A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: A Copper(I)-Catalyzed Enantioselective γ-Boryl Substitution of Trifluoromethyl-substituted Alkenes: Synthesis of Enantioenriched γ,γ-gem-Difluoroallylboronates

Authors: Ryoto Kojima, Sota Akiyama, and Hajime Ito

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201803663
Angew. Chem. 10.1002/ange.201803663

Link to VoR: http://dx.doi.org/10.1002/anie.201803663
http://dx.doi.org/10.1002/ange.201803663

WILEY-VCH

10.1002/anie.201803663

WILEY-VCH

COMMUNICATION

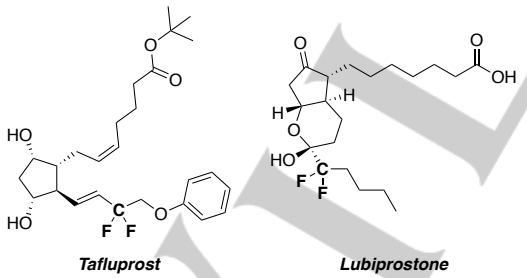
A Copper(I)-Catalyzed Enantioselective γ-Boryl Substitution of Trifluoromethyl-substituted Alkenes: Synthesis of Enantioenriched γ,γ-*gem*-Difluoroallylboronates

Ryoto Kojima, Sota Akiyama and Hajime Ito*[a]

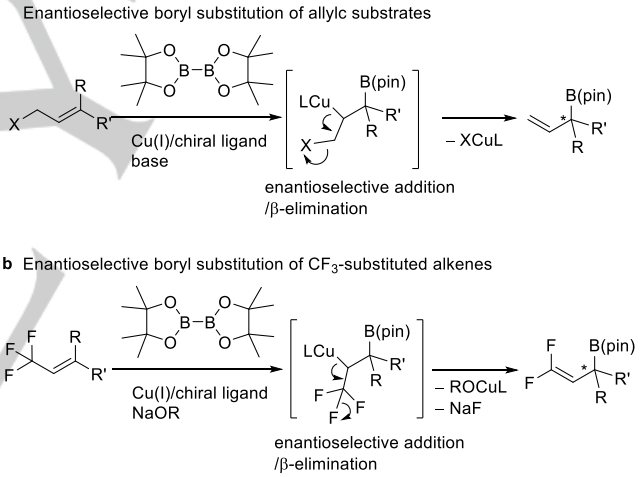
Abstract: The first catalytic enantioselective γ-boryl substitution of CF_3-substituted alkenes is reported. A series of CF_3-substituted alkenes was treated with a diboron reagent in the presence of a copper(I)/Josiphos catalyst to afford the corresponding optically active γ,γ-*gem*-difluoroallylboronates in high enantioselectivity. The thus obtained products could be readily converted into the corresponding difluoromethylene-containing homoallylic alcohols using highly stereospecific allylation reactions.

The selective synthesis of fluorinated compounds is one of the most important research subjects in pharmaceutical and agrochemical science, as the molecular properties of substrates change dramatically upon the introduction of fluorine atom(s).[1] Similar to the trifluoromethyl group (-CF_3), the introduction of the difluoromethylene (-CF_2-) group often induces beneficial effects to biologically active target molecules, and a variety of difluoromethylene-containing drugs and agrochemicals, such as Tafluprost and Lubiprostone, has been developed (Figure 1).[2] In the area of pharmaceutical science, the demand for optically active organic compounds has increased steadily, and enantioselective difluoromethylation methods have been developed accordingly.

Figure 1. Representative Bioactive *gem*-Difluoromethylene-containing Molecules.



Several approaches have been reported that generate a chiral center at the same time. For example, the enantioselective addition of fluorinated nucleophiles to carbonyl compounds is a powerful approach to generate alcohols. Early studies on the enantioselective addition of trifluoromethyl nucleophiles (CF_3Nu) to carbonyl compounds have been reported by e.g. Feng,[3] Mukaiyama,[4] and Shibata[5], and many others.[6] The enantioselective addition of difluoromethyl nucleophiles (CHF_2Nu) to carbonyl compounds is limited to one case reported by Hu and co-workers that proceeded in moderate enantioselectivity (up to 64% ee).[7] Jacobsen has recently reported a unique catalytic method for the asymmetric difluorination of alkenes to generate difluoromethylated stereocenters.[8]



Scheme 1. Catalytic Enantioselective Synthesis of Allyl Boronates

Asymmetric copper-catalyzed borylations represent a powerful tool for the synthesis of optically active organoboron compounds.[9] We and other groups have reported the asymmetric synthesis of allylboron compounds via the asymmetric boryl substitution of allylic compounds (Scheme 1a).[10] The allylboration of aldehydes with enantio-enriched allylboronates generally proceeds in a highly stereospecific manner.[11] The reaction mechanism should include the enantioselective addition of a borylcopper intermediate and the β-elimination of the heteroatom and the copper moiety. In 2011, Hoveyda and co-workers reported *N*-heterocyclic carbene/copper(I)-catalyzed borylations of an α-(trifluoromethyl)styrene derivative that produce an achiral β,β-difluorostyrene derivative, wherein the β-fluorine elimination is involved in the catalytic cycle.[12,13] Recently, Zhou and co-workers have reported the synthesis of γ,γ-*gem*-difluoroallylboronates via

[a] Dr. R. Kojima, S. Akiyama and Prof. Dr. H. Ito
Division of Applied Chemistry and Frontier Chemistry Center,
Faculty of Engineering, Hokkaido University
Kita 13 Nishi 8 Kita-ku, Sapporo, Hokkaido 060-8628 (Japan)
E-mail: hajito@eng.hokudai.ac.jp

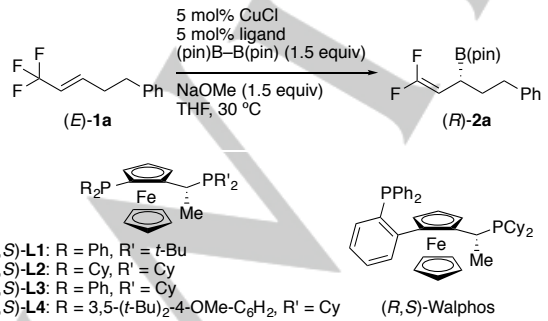
Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201803663

iron-catalyzed boryl substitutions.[14,15] However, to the best of our knowledge, examples for the catalytic enantioselective synthesis of *gem*-difluoroallylboronates have not yet been reported. We anticipated that γ,γ-*gem*-difluoroallylboronates with a chiral C–B bond could potentially be synthesized from CF_3-substituted alkenes via a similar mechanism, provided that the addition of the borylcopper proceeds enantioselectively (Scheme 1b). We hypothesized that this reaction may offer an efficient pathway to stereodefined β,β-difluoro homoallylic alcohols. Herein, we report an enantioselective γ-boryl substitution of CF_3-substituted alkenes with a diboron compound that is catalyzed by a copper(I)/Josiphos catalyst system, and that provides optically active *gem*-difluoroallylboronates. Subsequently, these boronates were converted into the corresponding difluoromethylene-containing homoallylic alcohols via allylation reactions (Scheme 2).

The reaction between CF_3-substituted alkene (*E*)-**1a** and bis(pinacolato)diboron (1.5 equiv) in the presence of a CuCl complex of the Josiphos-type ligand (*R*,*S*)-**L1** (5 mol%) and NaOMe (1.2 equiv) in THF at 30 °C afforded (*R*)-**2a** in high yield (91%) and excellent enantioselectivity (97% ee) (Table 1, entry 1). Upon decreasing the amount of NaOMe to 10 mol%, the boryl substitution scarcely proceeded (Table 1, entry 2). The absolute configuration of the product **2a** was determined by single crystal X-ray structure analysis (Supporting Information p S19–20). When the reaction was conducted at 0 °C, the yield decreased slightly (84%, 97% ee; Table 1, entry 3). Several other Josiphos-type ligands [(*R*,*S*)-**L2**–(*R*,*S*)-**L4**] were also evaluated, but these afforded (*R*)-**2a** in lower enantioselectivity than that obtained in entry 1 (Table 1, entries 4–6). The use of (*R*,*S*)-Walphos also provided (*R*)-**2a** (91% yield), albeit in much lower enantioselectivity than (*R*,*S*)-**L1** (entry 7). The reaction was also evaluated using other types of chiral bisphosphine ligands. The use of (*R*,*R*)-BenzP* and (*R*,*R*)-QuinoxP*, which are effective for enantioselective allylic boryl substitutions,[10] afforded (*R*)-**2a** in lower enantioselectivity than (*R*,*S*)-**L1** (Table 1, entries 8 and 9). The use of (*R*)-Segphos and (*R*,*R*)-Me-Duphos also afforded inferior results (Table 1, entries 10 and 11). Interestingly, the application of the optimum reaction conditions to (*Z*)-**1a** instead of (*E*)-**1a** resulted in a significantly lower enantioselectivity (Table 1, entry 12).

Table 1. Optimization of the Reaction Conditions for the Copper(I)-Catalyzed Enantioselective Boryl Substitution of CF_3-substituted Alkene (*E*)-**1a**.[a]



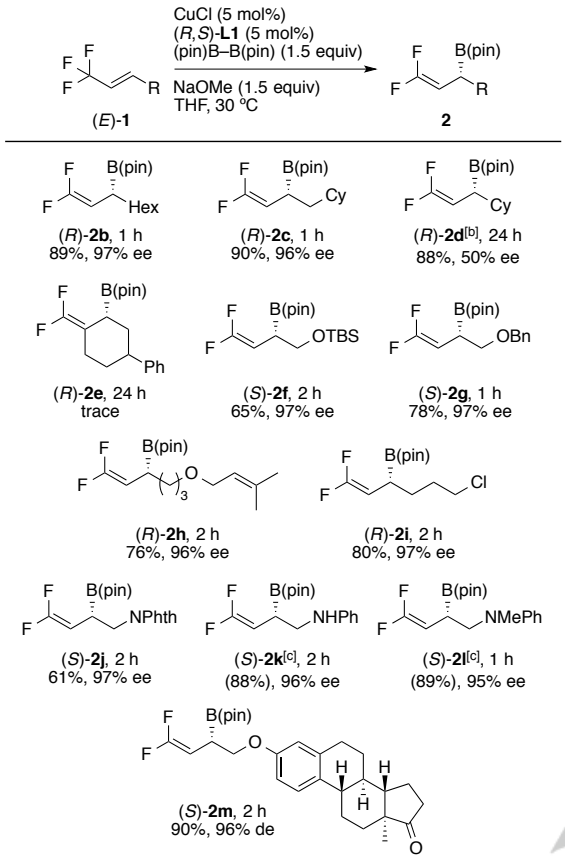
Entry	Chiral Ligand	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	(*R*,*S*)-**L1**	2	91 (85)	97
2[e]	(*R*,*S*)-**L1**	24	<5	–
3[f]	(*R*,*S*)-**L1**	4	84	97
4	(*R*,*S*)-**L2**	2	94	46
5	(*R*,*S*)-**L3**	2	91	96
6	(*R*,*S*)-**L4**	2	89	93
7	(*R*,*S*)-Walphos	1	91	–5
8	(*R*,*R*)-BenzP*	1	90	–84
9	(*R*,*R*)-QuinoxP*	21	80	84
10	(*R*)-Segphos	1	92	50
11	(*R*,*R*)-Me-Duphos	8	92	40
12[g]	(*R*,*S*)-**L1**	2	97	–61

[a] Reagents and conditions: CuCl (0.013 mmol), ligand (0.013 mmol), (*E*)-**1a** (0.25 mmol), bis(pinacolato)diboron (0.38 mmol), and NaOMe (0.38 mmol) in THF (0.5 mL) at 30 ºC. [b] NMR yield. The isolated yield is shown in parentheses. [c] The ee value of (*R*)-**2a** was determined by HPLC analysis of the alcohol derived from the obtained boronate. [d] 0.5 mmol scale. [e] 10 mol% of NaOMe. [f] T = 0 ºC. [g] (*Z*)-**1a** was used as the substrate.

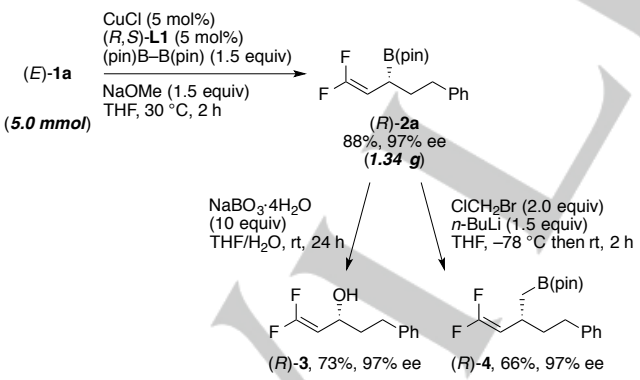
With the optimized conditions in hand, we proceeded to evaluate the substrate scope of this reaction (Table 2). Substrates containing a hexyl or methylcyclohexyl group [(*E*)-**1b**–**c**] also afforded the corresponding products in high yield and excellent enantioselectivity [(*R*)-2**b**: 89% yield, 97% ee; (*R*)-**2c**: 90% yield, 96% ee]. The branched CF_3-substituted alkene (*E*)-**1d**, which is sterically congested around its C=C bond, also smoothly afforded the corresponding product (88% yield, 50% ee). Interestingly, tetra-substituted *gem*-difluoroallylboronate (*R*)-**2e** was not formed, probably due to the steric hindrance. The CF_3-substituted alkenes (*E*)-**1f**–**1h**, which bear benzyl ether, silyl ether, or prenyloxy groups also smoothly furnished the corresponding products in high yield and excellent enantioselectivity [(*S*)-**2f**: 65% yield, 97% ee; (*S*)-**2g**: 78% yield, 97% ee; (*R*)-**2h**: 76% yield, 96% ee]. Substrate (*E*)-**1i**, which contains a chloro group that may engage in copper(I)-catalyzed boryl substitutions, could also be used under these conditions, and the formation of side-products was not detected [(*R*)-**2i**: 80% yield, 97% ee].[16] CF_3-substituted alkenes containing phthalimide [(*E*)-**1j**] or secondary/tertiary amino groups [(*E*)-**1k**–**l**] also furnished the target compounds in high yield and excellent enantioselectivity [(*S*)-**2j**: 61% yield, 97% ee; (*S*)-**2k**: 88% yield, 96% ee; (*S*)-**2l**: 89% yield, 95% ee]. The reaction of estrone-type substrate (*E*)-**1m** provided (*S*)-**2m** in high yield and excellent diastereoselectivity (90% yield, 96% de).

Table 2. Substrate Scope of the Copper(I)-Catalyzed Enantioselective Boryl Substitution of CF_3-substituted Alkene (*E*)-**1**.[a]

10.1002/anie.201803663



[a] Reagents and conditions: CuCl (0.025 mmol), ligand (0.025 mmol), (*E*)-**1** (0.5 mmol), bis(pinacolato)diboron (0.75 mmol), and NaOMe (0.75 mmol) in THF (1 mL) at 30 °C. The ee values of **2** were determined by HPLC analysis after oxidation or esterification. [b] T = 50 °C. [c] NMR yield of the boronate in the crude reaction mixture. The alcohol derivative was isolated after oxidation of the crude reaction mixture [(*S*)-**3k**: 78% isolated yield; (*S*)-**3l**: 70% isolated yield]. TBS = *tert*-butyldimethylsilyl. Phth = phthalimide.

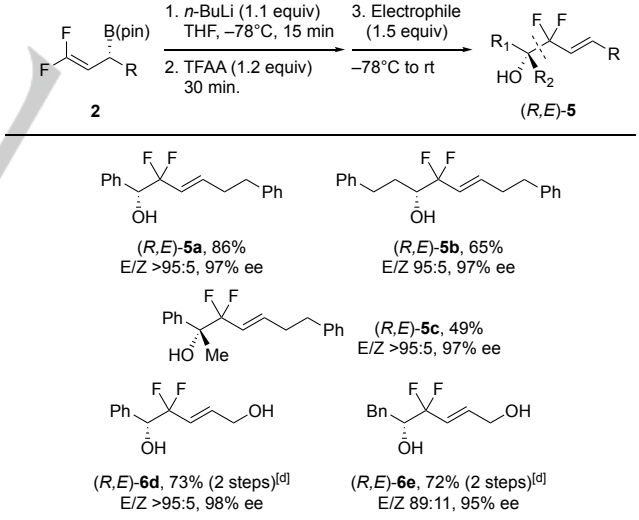


Scheme 2. Gram-Scale Synthesis of Enantioenriched Chiral *gem*-Difluoroallylboronates and Their Subsequent Derivatization.

To demonstrate the synthetic utility of this method, we investigated a gram-scale synthesis of *gem*-difluoroallylboronates (Scheme 2). When the boryl substitution of (*E*)-**1a** was carried out on a 5.0-mmol scale, (*R*)-**2a** was obtained in high yield and excellent enantioselectivity (88%, 97% ee). We also examined the transformation of *gem*-difluoroallylboronates. For that purpose, (*R*)-**2a** was subjected to an oxidation with $NaBO_3$ or to a homologation with a halomethyl lithium reagent.[17,18] These reactions afforded the corresponding alcohol (*R*)-**3** (73%, 97% ee) and homoallylboronate (*R*)-**4** (66%, 97% ee), respectively.

We then investigated the allylation of carbonyls with *gem*-difluoroallylboronate **2** (Table 3). The reaction of (*R*)-**2a** with benzaldehyde, 3-phenylpropionaldehyde, acetaldehyde, and acetophenone using Aggarwal's carbonyl allylation conditions[19] afforded the corresponding homoallylic alcohols [(*R*,*E*)-**5a–c**] in high stereoselectivity and stereospecificity. The absolute configuration of the product **5b** was confirmed by single crystal X-ray structure analysis (Supporting Information p S20–21). The reaction of (*S*)-**2f** with benzaldehyde or phenylacetaldehyde, followed by *t*-butyldimethylsilyl (TBS) deprotection using tetrabutylammonium fluoride (TBAF), provided diols (*R*,*E*)-**6d** and (*R*,*E*)-**6e**, respectively, in high stereoselectivity. Notably, (*R*,*E*)-**6d** and (*R*,*E*)-**6e** are important depsipeptide and dipeptide isostere intermediates. Taguchi and co-workers have reported the diastereoselective synthesis of functionalized (*Z*)-fluoroalkenes using a copper(I)-mediated alkyl transfer reaction and a subsequent oxidation of the primary hydroxyl group of the racemic (*E*)-4,4-difluoro-5-hydroxyallylic alcohol derivatives.[20] The method presented herein represents the first example of an enantioselective boryl substitution/stereoselective allylation sequence that should find further applications in synthetic and medicinal chemistry.

Table 3. Allylation of Carbonyl Compounds with *gem*-Difluoroallylboronate **2**.[a–c]



[a] Reagents and conditions: **2** (0.25 mmol), *n*-BuLi (0.28 mmol), TFAA (0.30 mmol), electrophile (0.38 mmol), in THF (2.5 mL); T= –78 °C → r.t. [b] The *E*/*Z* ratio of the products was determined by ^{1}H NMR spectroscopy and HPLC. [c] Isolated product yields. The ee values of the products were determined by HPLC. [d] The product was isolated after treatment with TBAF/THF. TFAA = trifluoracetic anhydride. TBAF = tetrabutylammonium fluoride.

In conclusion, we have developed the first example of an enantioselective copper(I)-catalyzed γ-substitution of CF_3-substituted alkenes that provides access to optically active γ,γ-*gem*-difluoroallylboronates. The synthetic utility of this borylation/allylboration procedure manifests in e.g. the modular

10.1002/anie.201803663

construction of difluoromethylene scaffolds; the enantioenriched *gem*-difluoroallylboronates can moreover be readily transformed into useful secondary products, such as depsipeptide isosteres.

Acknowledgements

The authors would like to thank Prof. T. Seki and T. Sumitani (Hokkaido University) for their technical assistance with the X-ray crystallographic analysis. This work was financially supported by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) via the "Program for Leading Graduate Schools" (Hokkaido University "Ambitious Leaders Program"), and by the Japan Society for the Promotion of Science via KAKENHI grants 15H03804 and 18H03907.

Keywords: Asymmetric catalysis • Boron • Copper • Fluorine • Synthetic methods

[1] a) D. O'Hagan, H. S. Rzepa, *Chem. Commun*. **1997**, 645; b) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37*, 320-330.

[2] D. O'Hagan, Y. Wang, M. Skibinski, A. M. Z. Slawin, *Pure Appl. Chem.* **2012**, *84*, 1587.

[3] H. Zhao, B. Qin, X. Liu, X. Feng, *Tetrahedron* **2007**, *63*, 6822.

[4] H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Lett*. **2007**, *36*, 666.

[5] S. Mizuta, N. Shibata, S. Akiti, H. Fujimoto, S. Nakamura, T. Toru, *Org. Lett.* **2007**, *9*, 3707.

[6] For other examples of enantioselective trifluoromethylation reactions, see: a) N. Shibata, S. Mizuta, H. Kawai, *Tetrahedron*: *Asymmetry* **2008**, *19*, 2633; b) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev*. **2015**, *115*, 826.

[7] C. Ni, F. Wang, J. Hu, *Beilstein J. Org. Chem.* **2008**, *4*, DOI: 10.3762/bjoc.4.21.

[8] a) S. M. Banik, J. W. Medley, E. N. Jacobsen, *Science* **2016**, *353*, 51; b) S. Sasaki, T. Yamauchi, M. Kanai, A. Ishii, K. Higashiyama, *Bull. Chem. Soc. Jpn.* **2015**, *88*, 200.

[9] For selected examples of copper(I)-catalyzed borylation reactions, see: a) H. Ito, H. Yamanaka, J. Tateiwa, A. Hosomi, *Tetrahedron Lett.* **2000**, *41*, 6821; b) K. Takahashi, T. Ishiyama, N. Miyaura, *Chem. Lett.* **2000**, 982; c) H. Ito, C. Kawakami, M. Sawamura, *J. Am. Chem. Soc*. **2005**, *127*, 16034; d) C. Kleeberg, L. Dang, Z. Lin, T. B. Marder, *Angew. Chem., Int. Ed.* **2009**, *48*, 5350; *Angew. Chem.* **2012**, *124*, 543; e) T. Itoh, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc*. **2016**, *138*, 7528; f) K. Kato, K. Hirano, M. Miura, *Angew. Chem., Int. Ed.* **2016**, *55*, 14400; *Angew. Chem.* **2016**, *128*, 14612; g) T. Fujihara, A. Sawada, T. Yamaguchi, Y. Tani, J. Terao, Y. Tsuji, *Angew. Chem., Int. Ed.* **2017**, *56*, 1539; *Angew. Chem.* **2017**, *129*, 1561; h) N. Kim, J. T. Han, D. H. Ryu, J. Yun, *Org. Lett.* **2017**, *19*, 6144; i) J. Lee, S. Radomkit, S. Torker, J. der Pozo, A. H. Hoveyda, *Nat. Chem.* **2018**, *10*, 99; j) B. Chen, P. Cao, Y. Liao, M. Wang, J. Liao, *Org. Lett.* **2018**, *20*, 1346; k) J. Royes, S. Ni, A. Farré, E. L. Cascia, J. J. Carbó, A. B. Cuenca, F. Maseras, E. Fernández, *ACS Catal.* **2018**, *8*, 2833; For a recent review on secondary boronates, see: l) B. S. L. Collins, C. M. Wilson, E. L. Myers, V. K. Aggarwal, *Angew. Chem., Int. Ed.* **2017**, *56*, 11700; *Angew. Chem.* **2017**, *129*, 11860.

[10] a) H. Ito, S. Ito, Y. Sasaki, K. Matsuura, M. Sawamura, *J. Am. Chem. Soc.* **2007**, *129*, 14856; b) H. Ito, T. Okura, K. Matsuura, M. Sawamura, *Angew. Chem., Int. Ed.* **2010**, *49*, 560; *Angew. Chem.* **2010**, *122*, 570; c) H. Ito, S. Kunii, M. Sawamura, *Nat. Chem.* **2010**, 2, 972; d) A. Guzman-Martinez, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10634; e) J. K. Park, H. H. Lackey, B. A. Ondrusek, D. T. McQuade, *J. Am. Chem. Soc.* **2011**, *133*, 2410; f) H. Ito, T. Miya, M. Sawamura, *Tetrahedron* **2012**, *68*, 3423; g) E. Yamamoto, Y. Takenouchi, T. Ozaki, T. Miya, H. Ito, *J. Am. Chem. Soc.* **2014**, *136*, 16515; h) L. J. Mao, K. J. Szabo, T. B. Marder, *Org. Lett.* **2017**, *19*, 1204; i) Y. Takenouchi, R. Kojima, R. Momma, H. Ito, *Synlett* **2017**, *28*, 270.

[11] a) *Boronic Acids: Preparation and Applications in Organic synthesis, Medicine and Materials*, 2nd revised ed.; D. G. Hall, Ed.; Wiley-VCH: Weinheim, 2011; b) C. Diner, K. J. Szabó, *J. Am. Chem. Soc.* **2017**, *139*, 2.

[12] R. Corberán, N. W. Mszar, A. H. Hoveyda, *Angew. Chem., Int. Ed.* **2011**, *50*, 7079; *Angew. Chem.* **2011**, *123*, 7217.

[13] For selected recent examples on copper(I)-catalyzed defluoroborylation reactions, see: a) R. Kojima, K. Kubota, H. Ito, *Chem. Commun*. **2017**, *53*, 10688; b) H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi, T. Hosoya, *J. Am. Chem. Soc*. **2017**, *139*, 12855; c) J. Zhang, W. Dai, Q. Liu, S. Cao, *Org. Lett*. **2017**, *19*, 3283; d) J. Hu, X. Han, Y. Yuan, Z. Shi, *Angew. Chem., Int. Ed.* **2017**, *56*, 13342; *Angew. Chem.* **2017**, *129*, 13527; e) D.-H. Tan, E. Lin, W.-W. Ji, Y.-F. Zeng, W.-X. Fan, Q. Li, H. Gao, H. Wang, *Adv. Synth. Catal.* **2018**, *360*, 1032.

[14] Y. Liu, Y. Zhou, Y. Zhao, J. Qu, *Org. Lett.* **2017**, *19*, 946.

[15] For stoichiometric preparation methods of *gem*-difluoroallylboronates, see: a) P. V. Ramachandran, A. Chatterjee, *Org. Lett*. **2008**, *10*, 1195. b) B. Zhang, X. Zhang, *Chin. J. Chem.* **2016**, *34*, 477. c) P. V. Ramachandran, A. Tafelska-Kaczmarek, A. Chatterjee, *J. Org. Chem.* **2012**, *77*, 9329.

[16] a) H. Ito, K. Kubota, *Org. Lett.* **2012**, *14*, 890; b) C.-T. Yang, Z.-Q. Zhang, H. Tajuddin, C.-C. Wu, J. Liang, J.-H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder, L. Liu, *Angew. Chem., Int. Ed*. **2012**, *51*, 528; *Angew. Chem.* **2012**, *124*, 543.

[17] . W. Kabalka, T. M. Shoup, N. M. Goudgaon, *J. Org. Chem.* **1989**, *54*, 5930.

[18] K. M. Sadhu, D. S. Matteson, *Organometallics* **1985**, *4*, 1687.

[19] a) J. L.-Y. Chen, H. K. Scott, M. J. Hesse, C. L. Willis, V. K. Aggarwal, *J. Am. Chem. Soc.* **2013**, *135*, 5316; b) J. L.-Y. Chen, V. K. Aggarwal, *Angew. Chem., Int. Ed.* **2014**, *53*, 10992; *Angew. Chem.* **2014**, *126*, 11172.

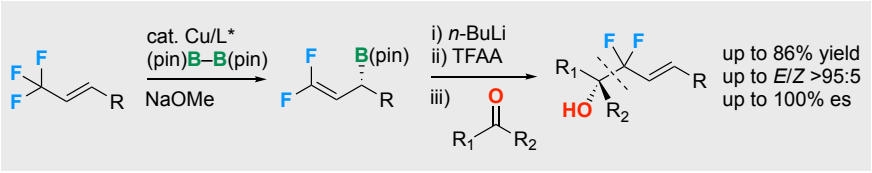
[20] a) M. Okada, Y. Nakamura, A. Saito, A. Sato, H. Horikawa, T. Taguchi, *Tetrahedron Lett.* **2002**, *43*, 5845; b) M. Okada, Y. Nakamura, A. Saito, A. Sato, H. Horikawa, T. Taguchi, *Chem. Lett.* **2002**, *31*, 28; c) Y. Nakamura, M. Okada, A. Sato, H. Horikawa, M. Koura, A. Saito, T. Taguchi, *Tetrahedron* **2005**, *61*, 5741.

10.1002/anie.201803663

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



The first catalytic enantioselective γ-boryl substitution of CF_3-substituted alkenes was accomplished by treatment of a series of CF_3-substituted alkenes with a diboron reagent in the presence of a copper(I)/Josiphos catalyst, which afforded the corresponding optically active γ,γ-*gem*-difluoroallylboronates in high yield and enantioselectivity.

*Ryoto Kojima, Sota Akiyama and Hajime Ito**

Page No. – Page No.

A Copper(I)-Catalyzed Enantioselective γ-Boryl Substitution of Trifluoromethyl-substituted Alkenes: Synthesis of Enantioenriched γ,γ-gem-Difluoroallylboronates