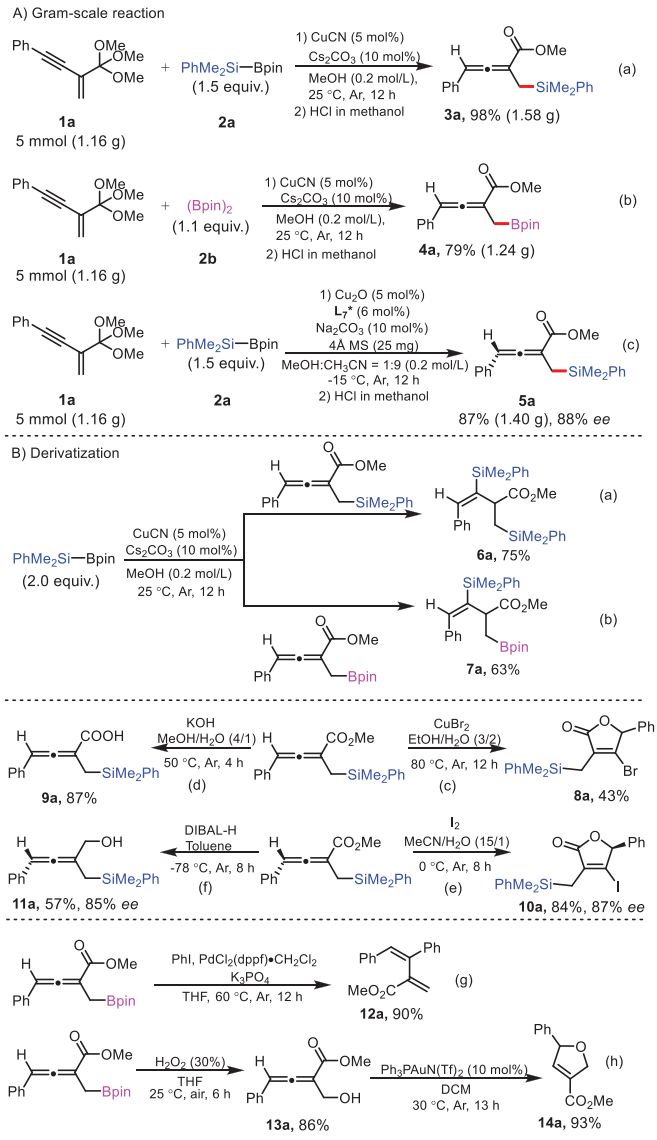
Scheme 3. Substrate scope of 1,4-protoborylation-hydrolyzation of enynic orthoesters. Unless otherwise noted, reaction was run under the following reaction condition: **1a** (0.2 mmol), **2b** (0.22 mmol), CuCN (5 mol%), Cs_2CO_3 (10 mol%) in 1.0 mL anhydrous MeOH at 25 °C for 12 h under argon atmosphere. Isolated yield.



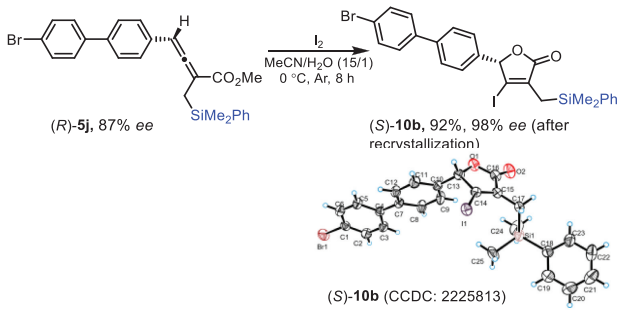
Scheme 4. Substrate scope of asymmetric 1,4-protosilylation-hydrolyzation of enynic orthoesters. Unless otherwise noted, the reaction was run under the following condition: **1a** (0.2 mmol), **2a** (0.3 mmol), Cu_2O (5 mol%), Na_2CO_3 (10 mol%), $\mathbf{L_7}$ (6 mol%) and 4 Å molecular sieves (0.0250 g) were stirred in 1.0 mL anhydrous CH_3CN/MeOH (9:1) at −15 °C for 12 h under argon atmosphere. Isolated yield and the *ee* was determined by HPLC.

yields and with good enantioselectivities. Similarly, the products containing halogen atoms on the phenyl ring were also obtained in good yields and with slightly lower ee values (**5b**, **5c**). Moreover, 1-naphthyl and 3-thienyl substituted enynic orthoester substrates could react smoothly under the optimal conditions and furnished the corresponding chiral homoallenylsilanes in high yields and with good *ee* values (**5h**, **5i**).

The gram-scaled synthesis of the racemic homoallenylsilane **3a**, homoallenylboronate **4a** and enantioenriched homoallenylsilane **5a** were carried out smoothly without diminishing efficiency (Scheme 5A). To show the synthetic utility of this method, diverse transformations of the products were tested (Scheme 5B). Interestingly, the allenyl fragments of products **3a** and **4a** could further react with $PhMe_2Si$-Bpin under the above-established optimized reaction conditions to produce the corresponding products **6a** and **7a** in high yields. Remarkably, as a kind of useful intermediates in organic synthesis, the 2,3-allenoates can proceed a variety of transformations. For example, in the presence of $CuBr_2$, the allenoate **3a** underwent a five-membered cyclization reaction to afford the multi-substituted lactone **8a**. Treatment of product **3a** with sodium hydroxide could generate the trisubstituted allenyl acid **9a** in a high yield. Furthermore, the transformation of axial chiral **5a** to central chiral product **10a** was achieved without erosion of the enantioselectivity. The reduction of **5a** with DIBAL-H could also provide the enantioenriched allenol **11a** with retention of the enantioselectivity. Additionally, a Pd-catalyzed coupling reaction of homoallenylboronate **4a** with iodobenzene was performed. The corresponding coupling product **12a** was obtained in a high yield with excellent stereoselectivity. The homoallenyl alcohol **13a** was formed in good yield *via* an oxidation of **4a** with using H_2O_2. Subsequently, **13a** was converted to the cyclic product 2,5-dihydrofuran **14a** in 93% yield catalyzed by $Ph_3PAuN(Tf)_2$. Finally, the absolute configuration of the 2,3-allenoate **5j** was assigned as *R* [60], on the basis of the absolute configuration of (*S*)−**10b** determined by an X-ray diffraction analysis (CCDC: 2225813) (Scheme 6).



Scheme 5. Gram-scaled synthesis of allene compounds and their derivatization.



Scheme 6. Iodolactonization of the 2,3-allenoate (*R*)−**5j**.

In conclusion, we have developed a practical strategy for the preparation of allenoate derivatives *via* copper-catalyzed 1,4-protosilylaiton-hydrolyzation and 1,4-protoborylation-hydrolyzation reaction of enynic orthoesters in one-pot. The derivatizations of allenoate products were conducted, which demonstrated their potential utility in organic synthesis. Moreover, this work disclosed an efficient method to produce the functionalized enantioenriched homoallenylsilanes. The monopyridine

imidazoline ligand was suitable for this asymmetric reaction to offer high reactivity and enantioselectivity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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