

Synthesis of Highly Substituted Racemic and Enantioenriched Allenylsilanes via Copper-Catalyzed Hydrosilylation of (Z)-2-Alken-4-ynoates with Silylboronate

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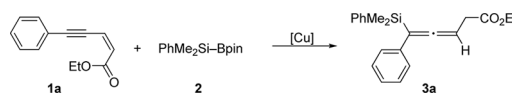
Supporting Information

ABSTRACT: Copper-catalyzed highly efficient hydrosilylation reaction of enynoates was developed. Under simple reaction conditions, various di-, tri-, and tetrasubstituted racemic allene products could be obtained in high yields. The asymmetric 1,6-addition of silyl group to the (Z)-2-alken-4-ynoates could be achieved under mild reaction conditions to afford the silyl-substituted enantioenriched chiral allene products in good yields and with high enantioselectivities.

Chiral allenes are featured in many natural products, drugs, and advanced materials.¹ They can also serve as useful synthetic building blocks in organic synthesis.² Accordingly, we have witnessed an increase in the development of new methods for the synthesis of enantioenriched chiral allenic compounds including the use of transition metals and chiral organocatalysts.³ Inspired by Elsevier's pioneering work on the transition-metal-catalyzed chiral allene synthesis in 1989,⁴ many groups have developed efficient catalytic enantioselective systems. For example, Hayashi,⁵ Ogasawara,⁶ Ma,⁷ and Frantz⁸ groups have elegantly developed an array of palladium- or rhodium-catalyzed enantioselective reactions for the synthesis of axially chiral allenes in moderate to excellent enantioselectivity. However, the research groups of Arai with Shioiri,⁹ Tan,¹⁰ Zhang with Sun,¹¹ Gong,¹² Maruoka,¹³ etc.,^{14–16} have successfully applied chiral organocatalysts in the catalytic synthesis of enantioenriched allenes (Scheme 1, pathway c). Despite all these successes in

catalytic systems, there are still limitations with existing methods such as the need to use expensive metals, limited substrate scopes such as the need to use symmetrical allenes as starting materials, the possible formation of homopropargylic alcohols as byproducts and the moderate selectivities obtained still provide opportunity for the development of more efficient methods (Scheme 1, pathways a and b). Furthermore, enantio- and regioselective synthesis of trisubstituted¹⁷ and tetrasubstituted allenes^{13,18} as well as heteroatom substituted allenes^{5c,d,g,19} are still not well-established. Herein, in connection with our interest in the development of copper-catalyzed hydrosilylation reaction of unsaturated carbon–carbon bonds,²⁰ we report an efficient method to obtain silyllallenes in good yields and with high regio- and enantioselectivity based on the use of cheap copper-catalyst and silylboronate²¹ for the 1,6-silyl addition to enynoates (Scheme 1, pathway d).^{18,22}

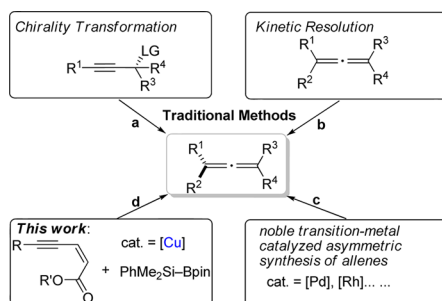
Chart 1. Screening the Optimized Reaction Conditions of Copper-Catalyzed Hydrosilylation of Enynoate 1a with PhMe₂Si-Bpin^a



entry	cat. (mol %)	additive (mol %)	yield (%) ^b
1	CuCl (10)	Et ₃ N (10)	90
2	CuBr (10)	Et ₃ N (10)	92
3	CuI (10)	Et ₃ N (10)	88
4	Cu(OAc) ₂ (10)	Et ₃ N (10)	90
5	CuTc (10)	Et ₃ N (10)	57
6	CuBr (10)	pyridine (10)	78
7	CuBr (10)	DABCO (10)	50
8	CuBr (10)	NaOAc (100)	75
9	CuBr (10)	--	--
10	--	Et ₃ N (10)	--

^aUnless noted otherwise, the reaction was conducted with 1a (0.2 mmol), 2 (0.4 mmol, 2.0 equiv), copper catalyst (0.02 mmol, 10 mol %), and NEt₃ (0.02 mmol, 10 mol %) in anhydrous MeOH (1 mL) for 24 h at 28 °C under argon atmosphere. ^bIsolated yield.

Scheme 1. Methods for Enantioselective Synthesis of Chiral Allenes



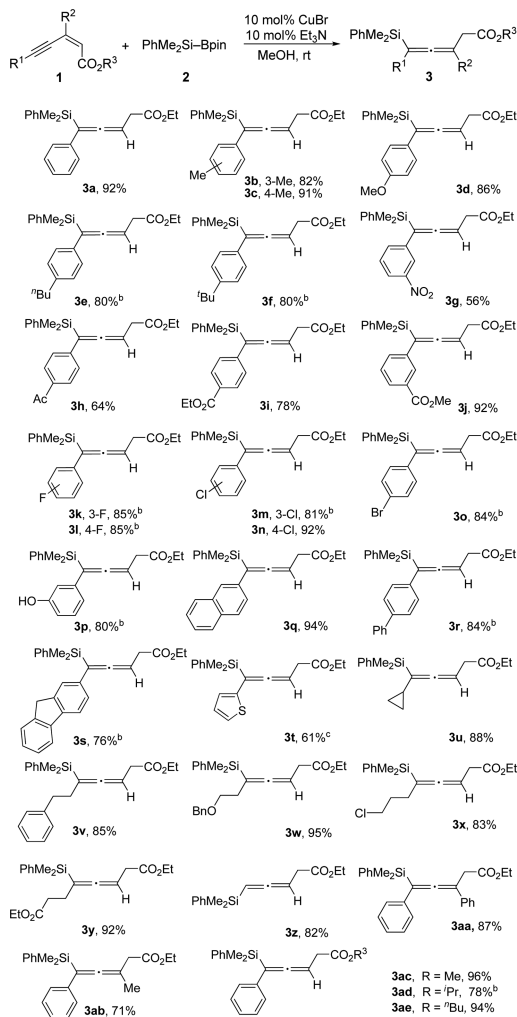
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First, the copper-catalyzed hydrosilylation of enynoates was investigated, and the results are shown as in **Chart 1**. It was found that both Cu(I) and Cu(II) catalysts could afford the desired allenylsilane product **3a** in high yield in the presence of 10 mol % triethylamine as the additive²³ (**Chart 1**, entries 1–5). However, the use of pyridine would slightly lower the product yield to 78% (**Chart 1**, entry 6). The use of DABCO or inorganic base sodium acetate would significantly hinder the product's formation (**Chart 1**, entries 7 and 8 respectively). It was also noted that no desired product could be obtained in the absence of either base as additive or copper salt as catalyst (**Chart 1**, entries 9 and 10, respectively). Therefore, the more air-stable and nonmoisture sensitive CuBr was chosen as the catalyst for this silylation reaction and 10 mol % triethylamine as additive in MeOH solution at room temperature.²⁴

With the optimized reaction conditions in hand, various enynoates as substrates were tested, and the results are summarized in **Chart 2**. First, the electronic and steric effects of different functional groups on the phenyl ring were examined,

Chart 2. Hydrosilylation of Various Enynoates with PhMe₂Si-Bpin^{a,d}

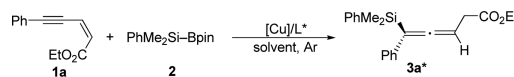


^aUnless noted otherwise, the reaction condition was performed under the following reaction conditions: 0.2 mmol enynoate **1**, 0.4 mmol **2** (2.0 equiv), 10 mol % CuBr, and 10 mol % Et₃N in 1 mL of anhydrous MeOH at 28 °C under argon atmosphere for 24 h. ^bThe reaction time was 48 h. ^cThe reaction time was 72 h. ^dIsolated yield.

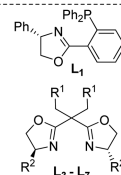
and it was found that regardless of the electron-donating or electron-withdrawing groups installed on the substrates all could afford the desired products in high yields albeit the nitro group leading to a dramatically decreased yield (**3g**). When the thiophene group was used as substituent, only moderate yield of the product could be observed along with the recovering of the unreacted starting material. The lower conversion was probably caused by the strongly coordinating ability of the heteroatom with copper catalyst (**3t**). There was no obvious negative effect on the product's formation when the bulky cyclopropyl moiety was applied as the substituent (**3u**). Other aliphatic substituents with different functionalities could also be tolerated in reaction and afford the corresponding products in excellent yields (**3v–3y**). Furthermore, the formation of di- and tetrasubstituted allenylsilanes was studied, and the products **3z**, **3aa**, and **3ab** could be generated in high yields respectively under the standard reaction conditions. Finally, other esters substituted enynoates were applied to reaction, and high yields of products could be observed (**3ac–3ae**).

As mentioned above, so far the reported species of enantio-enriched allenes especially the heteroatom-substituted examples remain limited. Therefore, we embarked on the development of the synthesis of silyl-substituted allenes (**Chart 3**). After tedious

Chart 3. Optimization of Copper(I)-Catalyzed Asymmetric Hydrosilylation of 1a with PhMe₂Si-Bpin^a



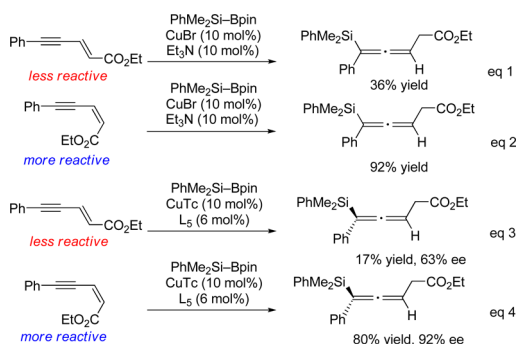
entry	cat. (mol%)	L (mol%)	solvent	T (°C)	t (h)	yield (%)	ee (%) ^c
1	CuBr (10)	L ₁ (12)	MeOH	rt	24	70	0
2	CuBr (10)	L ₂ (12)	MeOH	rt	24	40	25
3	CuBr (10)	L ₃ (12)	MeOH	rt	24	15	13
4	CuBr (10)	L ₄ (12)	MeOH	rt	24	46	55
5	CuBr (10)	L ₅ (12)	MeOH	rt	24	64	57
6	CuBr (10)	L ₅ (12)	^t AmOH	rt	24	47	84
7	CuCN (5)	L ₅ (6)	^t AmOH	rt	24	trace	-
8	Cu(CN) ₄ BF ₄ (5)	L ₅ (6)	^t AmOH	rt	24	74	70
9	CuTC (5)	L ₅ (6)	^t AmOH	rt	24	84	85
10	CuTC (5)	L ₅ (6)	^t AmOH	0	24	80	92
11	CuTC (5)	L ₅ (6)	^t AmOH	0	48	72	91
12	CuTC (5)	L ₇ (6)	^t AmOH	0	48	64	90
13	CuTC (5)	L ₅ (6)	^t AmOH	-10	48	52	93
14 ^b	CuTC (5)	L ₅ (6)	THF	rt	24	0	-
15 ^b	CuTC (5)	L ₅ (6)	DCM	rt	24	0	-



^aReaction was run under the following reaction conditions: 0.2 mmol enynoate **1**, 0.3 mmol **2** (1.5 equiv), 5 mol % CuTC, and 6 mol % L₅ in 1 mL of anhydrous ^tAmOH at 0 °C under argon atmosphere for 48 h. ^bThe reaction time was 72 h. ^cThe values of ee were determined by HPLC.

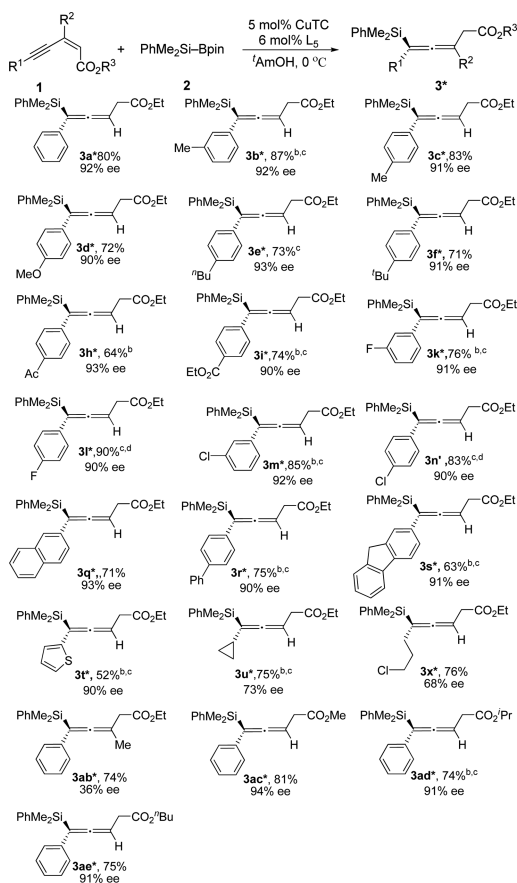
screening of the copper catalysts, solvents, and different chiral ligands, finally it was found that the desired enantioenriched silyl-substituted allene **3a*** could be obtained in 80% yield and with 92% enantiomeric excess in the presence of 5 mol % CuTC (copper(I) thiophene-2-carboxylate) and 6 mol % chiral bisoxazoline ligand L₅ in ^tAmOH (^tAm = *tert*-amyl) solution at 0 °C with stirring for 48 h (**Chart 3**, entry 10).

Subsequently, the enynoates with different functional groups including acetal (**Chart 4**, **3h***) and ester (**Chart 4**, **3i***) groups



on the phenyl ring were examined, and all the products could be obtained in good yields and with high ee values. When the 9*H*-fluoren- and thiophene-substituted enynaoates were examined, good enantioselectivity of the products albeit with slightly lower yields could be observed (Chart 4, 3s* and 3t*).

Chart 4. Copper(I)-Catalyzed Asymmetric Hydrosilylation of Various Enynaoates with PhMe₂Si-Bpin^{a,c}



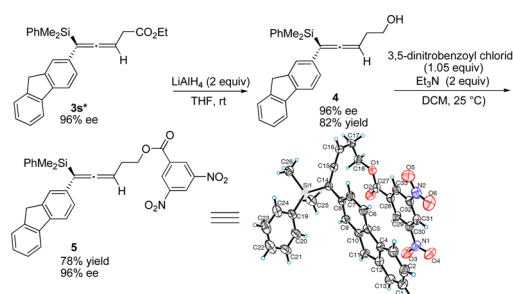
^aReaction was carried out according to the following reaction conditions: 0.2 mmol enynaoate 1, 0.3 mmol 2 (1.5 equiv), 5 mol % CuTC, 6 mol % and L₅ in 1 mL anhydrous ^tAmOH at 0 °C under argon atmosphere for 48 h. ^bThe reaction time was 72 h. ^cThe temperature was -5 °C. ^dThe reaction time was 96 h. ^eThe values of ee were determined by HPLC.

respectively). However, aliphatic substituents were unfavorable for the enantioselective hydrosilylation of enynaoate, the desired products were afforded with moderate enantioselectivity but in good yields (Chart 4, 3u* and 3x*). It is worth noting that an example of chiral *tetra*-substituted allene 3ab* could be

obtained in 74% yield, albeit with only 36% ee. The substituent effect of ester group was further investigated, and the results showed that neither the product's yield nor its enantiopurity could be affected (Chart 4, 3ac*, 3ad*, and 3ae*). Moreover, it was found that the enynaoate with *trans*-configuration was less reactive than the *cis*-one to generate the silyllallene product in low yield and with poor enantioselectivity (eqs 1–4).

The absolute configuration of 3s* was determined to be (*R*)-(+ by single-crystal X-ray diffraction analysis of compound 5, which could be obtained after two-step derivatization (Scheme 2). Thus, reduction of the ester 3s* with LiAlH₄²⁵

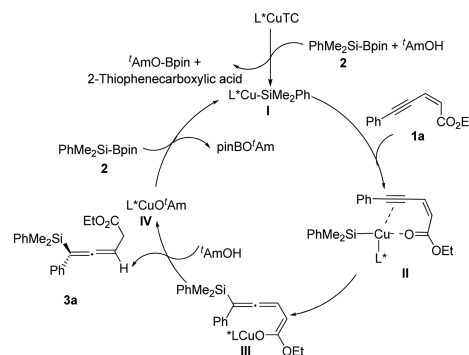
Scheme 2. Determination of the Absolute Configuration of Compound 3s*



afforded alcohol 4, which reacted with 3,5-dinitrobenzoyl chloride²⁶ to give 5 in high yield and with no loss of enantiomeric purity during the two steps.

A plausible mechanistic pathway of CuTC and chiral bisoxazoline ligand system catalyzed asymmetric hydrosilylation reaction of enynaoates was depicted as in Scheme 3. First, a

Scheme 3. Proposed Plausible Mechanism for the Copper-Catalyzed Asymmetric Hydrosilylation of Enynaoate



Cu–Si species I could be generated from silylboronate 2 with the help of CuTC in *tert*-amyl alcohol, followed by coordination with the enynaoate 1a to give the intermediate II. After silylation, the enolate copper species III generated *in situ* would be protonated to furnish the desired silyllallene product 3a. The released copper catalyst IV would be delivered to the next catalytic cycle.

In conclusion, a copper-catalyzed asymmetric synthesis of highly substituted chiral allenes was developed. In this work, the (*Z*)-enynaoates could react smoothly with the silylboronate, the corresponding racemic and enantioenriched silyl-substituted allene products could be obtained in good yields and high enantioselectivities under very mild reaction conditions, respectively. Therefore, current work provides an efficient method to prepare allenylsilanes, as well as expands the scope of heteroatom-substituted allene species.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08279.

Experimental procedures and spectral data for all new compounds (¹H NMR, ¹³C NMR, HRMS), and crystallographic data of compounds **5** in CCDC number 1435363 (PDF)

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Notes

The authors declare no competing financial interest.

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