Divergent Protosilylation and Protoborylation of Polar Enynes

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Supporting Information

ABSTRACT: Copper-catalyzed divergent conjugate protosilylation and protoborylation of polar enynes were developed. The corresponding β-boryldienoates and β-silyldienoates were obtained in moderate to good yields and with good stereoselectivity. In this protocol, novel cascade double protoborylation/protodeboronation processes of polar enynes that enabled access of the useful trisubstituted vinylboronates in up to 80% yield and with up to 98:2 Z/E ratio. Moreover, divergent transformations of the products thus obtained were also investigated.

Conjugate additions enable the convenient and concise formation of powerful carbon–carbon and carbon-hetero bonds, providing a rapid gateway into numerous molecules in organic and medicinal chemistry. Apart from classical electron-deficient conjugated acceptors with one double bond or triple bond, the prolonged conjugated systems, including 1,3-dienoate (1,3-dienone),2 hex-2-en-4-ynedioate,3 4-en-2-ynoate,4 and 4-en-2-ynoate5 are backbones for divergent synthesis, therefore attracting intensive studies. However, despite being an important member of conjugate acceptors, the 4-en-2-ynoates (abbreviated to enynoate) attracted less attention. Theoretically, the functionalization of enynoate via (cascade) conjugate addition can be roughly classified into four modes, as depicted in Scheme 1a. 1,4-Addition is the most universal mode, while generally only one enyne substrate was selected as a special instance of substituted propiolates in individual research on 1,4-addition.5a–5d Recently, we studied in detail the 1,4/1,6-cascade asymmetric conjugate addition of different enynes to synthesize the enantioenriched 1,3-bis(silyl)propenes.5i To the best of our knowledge, so far no 1,4/1,4- or 1,4/1,6-cascade conjugate addition reaction of enynoate has ever been reported. Boron and silicon containing organic compounds have been widely used in a variety of chemical transformations.5e–5h Copper-catalyzed boryl and silyl conjugate additions have provided efficient methods to construct C–B and C–Si bonds.5i–5k However, as mentioned, only a few examples were explored on the conjugate protoborylation and protosilylation of enynes (Scheme 1b). In 2014, Ohmiya and Sawamura reported a PBU3-catalyzed carborabration reaction of alkyynes, in which an aryl-substituted enynoate was selected as a substrate (Scheme 1b, eq 1).5l Sequentially, a hydroboration reaction of alkyynes was developed by the same group5m and Santos group5h in 2018 (Scheme 1b, eqs 1 and 2). A copper-catalyzed conjugate silylation reaction of alkynoate was accomplished by the Lipshutz5d group in 2014, and relevant borylation reaction was achieved by the Santos group5e–5g (Scheme 1b, eq 3). In these cases, only 3-(cyclohex-1-en-1-yl)propiolates were selected as the enynoate substrate. It is also noteworthy that, in 2011, the Santos group disclosed a protoborylation reaction of allenates with a preactivated diboron, which could provide the stereo- and regioisomers (Scheme 1c).7h Inspired by these works combined with our interest in the synthesis of functionalized alkenes and allenes,5e–5h,8 we constructed divergent and useful boron and silicon containing alkenyl moieties via copper-catalyzed conjugate addition of enynoates (Scheme 1d).

During our screening of the reaction conditions for the synthesis of chiral 1,3-bis(silyl)propene,5i it was found that the allylic silyl group could be removed in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) base. This unexpected result inspired us to investigate the preparation of the regio- and stereo-defined boryl counterpart, which is difficult to prepare via direct hydroboration of asymmetrical internal alkynes. To test our hypothesis, 1a was subjected to react with Bpin2 in the presence of a catalytic amount of DIPEA (N,N-Diisopropylethylamine) as base, CuCl as catalyst, and 2,2′-bipyridine as ligand in methanol. Pleasingly, the target product 3a was obtained in 81% yield (NMR), accompanied by formation of its stereo- and regioisomers. We then examined other commercially available dinitrogen ligands (Table 1, entries 1–9). It was found that both the regioselectivity and the yield were improved when the 3,4,7,8-tetramethyl-1,10-

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phenanthroline (L₉) was used as the ligand. The regioselectivity was further improved by increasing the loading of DIPEA without diminishing the product yield (Table 1, entries 9—11). The controlled experiment showed that no 3ₐ was formed without DIPEA as additive; only the β-boryldienoate 5ₐ was obtained as the sole product in quantitative NMR yield (Table 1, entry 12). Furthermore, catalytic amount of triethylamine (10 mol %) also furnished the product 5ₐ in a high NMR yield (79% isolated yield) (Scheme 6, entry 1).

After determining the optimal reaction conditions, we investigated the substrate scope of enynoates. In most cases, the δ-aryl-substituted enynoates afforded the borylalkenes in reasonable yields and with high stereoselectivity (3ₐ—e, 3g, 3u—w, Scheme 2). Different substituents including electron-donating and electron-withdrawing groups on the phenyl ring were compatible in this reaction. Moreover, the thienyl-substituted enynoate was also smoothly converted to the desired product in 63% yield. Unfortunately, the δ-alkyl-substituted enynoates were not suitable for this reaction, which produced complex mixtures.

Next, we analyzed the possible pathways of formation the alkenylboronate product 3 (Scheme 3). According to our

### Table 1. CuCl-Catalyzed Protoborylation of 1ₐ<sup>a</sup>  

| entry | ligand | DIPEA | yield (3ₐ) | (Z-3ₐ)/(E-3ₐ):4a-5ₐ |
|-------|--------|-------|------------|----------------------|
| 1     | L₉     | 0.12  | 81%        | 83:1-1:0             |
| 2     | L₉     | 0.12  | 80%        | 81:1:2:1:5            |
| 3     | L₉     | 0.12  | 81%        | 84:2:1:4:0            |
| 4     | L₉     | 0.12  | 92%        | 94:1:5:0              |
| 5     | L₉     | 0.12  | 49%        | 58:0:8:34             |
| 6     | L₉     | 0.12  | 87%        | 87:1:3:0              |
| 7     | L₉     | 0.12  | 85%        | 85:0:15:0             |
| 8     | L₉     | 0.12  | 90%        | 90:0:1:0              |
| 9     | L₉     | 0.12  | 95%        | 95:0:5:0              |
| 10    | L₉     | 0.5   | 96%        | 93:3:4:0              |
| 11    | L₉     | 2.0   | 99% (75%)<sup>b</sup> | 95:5:0:0              |
| 12    | L₉     | --    | --         | 0:0:1:00              |

<sup>a</sup>Reaction was run under the following reaction conditions: 0.1 mmol 1ₐ, 0.23 mmol B₂pin₂ (2.3 equiv), 10 mol % CuCl, 12 mol % ligand, and 0.2 mmol DIPEA (2.0 equiv) were stirred in 0.5 mL of MeOH at 30 °C for 12 h under argon atmosphere.  

<sup>b</sup>Isolated yield.

### Scheme 2. Copper-Catalyzed Protoborylation of Various Substrates with B₂pin₂.<sup>a</sup>
previous study, 5i 1,4/1,6-cascade double protoborylations followed by protodeborylation process seemed to be a reasonable pathway (Scheme 3, path a). Another plausible route is via 1,4/1,4-cascade double protoborylations and an allylic rearrangement (Scheme 3, path b). Further, 1,4-protoborylation/1,6-hydrogention tandem reactions also could yield the product 3 (Scheme 3, path c). To clarify the mechanism, controlled experiments were carried out, as shown in Scheme 4. First, when 5a reacted with HBpin (1.1 equiv) under the standard conditions, no 3a was detected with fully recovering 5a after reaction (Scheme 4, eq 1). Thus, the path c can be ruled out at this stage. To further probe the mechanism, B2pin2-d12 was prepared to react with 5a. A mixture of 3a-d6 and 3a was obtained in a ratio of 1:2 (determined by HRMS study) (Scheme 4, eq 2). The ratio lies between 0:1 and 1:1, implying that both paths a and b were possibly involved to furnish the product 3.

In addition, the utilities of the trisubstituted alkenylboronates were investigated. First, the Suzuki-coupling reaction between the model product 3a and methyl 4-iodobenzoate was performed, affording the alkene 8a in 85% yield and with full retention of configuration (Scheme 5, eq 1).9 Significantly, the stereoselective methylations could be well-controlled with configuration inversion by Zweifel olefination (9a)10 and retention by Suzuki coupling reaction (10a)11 (Scheme 5, eqs 2 and 3).

Subsequently, the synthesis of β-boryl dienoate product 5 was also examined under the following reaction conditions: the enynoate with B2pin2 (1.05 equiv) in the presence of CuCl (10 mol %) as catalyst with triethylamine (10 mol %) as additive in methanol at 30 °C (Scheme 6). Various β-aryl-substituted enynoates, regardless of bearing an electron-donating or electron-withdrawing group on the phenyl ring, reacted efficiently to deliver the corresponding β-boryldienotes in 50−83% yields (5a-f). It was found that only 34% yield of 5m was obtained when the hydroxyethyl-substituted enynoate was subjected to this reaction. Fortunately, the yield could be significantly improved by replacing NET3 with K2PO4. Under the modified conditions, other alkyl-substituted enynoates and TBS-substituted enynoate afforded the corresponding products in moderate to good yields (5n, 5j, 5t).

Following, the α,β-protosilylation of enynoates with silaboronate reagent (PhMe2Si-Bpin) was also studied. First, the β-silyldienote 11a was obtained in 74% yield along with formation 18% α-silyldienote 12a (Table 2, entry 1). Then, other bases were screened to improve the yield of product (Table 2, entries 1−3). When K2CO3 was used as the base, the yield of 11a was decreased significantly, while the yields of bis(silyl)propene 13a were increased. Pleasingly, when MeOH was replaced with ‘AmOH as solvent, the yield of desired

### Scheme 3. Possible Mechanistic Pathways

![Scheme 3](image)

### Scheme 4. Controlled Experiments: (a) Hydroborylation and (b) Isotope Labeled Experiment

![Scheme 4](image)

### Scheme 5. Stereoselective Arylation and Methylation of 3a

![Scheme 5](image)

**Conditions:** (1) 7a (1.3 equiv), Pd(dppf)Cl2 (5 mol %), K3PO4 (3.0 equiv), DMSO (0.07 M), 45 °C, 12 h. (2) CH3Li (1.1 equiv), −78 °C, Et2O (0.25 M); I2 (1.4 equiv), MeOH (0.25 M); CH3ONa (3.0 equiv). (3) Mel (6.0 equiv), P(dba)3 (5 mol %), P(o-tolyl)3 (10 mol %), K2CO3 (2.0 equiv), DMF/H2O (9:1, 0.5 M), 60 °C, 25 h.

### Scheme 6. Copper-Catalyzed Protoborylation of Various Enynoates with B2pin2

![Scheme 6](image)

**Reaction was run under the following reaction conditions: 0.2 mmol 1a, 0.21 mmol B2pin2 (1.05 equiv), 10 mol % CuCl, 10 mol % NET3 were stirred in 1.0 mL of MeOH at 30 °C for 12 h under argon atmosphere. K2PO4 (10 mol %) was used as the base instead of NET3.**
product 11a was greatly improved along with formation of trace amounts of side products 12a and 13a (Table 2, entry 4). Interestingly, it was noticed that adding a trace amount of water could ensure a stable yield of product 11a while leading to a slightly decreased yield by reducing the silaboronate to 1.3 equiv. Water could ensure a stable yield of product 11a.

Finally, the controlled experiments showed that the copper catalyst and the base were essential for this transformation (Table 2, entries 7 and 8). After establishing the reaction conditions, the scope of the enynoates was explored. All enynoates with diverse substituents on the phenyl ring were smoothly converted to the β-silyldienoates in high yields and with high regioselectivity (11a–g). Similarly, the 2-naphthyl or 2-thienyl substituted enynoates were also compatible for this conversion (11h and 11i). Next, the alkyl-substituted enynoates bearing with various functional groups such as halogens, free hydroxyl, protected hydroxyl, and amine also furnished the corresponding β-silyldienoates in high yields (11j–11n), but trace amount of side product 13 could be detected in several cases (11j–l, 11n–o). Besides the methyl enynoates, other enynoates and enamides 1s were also well-tolerated to give the corresponding desired products (11q–s).

Considering the substituted (hexa-)tetrahydropyridazines as core scaffolds in many natural products and pharmaceuticals, PTAD was then chosen as dienophile to react with 5a and 11a (Scheme 8). The target tetrahydropyridazine fragments with a boryl or silyl group were constructed. The stable bromo-subsitituted tetrahydropyridazine derivative 15a was formed in 51% yield in a one-pot manner (Scheme 8, eqs 1 and 2). Analogously, the silyl-substituted tetrahydropyridazine derivative 16a was obtained in 74% yield (dr = 93:7) (Scheme 8, eq 3).

In conclusion, we developed copper-catalyzed divergent borylations and silylation of 1,3-conjugated enynoates. After careful tuning of the reaction conditions, the substituted vinylboronate and boryl- and silyl-substituted dienoborates could be selectively obtained in good yields and with high stereoselectivity. These products can further undergo coupling reactions and Diels–Alder reaction to form various useful and complex molecular scaffolds.

### Scheme 7. Copper-Catalyzed β-Silylation of Various Substrates with PhMe2Si-Bpin

Reactions were carried out in 1AmOH/H2O (500:1, 0.2 M) in the presence of 1a–s (0.2 mmol), 10 mol % of CuBr, 10 mol % of K2CO3, and 1.3 equiv of PhMe2Si-Bpin at 30 °C under Ar for 12 h. 1AmOH/H2O (125:1, 0.2 M) was used as the solvent. 1AmOH/H2O (125:2, 0.2 M) was used as the solvent.

### Scheme 8. Diels-Alder Reactions of 5a and 11a with PTAD

**Conditions:** (1) PTAD (1.1 equiv), benzene (0.1 M), 30 °C, 24 h. (2) CuBr2 (2.0 equiv), THF/H2O (1:1, 0.1 M). (3) PTAD (1.1 equiv), benzene (0.1 M), 30 °C, 3 h.

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**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00995.

Description of experimental procedures, NMR spectra, and ESI-MS data (PDF)

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Notes
The authors declare no competing financial interest.