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Catalytic Asymmetric Conjugate Protosilylation and Protoborylation of 2-Trifluoromethyl Enynes for Synthesis of Functionalized Allenes

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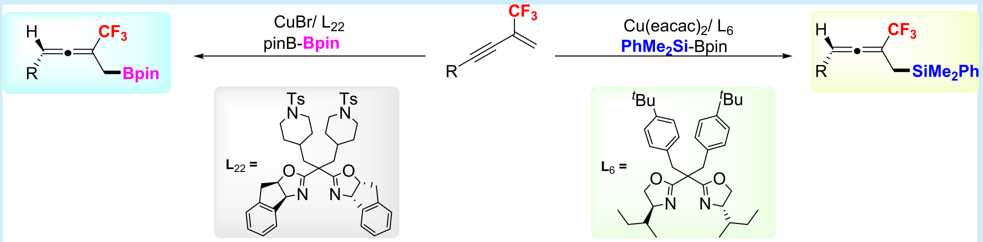
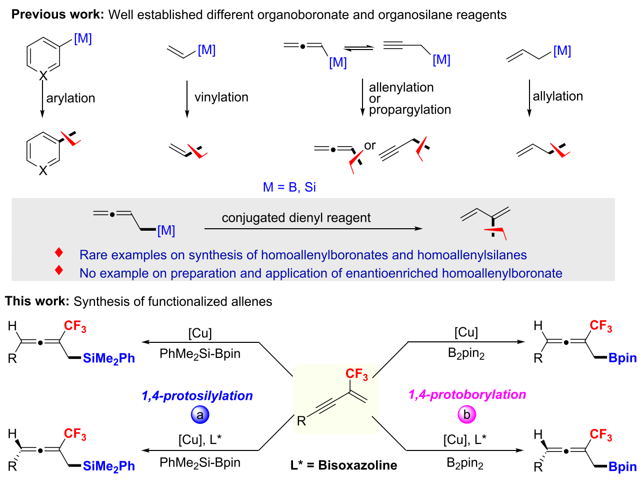


- ◆ New designed chiral bisoxazoline ligand
- ◆ The first example on synthesis of chiral homoallenylboronates
- ◆ High fidelity of enantiotransfer to generate the useful enantioenriched dienyl alcohols and 2,5-dihydrofurans

ABSTRACT: The Cu-catalyzed 1,4-protosilylation and protoborylation of trifluoromethyl-substituted conjugated enynes were developed to access functionalized homoallenylsilanes and homoallenylboronates. This protocol also provides a general method to synthesize optically active homoallenylsilanes and homoallenylboronates in moderate to excellent yields with high enantiomeric excess by using new designed chiral bisoxazoline ligands. Simultaneously, the transformations of homoallenylsilanes and homoallenylboronates were also explored to synthesize useful building blocks.

Scheme 1. Strategies for the Synthesis of Homoallenylsilanes and Homoallenylboronates



- ◆ Rare examples on synthesis of homoallenylboronates and homoallenylsilanes
- ◆ No example on preparation and application of enantioenriched homoallenylboronate

To date, various organoboron[1] and organosilane[2] reagents such as aryl, vinyl, allenyl or propargyl, and allyl compounds have been well documented for their versatile transformations. In stark contrast, less attention has been focused toward the study of homoallenylborons and homoallenylsilanes despite their highly potential worth as four-carbon synthons in organic synthesis. Early in 1994, Suzuki and co-workers developed pioneering work related to the copper-mediated coupling reaction between propargylic electrophiles and Knochel's (dialkoxyboryl)-methylzinc iodide to synthesize homoallenylboronates but afforded product in low to moderate yields.[3] The synthetic value of the homoallenylboronates was featured by their addition to the carbonyl compounds for the synthesis of useful 1,3-dienyl allylic alcohols.[4] On the other hand, Brown and co-workers reported an alternative method to prepare the homoallenylboronates via one-carbon homologation of allenylboronates.[5] Meanwhile, an approach of copper-catalyzed coupling reaction of *gem*-borazirconocene alkanes with propargyl bromide to give monosubstituted homoallenylboronate was explored by Srebnik et al.[6] In 2008, Moberg explored a Pt-catalyzed coupling reaction between silylboronate and large group substituted conjugated enynes to form silyl-substituted homoallenylboronate derivatives.[7] Except these examples, only sporadic cases on the derivation of homoallenylboronates were revealed.[8] Similarly, only rare examples on the synthesis of enantioenriched homoallenylsilanes have been reported,

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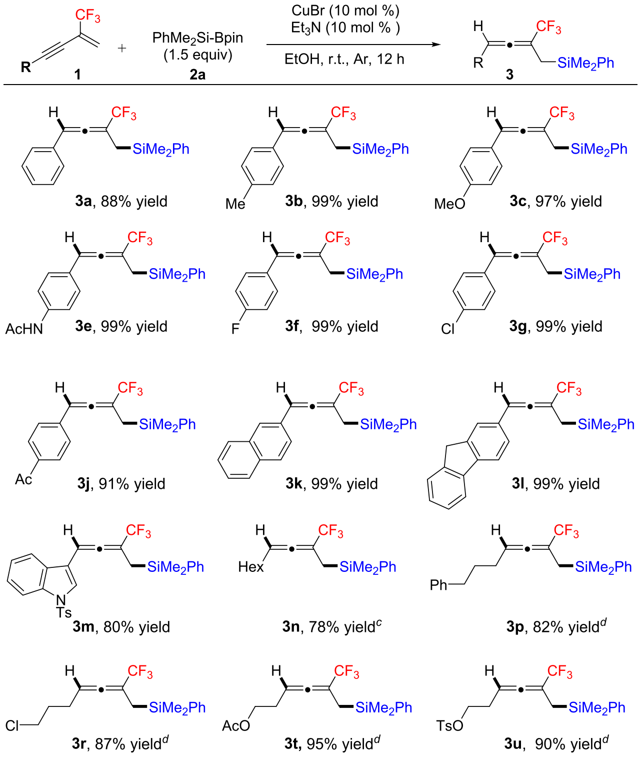
Scheme 2. Substrate Scope of Copper-Catalyzed Racemic 1,4-Protosilylation of CF$_3$-Substituted Conjugated Enyne[a,b]

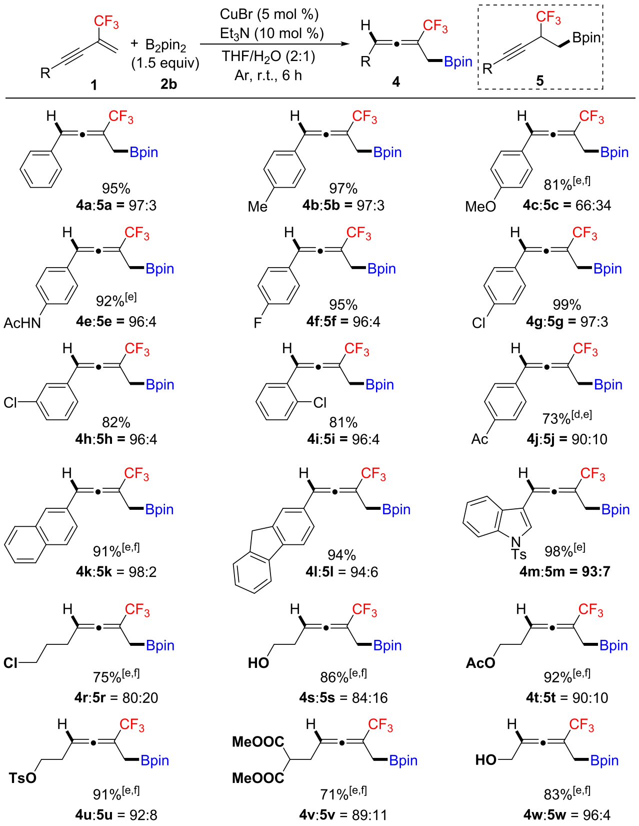


[a]The reactions were run under the following reaction conditions: the mixture of enyne **1** (0.2 mmol), **2a** (0.3 mmol), CuBr (10 mol %), and Et$_3$N (10 mol %) was stirred in anhydrous EtOH (1 mL) at rt under an argon atmosphere. [b]Isolated yield. [c]The loading of Et$_3$N was 30 mol %, and the reaction time was 16 h. [d]The loading of Et$_3$N was 30 mol %, and the reaction time was 17 h.

which greatly restricted their utility as chiral reagents.[9] In 2002, Hiemstra and co-workers used the commercially available enantiopure (*S*)-but-3-yn-2-ol as the starting material and prepared an optically active allene trimethyl(penta-2,3-dien-1-yl)silane to investigate the chirality transformation in an S$_E$′ reaction.[9b] Subsequently, the first asymmetric synthesis of enantioenriched homoallenylsilane products using a palladium catalyst was reported by the Ogasawara and Hayashi group.[9c] To the best of our knowledge, there is no method available to synthesize the enantioenriched axially chiral trisubstituted homoallenylsilanes. Despite these advances, the harsh reaction conditions, the narrow substrate scope, and the lack of diversity in application still spur us to discover practical and sustainable methods to prepare the functionalized homoallenylsilanes and homoallenylboronates and explore their new utilization in organic transformation. More importantly, regarding significance as privileged structural motifs in medicinal chemistry as well as agrochemistry and functional materials, CF$_3$-substituted functional allenes are largely ignored.[10]

Herein, we would like to communicate the copper-catalyzed regioselective and enantioselective 1,4-protosilylation and protoborylation reactions of 2-trifluoromethyl-1,3-enynes with silylboronate or bis(pinacolato)diboron to generate the homoallenylsilanes and homoallenylboronates, respectively (Scheme 1).[10f,j,11,12] In addition, enantioenriched homoallenylboronate can be used for the synthesis of chiral 1,3-dienyl allylic alcohols with high stereofidelity.[4]

Scheme 3. Substrate Scope of Copper-Catalyzed Racemic 1,4-Protoborylation of CF$_3$-Substituted Conjugated Enyne[a,b,c]

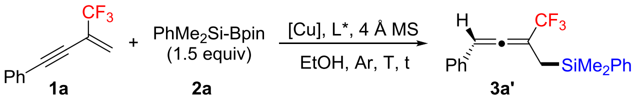


[a]The reactions were run under the following reaction conditions: the mixture of enyne **1** (0.2 mmol), **2b** (0.3 mmol), CuBr (5 mol %), and Et$_3$N (10 mol %) was stirred in THF/H$_2$O (2:1, 1 mL) at rt under an argon atmosphere for 6 h. [b]The ratio of **4** and **5** was determined by ^{1}H NMR analysis. [c]Isolated yield. [d]The loading of CuBr was 10 mol %. [e]The reaction time was 24 h. [f]The solvents were the mixture of 1,4-dioxane and H$_2$O (2:1, 1 mL).

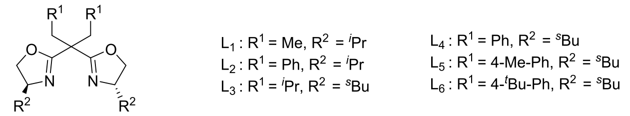
First, the 2-trifluoromethyl-1,3-enyne **1a** and silylboronate **2a** were chosen as model substrates to optimize the reaction conditions (see the details in the Supporting Information (SI)),[13,14] and the optimized reaction conditions were established as follows: in the presence of 10 mol % CuBr as catalyst and 10 mol % Et$_3$N as additive, the mixture of **1a** and **2a** in 1.0 mL of EtOH was stirred at room temperature for 12 h under an argon atmosphere. Then, various 2-trifluoromethyl-1,3-enynes were subjected to this reaction (Scheme 2). It was found that all the 2-trifluoromethyl-1,3-enynes could afford the desired products in good to excellent yields (Scheme 2, **3a**−**3m**). Moreover, the aliphatic substituted enynes with different functionalities were also compatible to give the desired products (Scheme 2, **3n**−**3u**).

Considering the fickle reactivity and wide usefulness of organoboron reagents, bis(pinacolato)diboron **2b** instead of **2a** was tested under modified optimized reaction conditions as follows: in the presence of 5 mol % CuBr as the catalyst and 10 mol % Et$_3$N as the additive, the mixture of **1a** and **2b** in 1.0 mL of THF/H$_2$O (2:1) solution was stirred at room temperature for 6 h under an argon atmosphere (see the details in the SI).

Table 1. Optimization of Reaction Conditions for Copper-Catalyzed Asymmetric 1,4-Protosilylation of CF_3-Substituted Conjugated Enyne 1a[a]



entry	[Cu] (mol %)	L* (mol %)	4 Å MS (mg)	T (°C)	t (h)	yield[b] (%)	ee[c] (%)
1	CuBr (10)	L_1 (12)	--	rt	12	46	52
2	CuBr (10)	L_2 (12)	--	rt	12	38	49
3	CuBr (10)	L_3 (12)	--	rt	12	53	70
4	CuBr (10)	L_4 (12)	--	rt	12	30	70
5	CuBr (10)	L_5 (12)	--	rt	12	20	64
6	CuBr (10)	L_6 (12)	--	rt	12	62	81
7	CuBr (10)	L_6 (12)	12.5	rt	12	90	81
8	CuF_2 (10)	L_6 (12)	12.5	rt	12	91	79
9	$Cu(eacac)_2$ (10)[d]	L_6 (12)	12.5	rt	12	92	82
10	$Cu(eacac)_2$ (10)	L_6 (12)	12.5	0	17	94	85
11	$Cu(eacac)_2$ (10)	L_6 (12)	12.5	-10	17	90	90
12	**$Cu(eacac)_2$ (5)**	**L_6 (6)**	**12.5**	**-10**	**17**	**93**	**90**

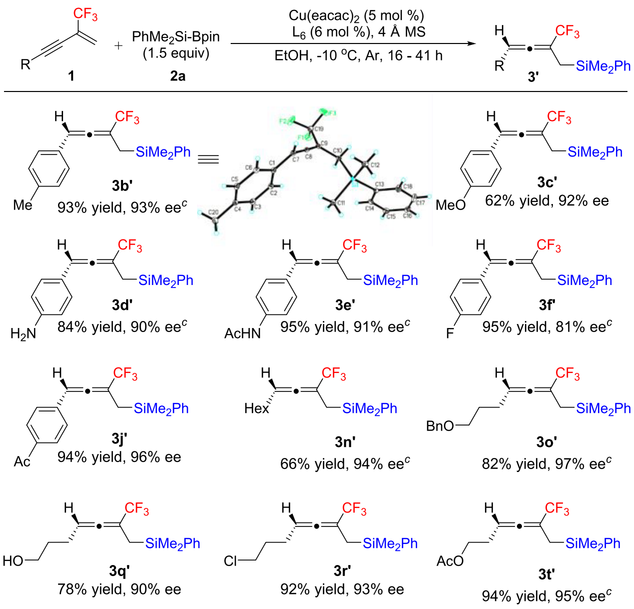


[a]The reactions were run under the following reaction conditions: the mixture of enyne **1a** (0.2 mmol), **2a** (0.3 mmol), $Cu(eacac)_2$, L*, and 4 Å molecular sieves in anhydrous EtOH (1.0 mL) was stirred under an argon atmosphere for the indicated time at the indicated temperature. [b]Isolated yield. [c]The values of ee were determined by HPLC. [d]$Cu(eacac)_2$ = copper ethylacetoacetate.

As described in Scheme 3, the 1,4-protoborylation of conjugated enynes toward homoallenylboronates gave yields ranging from moderate to excellent along with the formation of trace 1,2-protoborylation products, depending on the substrate structure and electronic properties of its substituents. Most aryl-substituted substrates could afford the desired homoallenylboronate product in moderate to high yield. Nonetheless, the substrate bearing 4-methoxyphenyl delivered homoallenylboronate **4c** and homopropargylboronate **5c** in 81% total yield but with poor regioselectivity (66/34). This could be attributed to the strong electron-donating effect of the methoxy group. Similarly, only moderate ratios between the homoallenylboronate **4** and homopropargylboronate **5** were observed when alkyl-substituted enynes were applied (**4r** and **4s**). Notably, the homoallenylboronate products could be obtained in high yields when electron-withdrawing groups were present on a distal position at the aliphatic chain (**4t**–**4w**). Unfortunately, when the cyclohexyl substituted enyne was applied in this reaction, only 3% desired product and 9% homopropargylboronate were observed along with recovering about 83% starting material judged from the crude ^1H NMR under the optimized reaction conditions.

Considering the importance of enantioenriched allenyl compounds for the synthesis of chiral natural products and biologically active molecules,[15] we embarked on investigating the catalytic synthesis of optically active trifluoromethyl-substituted homoallenylsilanes (Table 1). According to the previous reports on copper-catalyzed asymmetric silyl-addition reactions, we first screened various chiral ligands such as chiral bidentate P–N ligands,[16] bisoxazolines,[13l] pyridine-oxazolines,[17] etc. Fortunately, the use of 10 mol % CuBr catalyst and 12 mol % bisoxazoline ligand L_1 could afford the desired product **3a′** in 46% yield and with 52% ee value in ethanol solution at room temperature (Table 1, entry 1). Therefore, different substituted bisoxazolines were tested for this reaction (Table 1, entries 2–6). It was found that the ligand with an isobutyl-substituent on the oxazoline ring afforded a better result. Moreover, increasing the steric hindrance of the R^1 group of the bisoxazoline ligand could improve the product's enantioselectivity significantly. Especially, in the presence of ligand L_6 with a 4-*tert*-butyl substituent on the phenyl ring, the desired product was obtained in 62% yield and with 81% ee (Table 1, entry 6). Moreover, the introduction of 4 Å MS to the solution could improve the product's yield up to 90% and with the same ee value (Table 1, entry 7). After careful screening of various copper catalysts and temperature, finally the desired product **3a′** could be obtained in 93% yield and with 90% ee in the presence of 5 mol % $Cu(eacac)_2$ (Copper(II)-ethylacetoacetate) as th ecatalyst and 6 mol % chiral bisoxazoline L_6 as the ligand in anhydrous EtOH solution at −10 °C (Table 1, entries 8–12).

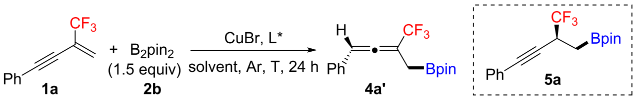
Scheme 4. Substrate Scope of Copper-Catalyzed Asymmetric 1,4-Protosilylation of CF_3-Substituted Conjugated Enyne[a,b]



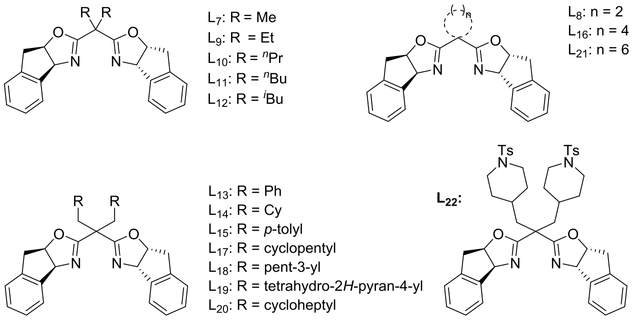
[a]The reactions were run under the following reaction conditions: the mixture of enyne **1** (0.2 mmol), **2a** (0.3 mmol), $Cu(eacac)_2$ (5 mol %), L_6 (6 mol %), and 4 Å molecular sieves (0.0125 g) in anhydrous EtOH (1.0 mL) was stirred at −10 °C under argon for the corresponding time. [b]Isolated yield. [c]30 mol % Anhydrous Et_3N was added.

Therefore, some typical CF_3-substituted conjugated enynes were subjected for the synthesis of enantioenriched homoallenylsilanes. In most—but not all—instances, the 2-trifluoromethyl-1,3-enynes afforded the desired homoallenylsilanes in good to excellent yield and with up to 97% ee value (Scheme 4, **3b′**–**3e′**, **3j′**–**3t′**). The long carbon chain and the ones bearing other functionalities such as hydroxyl, ester, chloro, and ether were also compatible to yield the desired products, respectively. The absolute configuration of the

Table 2. Optimization of Reaction Conditions for Copper-Catalyzed Asymmetric 1,4-Protoborylation of CF_3-Substituted Conjugated Enyne 1a[a]



entry	CuBr (mol %)	L* (mol %)	4 Å MS (mg)	solvent (1 mL)	T (°C)	yield[b] (%) 4a'	ee[c] (%)	yield[b] (%) 5a
1	10	L_7 (12)	--	EtOH	r.t.	61	7	2
2	10	L_8 (12)	--	EtOH	r.t.	40	16	2
3	10	L_9 (12)	--	EtOH	r.t.	34	17	trace
4	10	L_{10} (12)	--	EtOH	r.t.	46	30	1
5	10	L_{11} (12)	--	EtOH	r.t.	29	32	1
6	10	L_{12} (12)	--	EtOH	r.t.	20	52	1
7	10	L_{13} (12)	--	EtOH	r.t.	46	46	5
8	10	L_{14} (12)	--	EtOH	r.t.	82	74	9
9	10	L_{14} (12)	--	EtOH	-10	78	78	14
10	10	L_{15} (12)	--	EtOH	-10	69	43	trace
11	10	L_{16} (12)	--	EtOH	-10	74	8	trace
12	10	L_{17} (12)	--	EtOH	-10	70	68	trace
13	10	L_{18} (12)	--	EtOH	-10	63	66	3
14	10	L_{19} (12)	12.5	EtOH	-10	87	80	1
15	10	L_{20} (12)	12.5	EtOH	-10	78	76	1
16	10	L_{19} (12)	12.5	CyH/MeOH (1:1)	-10	92	82	trace
17	10	L_{21} (12)	12.5	CyH/MeOH (1:1)	-10	93	5	trace
18	10	L_{22} (12)	12.5	CyH/MeOH (1:1)	-10	90	89	trace
19	**5**	**L_{22} (6)**	**12.5**	**Hexane/MeOH (1:2)**	**-10**	**94 (97[d])**	**92**	**trace**

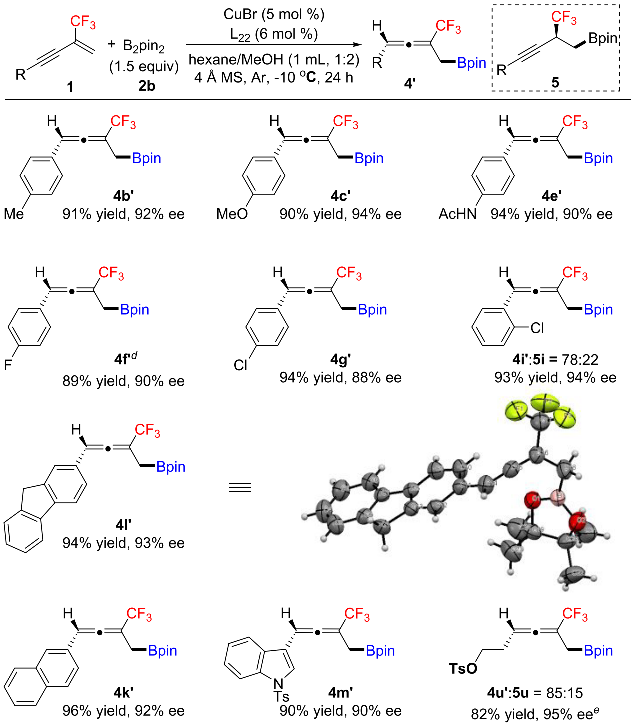


[a]Unless noted otherwise, the reactions were run under the following reaction conditions: the mixture of enyne **1a** (0.2 mmol), **2a** (0.3 mmol), Cu(I), L*, and 4 Å molecular sieves was stirred in the indicated solvent (1 mL) under an argon atmosphere at the indicated temperature for 24 h. [b]Determined by ^1H NMR analysis using mesitylene as the internal standard. [c]The values of ee were determined by HPLC. [d]Isolated yield, **4a′**:**5a** > 99:1 (determined by ^1H NMR analysis).

homoallenylsilane product **3b′** was determined to be (*R*) by single-crystal X-ray diffraction analysis of the recrystallized one (>99% ee, CCDC No. 1877293).

Subsequently, we investigated the asymmetric 1,4-protoborylation of CF_3-substituted conjugated enyne **1a** with bis(pinacolato)diboron **2b** at the above-established reaction conditions, the desired product was obtained in 87% NMR yield but with moderate regioselectivity (**4a′**:**5a′** = 79:21) and **4a′** with 77% ee. Next, different chiral ligands were evaluated for further screening (Table 2, entries 1−8). It was observed that the enantiomer ratio of desired product could be improved by increasing the steric effect of the substituents on the chiral indeno-bisoxazolines ligands (entries 8, 9, 14, and 16). On the basis of these results, by replacing the substituent with the more bulky tosyl protected piperidinyl group (L_{22}), the enantiomeric excess of product **4a′** was improved to 89%. Finally, tuning the mixed solvents to hexane and methanol could afford the homoallenylboronate **4a′** in 97% isolated yield and 92% ee.

Scheme 5. Substrate Scope of Copper-Catalyzed Asymmetric 1,4-Protoborylation of CF_3-Substituted Conjugated Enyne[a,b,c]

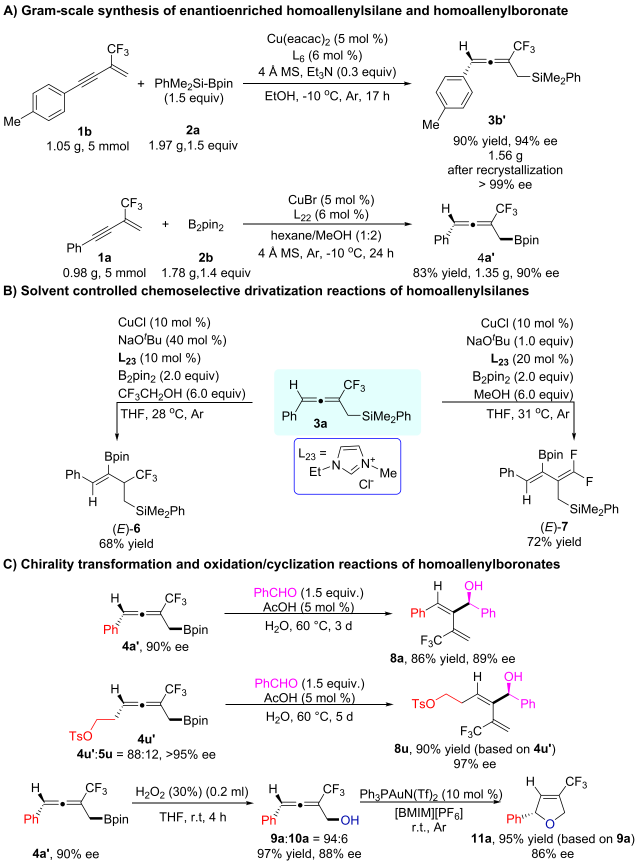


[a]Reaction conditions: a mixture of enyne **1** (0.2 mmol), **2a** (0.3 mmol), CuBr (5 mol %), L_{22} (6 mol %), and 4 Å molecular sieves (0.0125 g) was stirred in hexane/methanol (1:2, 1 mL) at −10 °C under argon for 24 h. [b]The ratio of **4′** and **5** was determined by ^1H NMR analysis. [c]Isolated yield. [d]The reaction time was 25 h. [e]The values of ee were determined by a two-step derivation (see the details in the SI).

Subsequently, other CF_3-substituted conjugated enynes were evaluated (Scheme 5). The aryl-substituted enynes could all afford the desired products in high to excellent yields and with high enantiomeric excess. The absolute configuration of the homoallenylboronate product **4l′** was determined to be (*S*) by single-crystal X-ray diffraction analysis (CCDC No. 1960811). Furthermore, the alkyl-substituted enyne such as **1u** also exhibited good reactivity, and the desired product **4u′** was isolated in 82% yield (**4u′**:**5u** = 85:15, determined by ^1H NMR) and with up to 95% ee. On the other hand, an aromatic enyne bearing an *ortho*-Cl showed slightly decreased regioselectivity, likely due to the unfavorable steric hindrance.

To show the synthetic utility, gram-scale synthesis of enantioenriched homoallenylsilane **3b′** and homoallenylboronate **4a′** was initiated and found to proceed smoothly (Scheme 6A). When the compound **3a** reacted with bis(pinacolato)-

Scheme 6. Gram-Scale Synthesis and Derivatization of Homoallenylsilanes and Homoallenylboronates



diboron catalyzed by CuCl in the 2,2,2-trifluoroethanol solution, a regioselective protoboronation product (*E*)-**6** was formed in 68% yield. When the solvent was changed to methanol, a difluorosubstituted diene product (*E*)-**7** was obtained in good yield (72%) via tandem addition/defluorination processes (Scheme 6B).[18] Additionally, the reaction of homoallenylboronates with benzaldehyde could proceed with high fidelity of enantiotransfer to afford the useful enantioenriched dienyl alcohols **8a** and **8u** (Scheme 6C). The oxidative derivatization of **4a′** afforded the corresponding chiral homoallenol **9a** in excellent yield and with high enantiopurity.[6a,8g,19] Subsequent conversion of axial homoallenol **9a** to central chiral product 2,5-dihydrofuran **11a** was achieved in 95% yield (based on **9a**) and with 86% ee via 5-*endo*-trig cyclization (Scheme 6C).[20]

In summary, we have developed the regio- and enantioselective copper-catalyzed 1,4-protosilylation and protoborylation of CF_3-substituted conjugated enynes. This work provides a practical and efficient method to prepare functionalized enantioenriched homoallenylsilanes and homoallenyboronates. Moreover, studies on application of homoallenylsilanes and homoallenylboronates were also demonstrated. The axial-to-central chirality transfer in the reactions of homoallenylboronates with aldehydes and homoallenol to 2,5-dihydrofuran could proceed with high fidelity. Further studies on the utility of homoallenylsilanes and homoallenylboronates in organic transformation are being pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04647.

Experimental procedures, characterization data (PDF)

Accession Codes

CCDC 1877293 and 1960811 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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