Preparation and Use of (γ,γ-Dioxyallyl)boronates

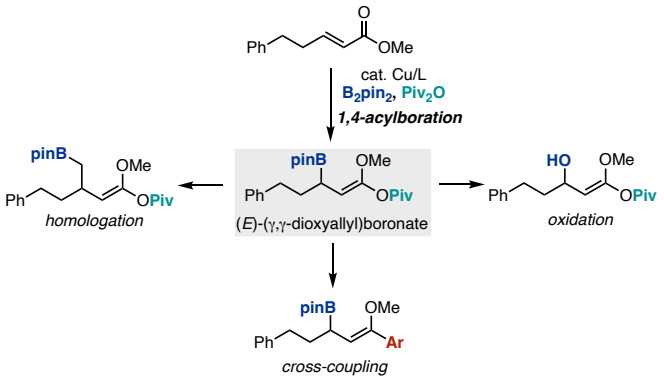
Soshi Nishino[a]
Yuji Nishii[a]
Koji Hirano*[a,b]

[a] Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[b] Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS-OTRI), Osaka University, Suita, Osaka 565-0871, Japan

k_hirano@chem.eng.osaka-u.ac.jp

Click here to insert a dedication.

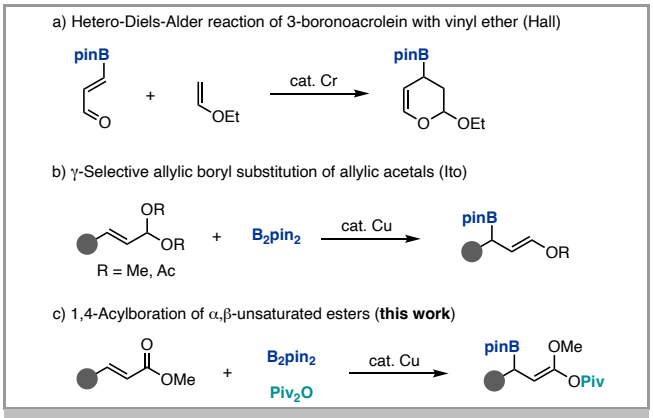


Received:
Accepted:
Published online:
DOI:

Abstract A copper-catalyzed stereoselective 1,4-acylboration of α,β-unsaturated esters with B_2pin_2 and pivalic anhydride has been developed to afford the corresponding (*E*)-allylboronates with two distinct oxygenated functionalities at the γ positions, which are difficult to prepare by other means. The chemoselective post functionalizations of Bpin and pivalate moieties in the product are also demonstrated.

Key words allylboronate, borylation, conjugate addition, copper, stereoselectivity

Allylborons constitute an important class of organoboron compounds in modern synthetic organic chemistry because they enable the chemo- and stereoselective allylation of organic molecules, after which the resulting allyl moiety can be transformable with high diversity.[1] Among them, the γ-oxyallylic boronate is particularly useful for introduction of oxygenated functionality together with the allylic fragment to rapidly increase the molecular complexity. However, its preparation largely relies on the classical methods such as allylic lithiation-electrophilic borylation[2] and hydroboration-isomerization sequences,[3] which still suffers from low functional group compatibility and sometimes careful and tedious temperature control. On the other hand, recent advances in transition metal catalysis allows the more concise and structurally diverse synthesis of γ-oxyallylic boronate. Hall reported the chromium-catalyzed highly selective hetero-Diels-Alder reaction of 3-boronoacrolein with ethyl vinyl ether to afford the cyclic γ-oxyallylic boronate (Scheme 1a).[4] More recently, Itoh developed the copper-catalyzed γ-selective allylic boryl substitution of allyl acetals and acylals, delivering the corresponding allylboronates with the alkoxy and acyloxy moieties, respectively, at the γ-position (Scheme 1b).[5] By using suitable chiral ligands, these protocols can also be applied to asymmetric synthesis. In this paper, we report an alternative approach to the targeted γ-oxyallylboronate: a copper-catalyzed 1,4-acylboration of α,β-unsaturated esters with B_2pin_2 and pivalic anhydride is described (Scheme 1c). The products obtained are (γ-acyloxy-γ-alkoxyallyl)boronates, which are non-trivial allylboron compounds, to the best of our knowledge. Synthetic transformations based on the Bpin and acyloxy group are also demonstrated.

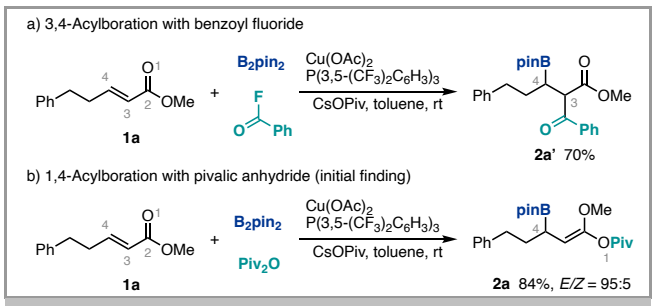


Scheme 1 Recent advances in transition-metal-catalyzed synthesis of γ-oxyallylic boronates with structural diversity.

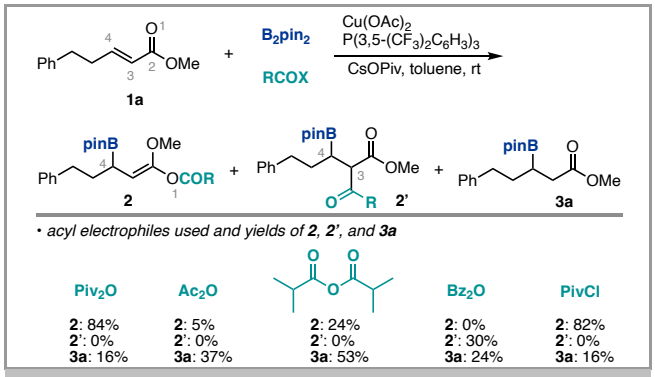
Recently, our research group developed the copper-catalyzed 3,4-acylboration of α,β-unsaturated ester **1a** with B_2pin_2 and benzoyl fluoride to afford the β'-boryl-β-ketoester **2a'** (Scheme 2a).[6] During the investigation of acyl electrophiles in the reaction, we serendipitously found that the use of pivalic anhydride (Piv_2O) totally switched the regioselectivity of the reaction to form the 1,4-acylboration product, that is, (γ,γ-dioxyallyl)boronate **2a** with high (*E*)-selectivity (Scheme 2b). The structure of product was assigned by ^{1}H, ^{13}C{^{1}H}, ^{11}B NMR and HR-MS, and finally determined by X-ray crystallographic analysis (vide infra).

Prompted by the aforementioned unexpected but intriguing result, we started optimization studies for the copper-catalyzed 1,4-acylboration of **1a**. Initially, the effect of acyl electrophile on

reaction efficiency and regioselectivity was examined in detail (Scheme 3). Smaller aliphatic acid anhydrides such as Ac_2O and $(iPrCO)_2O$ also afforded the corresponding 1,4-acylboration products **2** exclusively, but the yields were much lower probably because **2** gradually underwent in-situ hydrolysis to form the protoboration product **3a**.[7] On the other hand, as seen in our previous work,[6] the aromatic acid anhydride, Bz_2O, mainly delivered the 3,4-acylboration product **2'**. Notably, **2** was selectively obtained even with pivaloyl chloride, thus suggesting that the regioselectivity is controlled predominantly by steric/electronic nature of the carbon substituent rather than the leaving group in the acyl electrophile. In addition, the steric bulkiness to suppress the in-situ hydrolysis is necessary for the successful isolation of 1,4-acylboration product **2**.



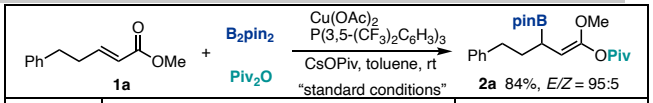
Scheme 2 Copper-catalyzed acylboration of α,β-unsaturated ester: previous work and serendipity.



Scheme 3 Effect of acyl electrophiles on efficiency and regioselectivity in copper-catalyzed acylboration of **1a**.

Representative results in screening of supporting ligand, base, and solvent are also summarized in Table 1. The ligand gave a large impact on the yield and *E/Z* selectivity, with the electron-withdrawing monodentate $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ proving to be best (entries 1–5). The pivalate-type external base was also essential to promote the acylboration; otherwise, the protoboration byproduct **3a** was mainly formed. In particular, the KOPiv base slightly increased the yield (entries 6–8). Final examination of solvent revealed that CPME was optimal, and the targeted **2a** was finally isolated in 82% yield with >99:1 *E/Z* selectivity (entry 10). In all attempts, the corresponding 3,4-acylboration product **2a'** was not detected at all, as far as Piv_2O was employed (see the Supporting Information for more details).

Table 1 Optimization Studies for Cu-Catalyzed 1,4-Acylboration of **1a** with B_2pin_2 and Piv_2O[a]

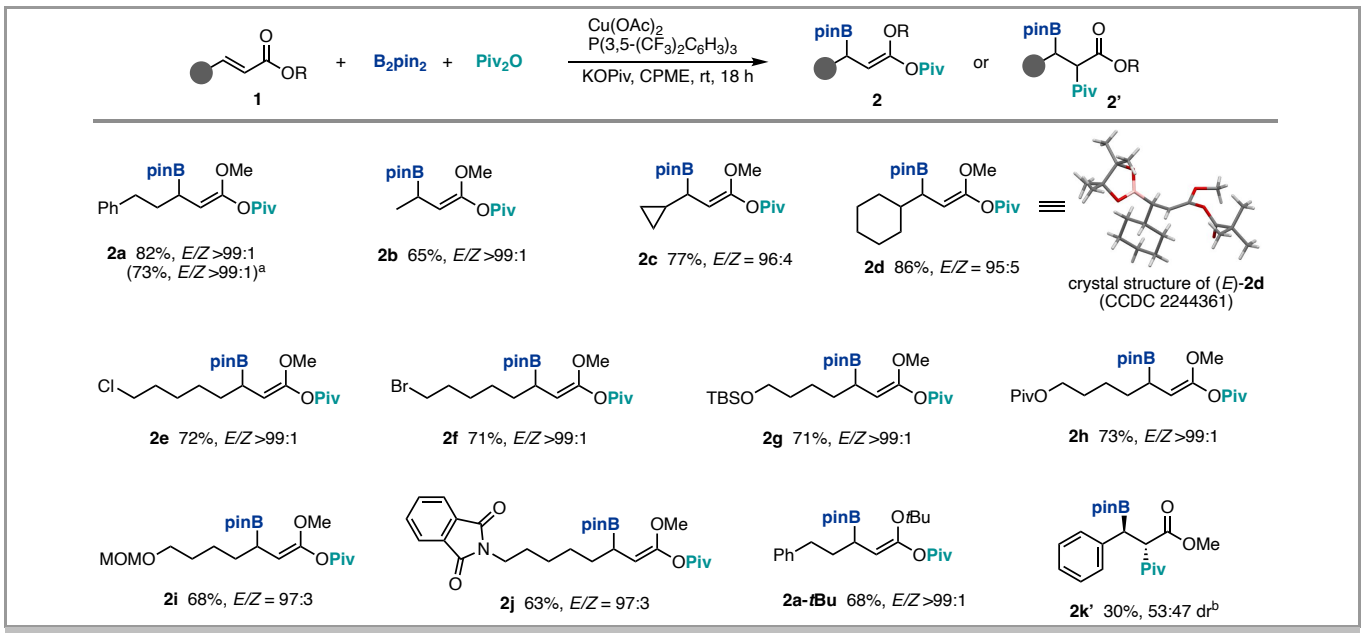


Entry	Deviations from standard conditions	Yield (%), *E/Z*[b]
1	none	84, 95:5
2	PPh_3 ligand	44, 84:16
3	$P(4\text{-}MeOC_6H_4)_3$ ligand	40, 83:17
4	$P(4\text{-}CF_3C_6H_4)$ ligand	52, 90:10
5	1,2-bis{$P(3,5\text{-}(CF_3)_2C_6H_3)_2$}benzene ligand[c]	<5, –
6	CsOAc base	30, 97:3
7	KOPiv base	88, 95:5
8	no base	<5, –
9	KOPiv base, 1,4-dioxane solvent	72, 94:6
10	KOPiv base, CPME solvent	91, 96:4 (82, >99:1)

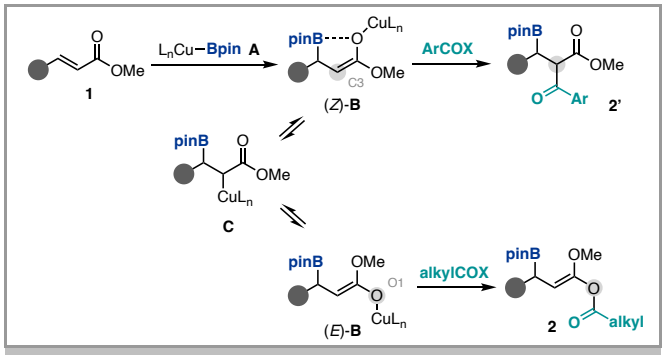
[a] Conditions: $Cu(OAc)_2$ (10 mol%, 0.025 mmol), ligand (20 mol%, 0.050 mmol), **1a** (0.25 mmol), B_2pin_2 (0.63 mmol), Piv_2O (0.38 mmol), base (0.75 mmol), solvent (1.0 mL), rt, 18 h. [b] Determined by ^1H NMR spectroscopy in the crude mixture with 1-methylnaphthalene internal standard. The values after isolation are shown in parentheses. [c] 10 mol% ligand.

With conditions in entry 10 of Table 1, we investigated the scope and limitation of α,β-unsaturated esters **1** (Scheme 4). In addition to the model substrate **1a**, the primary and secondary alkyl-substituted acrylates **1b–1d** underwent the 1,4-acylboration to form the corresponding (γ,γ-dioxyallyl)boronates **2b–2d** in good yields with high stereoselectivity. As a general trend, the (*E*)-selectivity slightly decreased with increasing the steric bulkiness of the substituent at the β-position (**2c** and **2d**). The structure of (*E*)-**2d** was unambiguously confirmed by the single-crystal X-ray analysis (CCDC 2244361). The copper catalysis was compatible with several functional groups, including the alkyl chloride, alkyl bromide, silyl ether, ester, and acetal (**2e–2i**). The protected amino group was also tolerated under the standard conditions (**2j**). The corresponding *tert*-butyl ester instead of the methyl ester also participated in the reaction (**2a-*t*Bu**). The reaction could be performed on a larger scale (2.0 mmol), and the desired product was obtained with comparable efficiency (**2a**). However, the cinnamate derivative **1k** showed the totally different selectivity and reactivity: the 1,4-acylboration product **2k** was not formed, and only the 3,4-acylboration product **2k'** was isolated. We have no explanation for the reason at this time.[8]

Our proposed reaction mechanism is shown in Scheme 5. The α,β-unsaturated ester **1** undergoes the conjugate addition with the in-situ generated borylcopper species **A**[9] to initially produce the kinetically favored β-borylated *O*-bound copper enolate (*Z*)-**B**, which is generally favored by the strong intramolecular O-to-B coordination.[10] Thus, the electrophilic trapping with the aromatic acyl electrophile such as benzoyl fluoride (Scheme 2a) and Bz_2O (Scheme 3) generally occurs at the nucleophilic C3 position, giving the 3,4-acylboration product **2'**. However, when the aliphatic acyl electrophile is employed, this reaction mode is less favored due to steric and electronic reasons. Accordingly, (*Z*)-**B** is isomerized into the stereoisomer (*E*)-**B** through tautomerization via the corresponding *C*-bound copper enolate **C**. The open coordination form in (*E*)-**B** allows the electrophilic trapping at the more sterically accessible O1 position, thus affording the 1,4-acylboration product **2**.



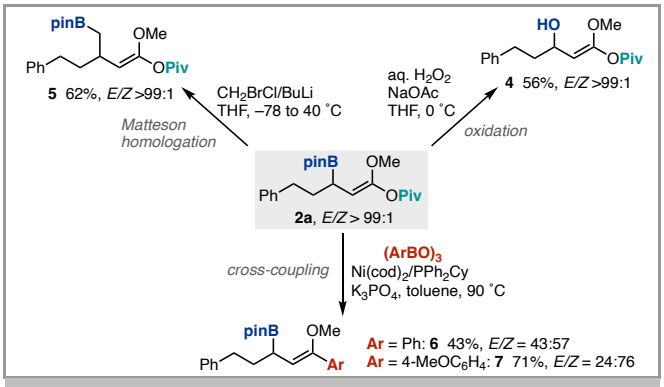
Scheme 4 Copper-catalyzed 1,4-acylboration of various α,β-unsaturated esters **1**. *Reagents and conditions*: $Cu(OAc)_2$ (10 mol%, 0.025 mmol), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20 mol%, 0.050 mmol), **1a** (0.25 mmol), B_2pin_2 (0.63 mmol), Piv_2O (0.38 mmol), KOPiv (0.75 mmol), CPME (1.0 mL), rt, 18 h, N_2. Isolated yields are shown. [a] On a 2.0 mmol scale. [b] With **1k** (0.50 mmol), Piv_2O (0.25 mmol), CsOPiv, and toluene.



Scheme 5 Proposed reaction mechanism: electrophile-dependent 1,4-acylboration vs 3,4-acylboration.

We finally attempted derivatizations of the (γ,γ-dioxyallyl)boronate **2a** (Scheme 6). The oxidation with aq. H_2O_2 under acetate buffer conditions[4] furnished the corresponding allylic alcohol **4** with maintenance of the ketene acetal moiety, which can be a good synthetic handle for further manipulations.[11] Matteson homologation[12] could also be conducted to afford the functionalized homoallylic boronate **5** in 62% yield. The nickel-catalyzed C–O cross-coupling reaction[13] with the arylboroxine proceeded to give the vinyl ethers **6** and **7** with the Bpin function left intact albeit with some erosion of the *E/Z* stereochemistry.

In conclusion, we have developed an approach to a new class of allylboronates, (γ,γ-dioxyallyl)boronates, by using a copper-catalyzed boryl conjugated addition to α,β-unsaturated esters.[14] The regioselective electrophilic trapping with Piv_2O at the O atom in a β-borylated copper enolate intermediate allows the first successful synthesis; there is no preparative method for such boronates in the literature, to the best of our knowledge. Some preliminary functionalizations of newly obtained (γ,γ-dioxyallyl)boronate are also demonstrated. Additional synthetic applications such as an allylboration of carbonyls[15] and catalytic asymmetric synthesis[16] are now under investigation in our laboratory.



Scheme 6 Transformations of (γ,γ-dioxyallyl)boronate **2a**.

Funding Information

This work was supported by JSPS KAKENHI Grants. JP 22J10951 (Grant-in-Aid for JSPS Research Fellow to S.N.) and JP 22H02077 [Grant-in-Aid for Scientific Research(B) to K.H.] as well as by the JST FOREST Program (Grant JPMJFR211X to K.H.).

Supporting Information

YES

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References and Notes

(1) (a) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, **1988**. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Davison, M.; Hughes, A. K.; Marder, T. B.; Wade, K. *Contemporary Boron Chemistry*; The Royal Society of Chemistry: Cambridge, U.K., **2000**. (d) Hall, D. G. Ed. *Boronic Acids*, 2nd ed.; Wiley-VCH: Weinheim, Germany, **2011**. (e) Huo, H.-H.; Duvall, J. R.; Huang, M.-Y.; Hong, R. *Org. Chem. Front.* **2014**, *1*, 303. (f) Diner, C.; Szabó, K. J. *J. Am. Chem. Soc.* **2017**, *139*, 2. (g) Clement, H.; Hall, D. G. Recent Advances in the Stereoselective Additions of Allylic Boronates to Carbonyl Compounds in *Organoboron Compounds (2019), PATAI'S Chemistry of Functional Groups.*: John Wiley & Sons.

(2) (a) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1981**, *22*, 5263. (b) Wuts, P. G. M.; Bigelow, S. S *J. Org. Chem.* **1982**, *47*, 2498. (c) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535. (d) Muñoz-Hernández, L.; Soderquist, J. A. *Org. Lett.* **2009**, *11*, 2571.

(3) (a) Moriya, T.; Suzuki, A.; Miyaura, N. *Tetrahedron Lett.* **1995**, *36*, 1887. (b) Yamamoto, Y.; Miyairi, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem.* **1999**, *64*, 296. Hall also reported the related palladium-catalyzed olefin isomerization and consecutive allylic borylation of alkenyl triflates. (c) Lessard, S.; Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 9612.

(4) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308.

(5) (a) Yamamoto, Y.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am. Chem. Soc.* **2014**, *136*, 16515. (b) Takenouchi, Y.; Kojima, R.; Momma, R.; Ito, H. *Synlett* **2017**, *28*, 270.

(6) Nishino, S.; Hirano, K. *Asian J. Org. Chem.* **2023**, *12*, e202200636.

(7) In the case with $(i\text{PrCO})_2O$, the Piv group derived from CsOPiv was also incorporated into the product, and the Piv-derived 1,4-acylboration product was also detected in ca. 5% ^{1}H NMR yield. We also tried the reaction with a 1:1 mixture of Piv_2O and Ac_2O. The corresponding Piv- and Ac-derived 1,4-acylboration products were formed in 21% and 2%, yields, respectively. Additionally, the protoboration byproduct **3a** was also detected in 40% yield. Given that **3a** mainly arose from the Ac-derived 1,4-acylboration product via in-situ hydrolysis, the electrophilic trapping ability of Ac_2O is higher than that of Piv_2O.

(8) We also monitored the reaction progress of **1k** in toluene-d_8 by ^{1}H NMR spectroscopy, but **2k'** was the primary product under the catalytic conditions: any acyl migration from **2k** to **2k'** was not observed. See the Supporting Information for details and a related paper: Zeng, L.; Lai, Z.; Cui, S. *J. Org. Chem.* **2018**, *83*, 14834.

(9) For pioneering work, see: (a) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982. For recent reviews, see: (c) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Tetrahedron* **2015**, *71*, 2183. (d) Hemming, D.; Fritzemeier, R.; Westcott, S. A.; Santos, W. L.; Steel, P. G. *Chem. Soc. Rev*. **2018**, *47*, 7477. (e) Xue, W.; Oestreich, M. *ACS Cent. Sci.* **2020**, 6, 1070. (f) Fujihara. T. *Asian J. Org. Chem.* **2022**, *11*, e202200535. (g) Das, K. K.; Mahato, S.; Hazra, S.; Panda, S. *Chem. Rec.* **2022**, *22*, e202100290.

(10) (a) Whiting, A. *Tetrahedron Lett.* **1991**, *32*, 1503. (b) Mears, R. J.; Whiting, A. *Tetrahedron,* **1993**, *49*, 177. (c) Conole, G.; Mears, R. J.; De Silva, H.; Whiting, A. *J. Chem. Soc. Perkin Trans. 1*, **1995**, 1825. (d) Mears, R. J.; Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3250. (e) Sailes, H. E.; JWatts, . P.; Whiting, A. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3362. (f) Zhan, M.; Ding, Z.; Du, S.; Chen, H.; Feng, C.; Xu, M.; Liu, Z.; Zhang, M.; Wu, C.; Lan, Y.; Li, P. *Nat. Commun*. **2020**, *11*, 792. (g) Zuo, Y.-J.; Chang, X.-T.; Hao, Z.-M.; Zhong, C.-M. *Org. Biomol. Chem.* **2017**, *15*, 6323. (h) Zuo, Y.-J.; Zhong, Z.; Fan, Y.; Li, X.; Chen, X.; Chang, Y.; Song, R.; Fu, X.; Zhang, A.; Zhong, C.-M. *Org. Biomol. Chem*. **2018**, *16*, 9237. (i) Bi, Y.-P.; Wang, H.-M.; Qu, H.-Y.; Liang, X.-C.; Zhou, Y.; Li, X.-Y.; Xu, D.; Shen, M.-H.; Xu, H.-D. *Org. Biomol. Chem.* **2019**, *17*, 1542. (j) Larin, E. M.; Loup, J.; Polishchuk, I.; Ross, R. J.; Whyte, A.; Lautens, M. *Chem. Sci*. **2020**, *11*, 5716. (k) Nishino, S.; Nishii, Y.; Hirano, K. *Chem. Sci*. **2022**, *13*, 14387.

(11) McElavin, S. M. *Chem. Rev.* **1949**, *45*, 453.

(12) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535.

(13) Yin, J.; Bai, Y.; Mao, M.; Zhu, G. *J. Org. Chem.* **2014**, *79*, 9179.

(14) **Experimental Procedures and Characterization Data**

Synthesis of 2a (Scheme 4, 0.25 mmol scale)

$Cu(OAc)_2$ (4.5 mg, 0.025 mmol), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (33.5 mg, 0.050 mmol), and KOPiv (105.2 mg, 0.75 mmol) were placed in a 20 mL Schlenk tube, which was filled with nitrogen by using the Schlenk technique. CPME (1.0 mL) was then added to the tube, and the suspension was stirred for 15 min at ambient temperature. Bis(pinacolato)diboron (158.7 mg, 0.63 mmol) was then added in one portion, and the resulting solution was stirred at the same temperature. After 5 min, pivalic anhydride (69.8 mg, 0.38 mmol) and methyl (*E*)-5-phenylpent-2-enoate (**1a**, 40.5 mg, 0.25 mmol) were added dropwise. The reaction solution was stirred at room temperature for additional 18 h. The resulting mixture was directly filtered through a short pad of neutral alumina and Na_2SO_4. The filtrate was evaporated in vacuo and purified by silica gel column chromatography on neutral silica gel with hexane/ethyl acetate (20/1 → 10/1, v/v) and GPC ($CHCl_3$) to give 1-methoxy-5-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-1-yl pivalate (**2a**, 82.5 mg, 0.21 mmol) in 82% yield with >99:1 *E*/*Z* ratio.

(*E*)-1-Methoxy-5-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-1-en-1-yl pivalate ((*E*)-2a)

82.5 mg (82%); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.23 (m, 2H), 7.21-7.19 (m, 2H), 7.15 (t, *J* = 7.1 Hz, 1H), 4.34 (d, *J* = 9.9 Hz, 1H), 3.55 (s, 3H), 2.74 (ddd, *J* = 13.6, 10.5, 5.4 Hz, 1H), 2.59 (ddd, *J* = 13.6, 10.4, 6.0 Hz, 1H), 2.09-2.03 (m, 1H), 1.89-1.80 (m, 1H), 1.73-1.65 (m, 1H), 1.28 (s, 9H), 1.25 (s, 12H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 176.5, 150.6, 142.9, 128.7, 128.3, 125.6, 98.2, 83.3, 57.1, 39.1, 35.4, 33.4, 27.2, 24.9, 24.8, 20.5 (broad); ^{11}B NMR ($CDCl_3$, 128 MHz): δ 32.7; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{23}H_{36}BO_5$: 403.2654, found: 403.2666.

(15) We preliminary tested several reported conditions, including simple heating, $Sc(OTf)_3$ catalyst, and $ZnBr_2$ catalyst, for the allylation of benzaldehyde with **2a**, **6**, and **7**. However, the allylic boronates just decomposed, and the corresponding homoallylic alcohols were not detected at all. Additional investigations are still necessary.

(16) We preliminary tried enantioselective conditions using several chiral phosphine ligands. However, the maximum enantiomeric ratio was 75:25 with a phosphoramidite ligand. See the Supporting Information for more details.