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**Development of Copper(I)-Catalyzed
Synthesis of Functionalized Organofluorine
and Organoboron Compounds**

Ryoto Kojima

2018

Contents

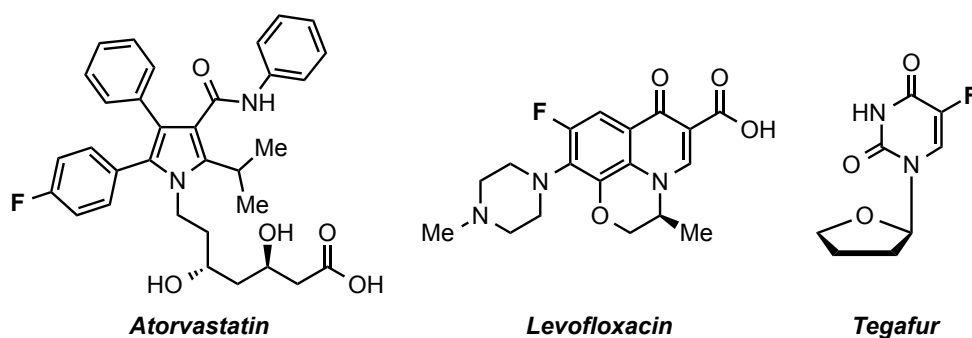
	General Introduction	2
Chapter 1.	Copper(I)-Catalyzed Stereodivergent Hydrodefluorination of <i>gem</i> -Difluoroalkenes	13
Chapter 2.	Copper(I)-Catalyzed Enantioselective γ -Boryl Substitution of Trifluoromethyl Alkenes	49
Chapter 3.	Copper(I)-Catalyzed Diastereoselective Borylative <i>Exo</i> -Cyclization of Alkenyl Aryl Ketones	94
	List of Publications	122
	Acknowledgments	123

General Introduction

1. Organofluorine Compounds

Organofluorine compounds have attracted considerable interest because of their unique physical properties or bioactivities in fields such as medicine, agrichemicals and electronic materials. By introducing a fluorine atom into a molecule, it brings many merits such as improving the lipophilicity of the molecule. In fact, 20% of pharmaceuticals and 30% of agricultural chemicals contain fluorine atoms.¹ Various fluorine-containing bioactive compounds such as atorvastatin, an HMG-CoA reductase inhibitor fluorine, levofloxacin, an antibacterial fluoroquinolone, and tegafur, an antitumor fluoronucleoside, have been reported (Figure 1).

Figure 1. Fluorine-containing bioactive compounds.

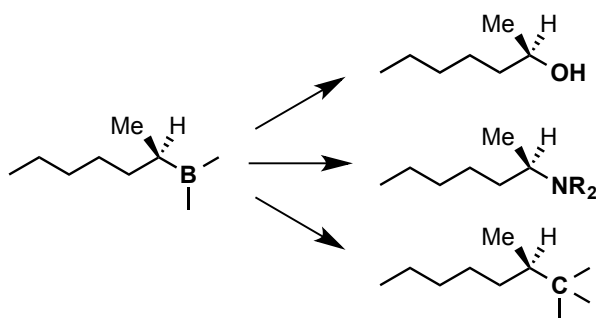


By the way, almost no fluorine-containing organic compound exist in nature. Therefore, fluorination at a stage of synthesis is required. Various fluorination reactions and fluorination reagents have been developed so far, but development of a currently efficient and highly selective synthesis method is still desired.

2. Organoboron Compounds

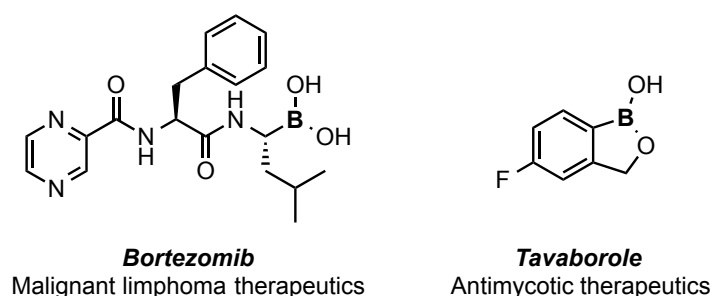
Organoboron compounds are widely used in the field of organic synthesis. Although many organometallics compounds such as Grignard reagents and organolithium compounds used in synthetic reactions require special care in handling and storage, organoboronate esters normally show reasonable stability under normal atmospheric conditions. When an appropriate activation procedure is adopted, the organoboronate esters are also sufficiently reactive for use in organic synthesis. The carbon-metal bonds in the organoboron compounds are shorter than the carbon-metal bonds in the other organometallic reagents, which generally provided high stereoselectivity as a result of the tight transition states in the selectivity-determining step. Many stereoselective reactions can be carried out with organoboron compounds under mild conditions, making them very attractive reagents. Enantioenriched alkylboronate esters are the most important class of organoboron compounds because they undergo stereospecific reaction of stereogenic C–B bonds forming C–O, C–N, or C–C bonds (Figure 2).²

Figure 2. Stereospecific transformations of enantioenriched alkylboronate esters.



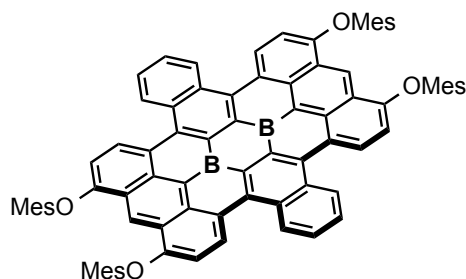
In addition to their great synthetic utility, organoboron compounds have been used in other fields, such as medicinal chemistry.³ For examples, chiral boronic acid Bortezomib has been widely used as malignang lymphoma therapeutics. Futhermore, Tavaborole has been known to show an antimycotic property (Figure 3).

Figure 3. Boron-containing pharmaceutical drugs.



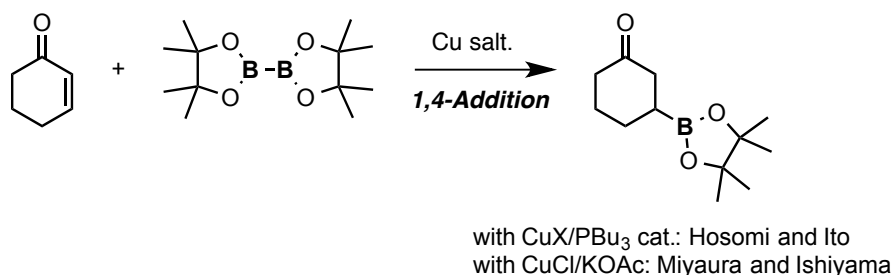
Recently, organoboron compound has been utilized in material chemistry because the optical properties can be controlled by π -accepter character of a boryl group. For examples, nanographene molecule, bearing two boron atoms at the central positions has been reported to be an active material for Li battery electrodes.⁴

Figure 4. Selected example for boron-doped nanographene.



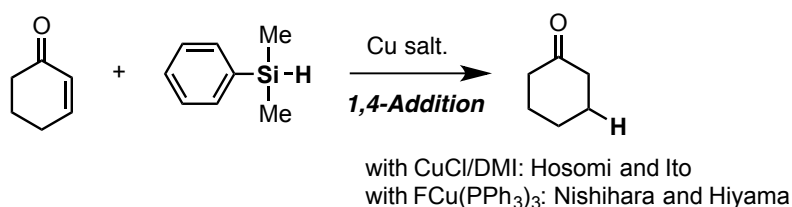
In 2000, Hosomi and Ito reported the borylation reaction of α,β -unsaturated carbonyl compounds using copper(I)/diboron catalytic system, which provided the corresponding 1,4-boryl addition products (Scheme 1).⁵ As for this reaction, Miyaura and Ishiyama also reported the similar reaction at the same time.⁶

Scheme 1. Copper(I)-catalyzed borylation of conjugated enones.



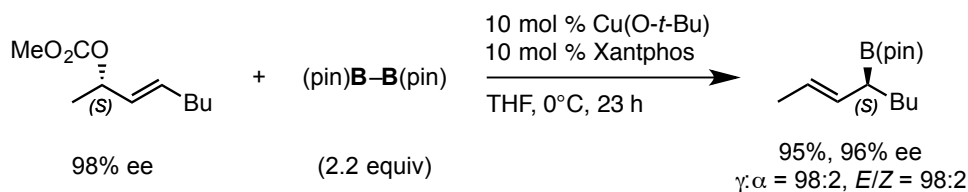
In 1997, the reduction of α,β -unsaturated carbonyl compounds using copper(I)/hydrosilane system, which provided the corresponding saturated ketones, were also developed by Hosomi and Ito, and Nishihara and Hiyama groups independently (Scheme 2).^{6,7} These reactions are the first examples of activation of a Si–H bond with a copper(I) salt to generate copper(I) hydride species. After that, Ito and Sawamura utilized this catalyst system for dehydrogenative alcohol silylation in 2005.⁸

Scheme 2. Copper(I)-mediated reduction of conjugated enones.



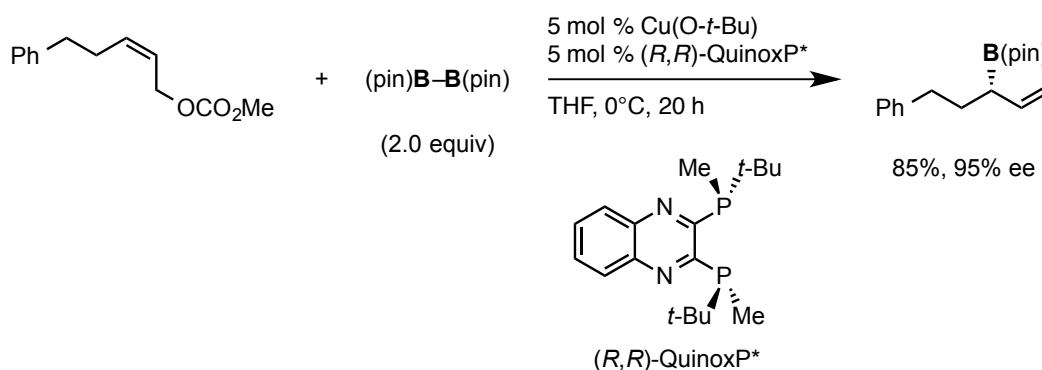
Since 2005, Ito and Sawamura reported various asymmetric or non-asymmetric borylations using copper(I)/diboron catalyst system. The reaction of allylic carbonates and diboron in the presence of Cu(O-*t*-Bu)/Xantphos catalyst proceeded to give the corresponding allylboronate esters with almost complete chirality transfer and γ -selectivity (Scheme 3).⁹ The observed stereochemical outcome can be explained by the *anti*-attack of the borylcopper to an allyl carbonate in a conformation that avoids an allylic 1,3-strain.

Scheme 3. Copper(I)-catalyzed stereospecific boryl substitution of allylic carbonates.



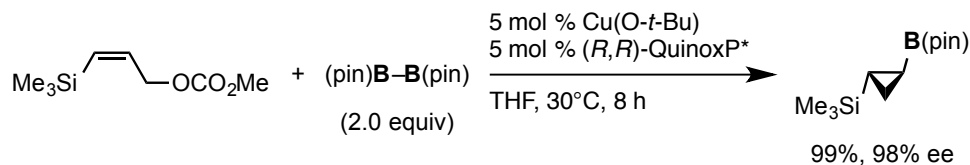
Enantioselective boryl substitution was achieved with chiral bisphosphine ligand.¹⁰ The reaction of (*Z*)-allylic carbonate with diboron using the copper(I)/(*R,R*)-QuinoxP* catalyst afforded the corresponding optically active allylboronate with high enantiomeric excess (Scheme 4). This enantioselective boryl substitution was applied to desymmetrization of *meso*-1,4-diol derivatives, direct enantio-convergent of racemic substrates and so on.^{11,12}

Scheme 4. Copper(I)-catalyzed enantioselective boryl substitution of allylic carbonates.



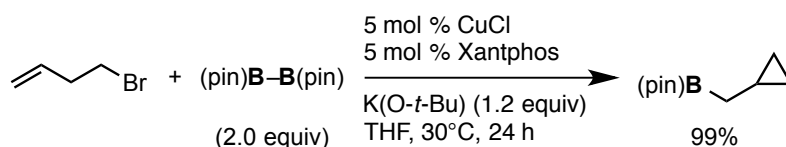
In 2008, Ito and Sawamura reported a drastic product switch from allyl boronates to cyclopropylboronates when allylic carbonates with a γ -silicon substituent were employed instead of alkyl-substituted ones (Scheme 5).¹³ Similar types of borylative *endo*-cyclizations using aryl-substituted allylic phosphates and homoallylic sulfonates were also reported.^{14,15}

Scheme 5. Copper(I)-catalyzed borylative *endo*-cyclization of silyl-substituted allylic carbonates.



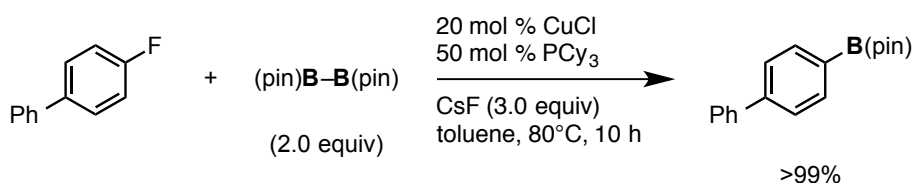
Borylative cyclization of alkenyl halide containing unactivated double bond was also achieved in 2013 (Scheme 6).¹⁶ This is the first example of copper(I)-catalyzed borylation of unactivated terminal alkenes. The reaction includes the regioselective addition of a boryl copper(I) intermediate to terminal alkenes, followed by intramolecular substitution of the resulting alkylcopper(I) moiety for the halide leaving groups.

Scheme 6. Copper(I)-catalyzed borylative *exo*-cyclization of alkenyl halides.



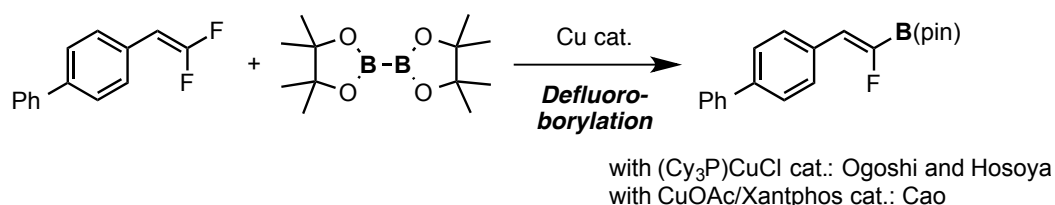
Copper(I)/diboron catalyst system was also effective for defluoroborylation. Niwa and Hosoya reported defluoroborylation of fluoroarenes using nickel(0)/copper(I) cocatalyst system.¹⁷ After that, they also found that this reaction proceeded in the absence of nickel(0) catalyst (Scheme 7).¹⁸ This result indicates the possibility of achieving efficient defluoroborylation using a copper(I) catalyst alone.

Scheme 7. Copper(I)-catalyzed defluoroborylation of fluoroarenes.



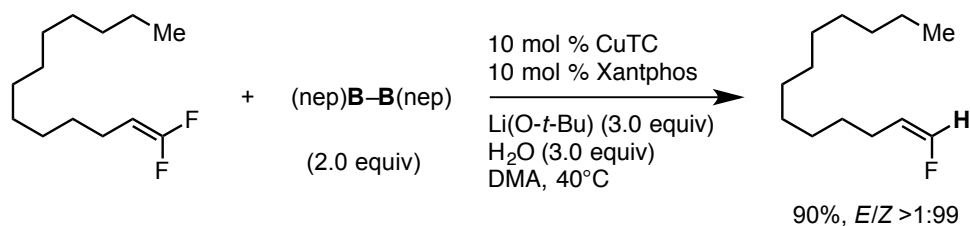
During the preparation of author's work about Chapter 1, Ogoshi and Hosoya group reported stereoselective defluoroborylation of aromatic *gem*-difluoroalkenes, which provided the corresponding monofluoroalkenyl boronate esters (Scheme 8).¹⁹ As for this reaction, Cao and co-workers also reported similar reactions at the same time.²⁰

Scheme 8. Copper(I)-catalyzed stereoselective defluoroborylation of aromatic *gem*-difluoroalkenes.



At the same time as the acceptance of authos's paper about Chapter 1, Shi and co-workers reported stereoselective hydrodefluorination of *gem*-difluoroalkenes, which provided the corresponding terminal monofluoroalkenes (Scheme 9).²¹ This reaction proceeds through a copper(I)-catalyzed defluoroborylation/deborylation pathway.

Scheme 9. Copper(I)-catalyzed stereoselective hydrodefluorination of *gem*-difluoroalkenes.

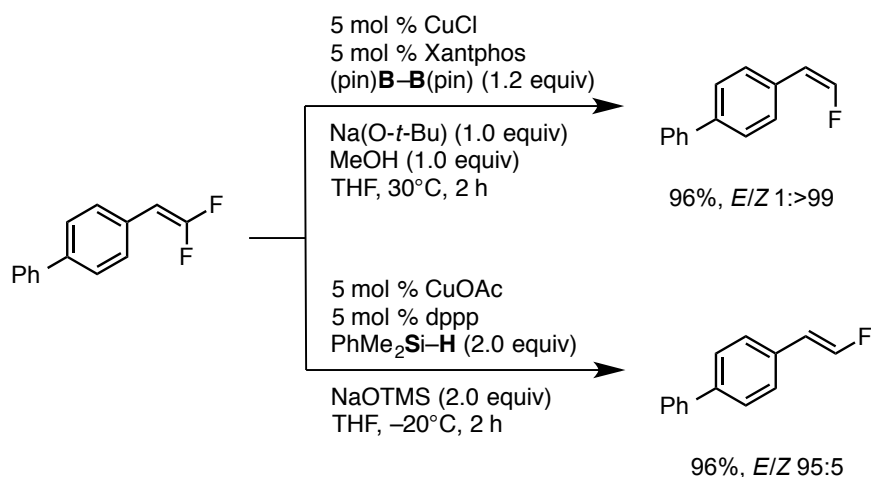


3. Overview of This Thesis

The author also focuses on the reactivity of borylcopper(I) or copper(I) hydride complex and pursues the development of novel catalytic reactions based on the above results. This thesis describes several new types of reactions for organofluorine and organoboron synthesis: stereodivergent hydrodefluorination of *gem*-difluoroalkenes (Chapter 1), enantioselective γ -boryl substitution of trifluoromethyl alkenes (Chapter 2) and stereoselective defluoroborylation of alkyl *gem*-difluoroalkenes (Chapter 3).

Chapter 1 describes the stereodivergent hydrodefluorination of *gem*-difluoroalkenes (Scheme 9).²² This reaction involves the regioselective boryl- or hydrocupuration of *gem*-difluoroalkenes, followed by stereoselective fluorine elimination from the resulting alkylcopper(I) intermediates to give the corresponding stereodefined monofluoroalkenes. To elucidate the stereoselectivity-determining step, density functional theory (DFT) calculations have also been conducted.

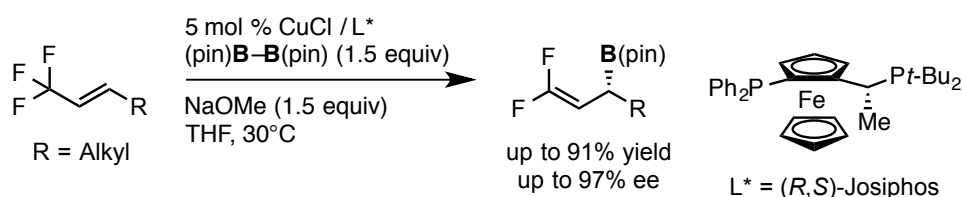
Scheme 9. Copper(I)-catalyzed stereodivergent hydrodefluorination of *gem*-difluoroalkenes.



Chapter 2 describes the first enantioselective γ -boryl substitution of trifluoromethyl alkenes (Scheme 10).²³ A series of trifluoromethyl alkenes reacted with a diboron compound in the presence of a copper(I)/Josiphos

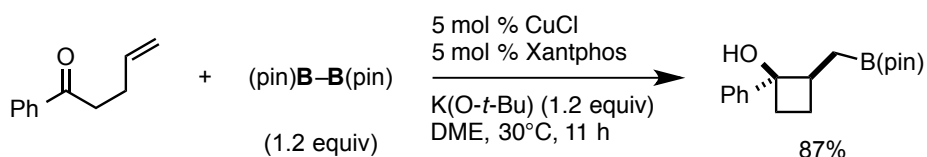
complex catalyst to give the corresponding optically active *gem*-difluoroallylboronate esters with excellent enantioselectivities.

Scheme 10. Copper(I)-catalyzed enantioselective γ -boryl substitution of trifluoromethyl alkenes.



Chapter 3 describes the diastereoselective borylative *exo*-cyclization of alkenyl aryl ketones (Scheme 11).²⁴ This reaction is the first example of borylative cyclization of alkenyl ketone substrates to provide *syn*-2-(borylmethyl)cycloalkanol derivatives in good yields with high *syn* selectivities. The synthetic utility of this protocol was demonstrated by the transformation of the products into various cyclobutanol derivatives.

Scheme 11. Copper(I)-catalyzed diastereoselective borylative *exo*-cyclization of alkenyl aryl ketones.



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Chapter 1.

**Copper(I)-Catalyzed Stereodivergent
Hydrodefluorination of *gem*-Difluoroalkenes**

Abstract

The author reports a novel approach for the stereodivergent hydrodefluorination of *gem*-difluoroalkenes using copper(I) catalysts to obtain stereodefined monofluoroalkenes. Both (Z)- and (E)-terminal monofluoroalkenes were obtained by hydrodefluorination of *gem*-difluoroalkenes in the presence of copper(I) catalysts and diboron or hydrosilane, respectively, with high stereoselectivity. DFT calculations were conducted to elucidate the stereoselectivity.

Introduction

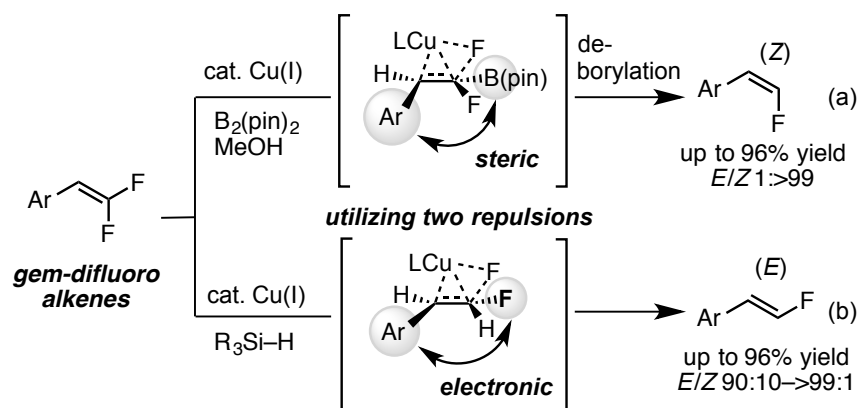
Terminal monofluoroalkenes are important structural motifs in materials¹ and medicinal chemistry² due to the unique properties of fluorine.³ The bioactivity of monofluoroalkenes varies widely according to their stereochemistry. For instance, Sayre and co-workers reported that an inhibitor for bovine plasma amine oxidase (BPAO) with a (Z)- β -monofluoroalkene structure exhibited a 10-fold effective inhibition ability compared with its *E*-stereoisomer on the basis of the IC₅₀ values.⁴ Thus, their stereodefined synthesis is very important.⁵ Our research focuses on the stereodivergent hydrodefluorination of *gem*-difluoroalkenes, which are easily available from the corresponding carbonyl compounds. This is expected to be a powerful method for the preparation of stereodefined terminal monofluoroalkenes with both *Z*- and *E*-configurations from one synthetic intermediate.⁶⁻⁸

A major challenge in achieving a stereodivergent hydrodefluorination of *gem*-difluoroalkenes is the selective cleavage of one of the two terminal C–F bonds under mild conditions. Carbon-fluorine bond is the strongest single bond known, and its cleavage often requires harsh conditions. The bond energy difference between the two C–F bonds is very small. Cao and co-workers reported an *E*-selective hydrodefluorination of *gem*-difluoroalkenes using a selective reduction with Red-Al®.^{8g} This reaction provides the corresponding (*E*)-monofluoroalkenes in high yield with good *E* selectivity (up to 99% yield, *E/Z* = 95:5). However, no *Z*-selective hydrodefluorination of *gem*-difluoroalkenes has been reported to date.⁹

Herein, we report the copper(I)-catalyzed stereodivergent

hydrodefluorination of *gem*-difluoroalkenes to provide (*Z*)- and (*E*)-terminal monofluoroalkenes (Scheme 1). We have been studying the copper(I)-catalyzed reactions of diboron^{10–12} and hydrosilanes,^{13,14} and envisioned that the regioselective addition of borylcopper(I) and copper(I)-hydride and subsequent stereoselective β -elimination of the Cu–F moiety could achieve a stereodivergent hydrodefluorination of *gem*-difluoroalkenes.¹⁵ By considering the transition state of the elimination of the Cu–F moiety of the adduct formed between the borylcopper(I) species and the *gem*-difluoroalkenes (Scheme 1a), the steric repulsion between the bulky B(pin) and the aromatic group (Ar) may result in the *Z* product after deborylation. Contrary, the electronic repulsion between the aromatic group (Ar) and F group in the elimination transition state of the copper(I)-hydride adducts would give the corresponding *E*-product (Scheme 1b).^{8g}

Scheme 1. Copper(I)-catalyzed selective defluorination of *gem*-difluoroalkenes (this work).

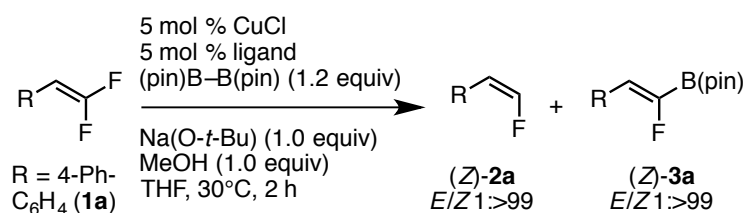


We found that the copper(I)-catalyzed reaction with diboron proceeded with perfect *Z*-selectivity (*E/Z*=1:>99, Scheme 1a). Furthermore, we found that the stereoselectivity of the defluorination of *gem*-difluoroalkenes could be drastically switched by swapping the diboron reagent for a hydrosilane (*E/Z*= from 90:10 to >99:1, Scheme 1b) for the first time. The DFT calculations suggested the stereoselectivity was determined at the defluorination steps.

Results and Discussion

We first investigated the optimal conditions for the selective hydrodefluorination of *gem*-difluoroalkenes by using a copper(I)/diboron catalytic system. The reaction of **1a** with bis(pinacolato)diboron (1.2 equiv) in the presence of CuCl/Xantphos (5 mol%), Na(O-*t*-Bu) (1.0 equiv), and MeOH (1.0 equiv) in THF (1.0 mL) at 30°C provided (*Z*)-**2a** in high yield with perfect *Z* selectivity, and the defluoroborylated product (*Z*)-**3a** was not observed (Table 1, entry 1). The reaction was also conducted without a ligand, which gave trace amount of the product with a low conversion of the substrate (entry 2). We also evaluated other ligands and found the inferior results (entries 3–6). In all of the reactions, no other by-products except for **3a** were observed, and the mass balance was unreacted **1a**. We also tested a *gem*-difluoroalkene (R=CH₂CH₂Ph) and found borylation product (*Z*)-**3** was obtained in a moderate yield (70%) as the major product.

Table 1. Optimization of the reaction conditions for the *Z*-selective synthesis.^a



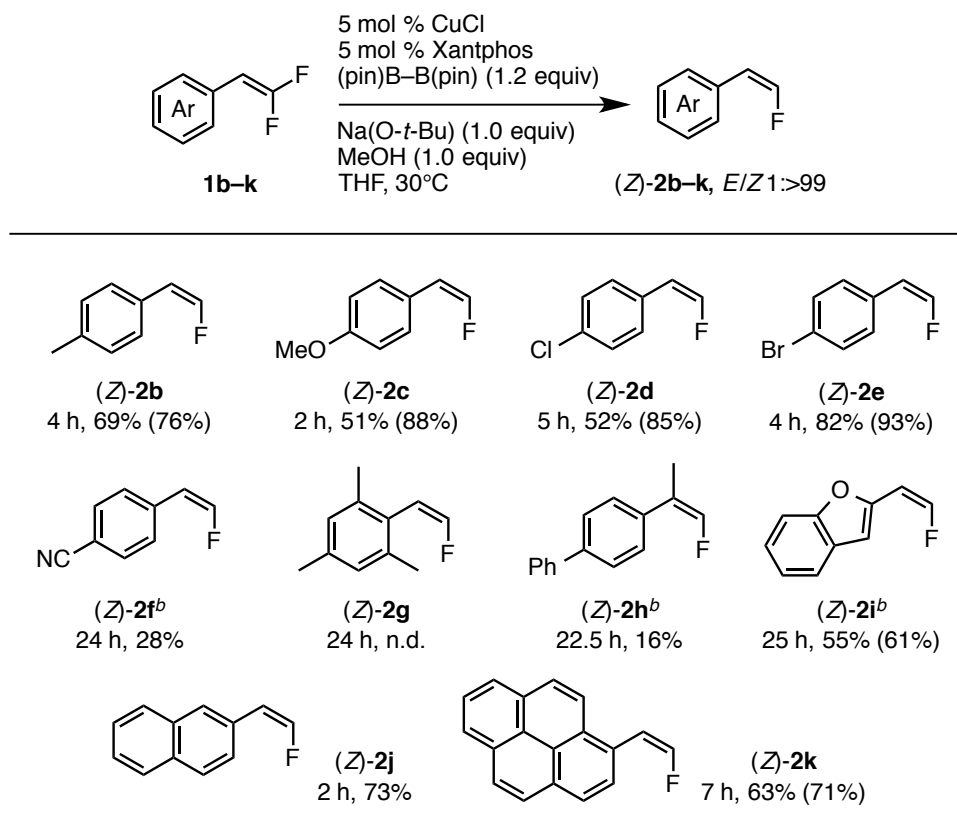
entry	ligand	yield of 2a^b (%)	yield of 3a^b (%)
1	Xantphos	96	0
2	none	2	2
3	PPh ₃	1	31
4	IPr-HCl	9	36
5	dppp	9	45
6	dppbz	12	38

^aConditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), bis(pinacolato)diboron (0.6 mmol), alcohol (0.5 mmol) and Na(O-*t*-Bu) (0.5 mmol) in THF (1.0 mL). ^bNMR yield.

The optimized conditions were used for further evaluation of the substrate scope of this reaction (Table 2). Aryl *gem*-difluoroalkenes bearing electron donating- and withdrawing-groups at the *para* position underwent the

defluorination reaction to give the desired product (Z)-**2b–e** in good yields and with excellent Z selectivity (76–93%, Z only). Cyano substituted and sterically hindered *gem*-difluoroalkene (**1f** and **1g**) showed low reactivity toward this Z-selective hydrodefluorination [(Z)-**2f**: 28%, (Z)-**2g**: n.d.]. Tetra-substituted *gem*-difluoroalkene **1h** also reacted to provide the corresponding monofluoroalkene (Z)-**2h** in low yield and with excellent Z selectivity (16%, Z only). The reaction of hetero-aryl-substituted *gem*-difluoroalkene **1i** proceeded smoothly to give the desired product (Z)-**2i** in good yield with excellent selectivity (61%, Z only). Substrates with other π -system (**1j** and **1k**) gave the corresponding defluorinated products (Z)-**2j** and (Z)-**2k** in high yields (73% and 71%, respectively).

Table 2. Substrate scope of the *Z*-selective defluorination of *gem*-difluoroalkenes.^a



^aReagents and conditions: CuCl (0.025 mmol), Xantphos (0.025 mmol), **1** (0.5 mmol), bis(pinacolato)diboron (0.6 mmol), Na(O-*t*-Bu) (0.5 mmol) and MeOH (0.5 mmol) in THF (1.0 mL) at 30°C. Yields of isolated products are reported. Yields determined by ¹H NMR analysis are shown in parentheses. The *E/Z* ratios of the products were determined by ¹H NMR and GLC analyses. ^b10 mol % of CuCl and Xantphos were used.

Next, we conducted the *E*-selective hydrodefluorination using the copper(I)/hydrosilane catalytic system. We found that the reaction of *gem*-difluoroalkene **1a** with PhMe₂SiH (2.0 equiv) in the presence of CuOAc/dppp (5 mol%), NaOTMS (2.0 equiv) in THF at -20°C afforded the (*E*)-monofluoroalkene, (*E*)-**2a**, in high yield with excellent *E* selectivity (Table 3, entry 1, 96%, *E/Z* = 95:5). The reaction of **1a** in the absence of ligand resulted in no reaction (entry 2). The results with other ligands were inferior to that with the dppp ligand (entries 3–6).

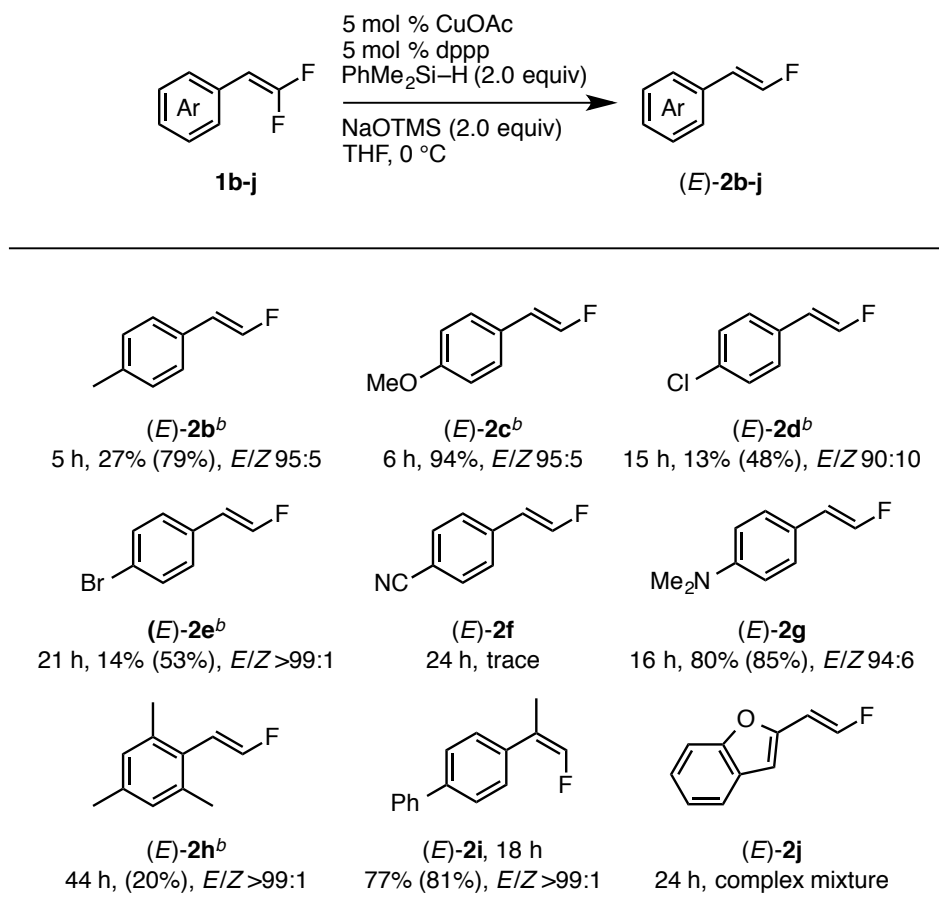
Table 3. Optimization of the reaction conditions for the (*E*)-selective synthesis.^a

$ \begin{array}{ccc} \text{Ar}-\text{C}(\text{F})=\text{C}(\text{F})-\text{H} & \xrightarrow[\text{THF, } -20^{\circ}\text{C, 2 h}]{\begin{array}{l} 5 \text{ mol \% CuOAc} \\ 5 \text{ mol \% ligand} \\ \text{PhMe}_2\text{Si-H (2.0 equiv)} \\ \text{NaOTMS (2.0 equiv)} \end{array}} & \text{Ar}-\text{CH}=\text{CH}-\text{F} \\ \text{Ar} = 4\text{-Ph-C}_6\text{H}_4 \text{ (1a)} & & \text{(E)-2a} \end{array} $			
entry	ligand	yield of 2a ^b (%)	<i>E/Z</i> ^c
1	dppp	96	95:5
2	none	0	—
3	IPr-HCl	9	—
4	PPh ₃	35	90:10
5	dppbz	30	92:8
6	Xantphos	70	93:7

^aConditions: CuOAc (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), PhMe₂SiH (1.0 mmol) and NaOTMS (1.0 mmol) in THF (0.5 mL). ^bNMR yield. ^c*E/Z* ratio was determined by GLC analysis.

With the optimized conditions in hand, we examined the scope of the selective defluorination with various *gem*-difluoroalkenes using the copper(I)/hydrosilane catalyst system (Table 4). Electron rich and deficient aryl *gem*-difluoroalkenes underwent the reaction to give the corresponding products, (*E*)-**2b–e** in moderate to high yields with high *E* selectivities (48–94%, *E/Z* 90:10–99:1). Reaction with a *gem*-difluoroalkenes bearing a cyano group (**1f**) afforded only a trace amount of the defluorinated product. A sterically congested, mesityl group-substituted *gem*-difluoroalkene **1g** showed low reactivity (20%, *E/Z* >99:1). This hydrodefluorination was also applied to tetra-substituted *gem*-difluoroalkene **1h** to give the corresponding product (*E*)-**2h** in high yield with perfect *E* selectivity (81%, *E/Z* >99:1). Heteroaryl *gem*-difluoroalkenes **1i** did not provide the defluorinated product. The reaction of **1l** afforded the desired defluorinated product (*E*)-**2l** in high yield and *E* selectivity (85%, *E/Z* 94:6).

Table 4. Substrate scope of the *E*-selective defluorination of *gem*-difluoroalkenes.^a



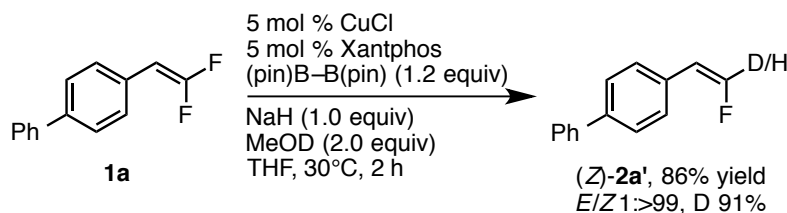
^aReagents and conditions: CuOAc (0.025 mmol), dppp (0.025 mmol), **1** (0.5 mmol), PhMe₂SiH (1.0 mmol) and NaOTMS (1.0 mmol) in THF (0.5 mL) at 0°C. Yields of isolated products are reported. Yields determined by ¹H NMR analysis are shown in parentheses. The *E/Z* ratios of the products were determined by ¹H NMR analyses.

^bTHF (1.0 mL) was used; 10 mol % of CuOAc and dppp were used.

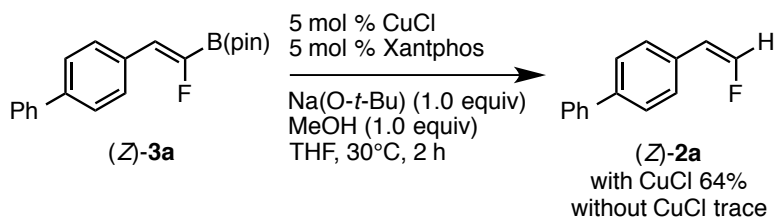
We next conducted several mechanistic experiments to support the proposed reaction mechanism. *Z*-Selective defluorination of **1a** under the optimized conditions with B₂(pin)₂ using MeOD instead of MeOH gave (*Z*)-**2a'**, bearing a deuterium at the β-position (D 91%) [(*Z*)-**2a'**: 86%, *Z* only, Scheme 2].¹⁶ We also conducted the mechanistic experiment regarding the deborylation step (Scheme 3). The monofluoroalkenyl boronate ester (*Z*)-**3a** was synthesized separately and treated with Na(*O-t*-Bu) and MeOH in the presence or absence of the copper(I) catalyst. With the copper(I) catalyst, the deborylated product was obtained in good yield (64%). In contrast, only a trace amount of the desired

product was obtained without the copper(I) catalyst. These results revealed that the deborylation proceeds through a copper(I)-catalyzed transmetallation/protonation pathway.¹⁷

Scheme 2. Deuterium labelling experiment about Z-selective synthesis.

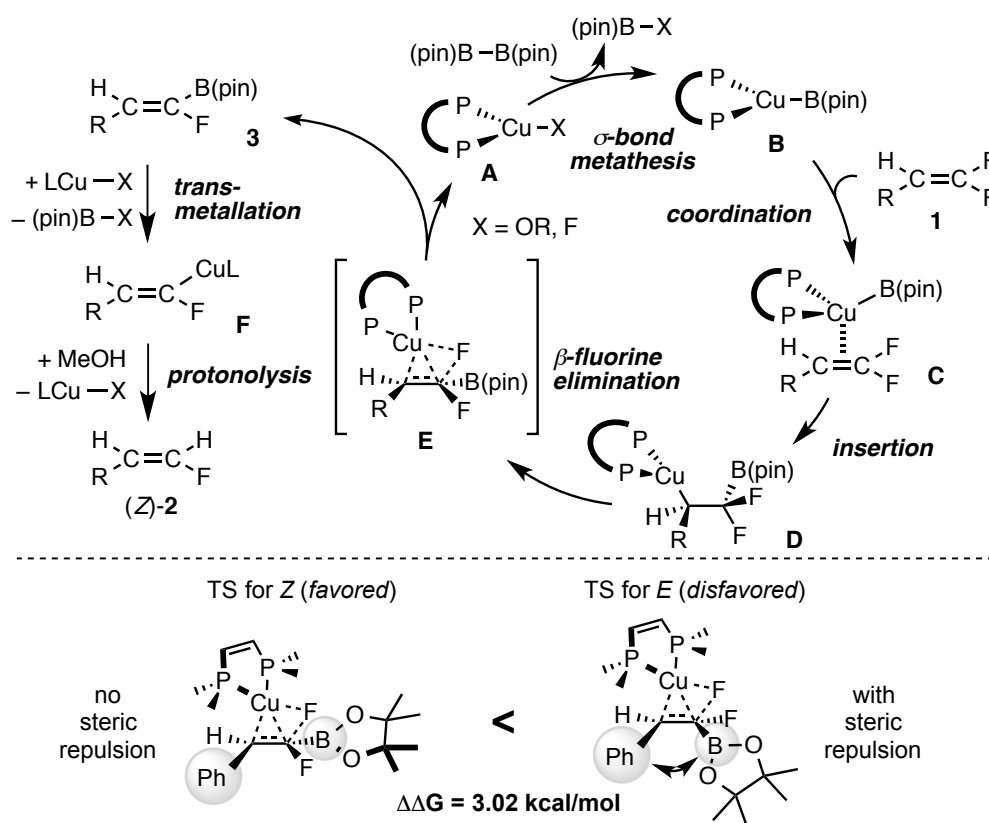


Scheme 3. Mechanistic study of the deborylation step.



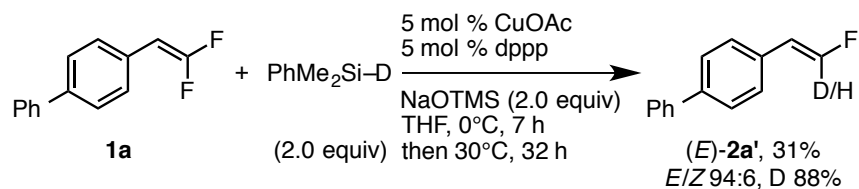
A proposed reaction mechanism for the Z-selective defluorination using the copper(I)/diboron system is shown in Figure 1. Copper(I) alkoxide **A** would initially react with diboron to afford the borylcopper(I) species **B**. The coordination of the *gem*-difluoroalkene **1** to species **B** would result in the formation of the π -complex **C**, which would undergo an insertion reaction to give the alkylcopper(I) intermediate **D**. Then *syn*-elimination from this intermediate **D** via transition state **E** would result in the formation of **3** followed by a copper(I)-catalyzed proto-deborylation to give the product **(Z)-2**.¹⁸⁷ DFT calculations (ω B97XD/cc-pVDZ) of model structures were conducted to elucidate the stereoselectivity-determining step (Figure S1, p. S22 in SI). The activation barrier for the transition state for the Z-isomer is +3.02 kcal/mol lower in energy than that for the E-isomer. This difference in the activation barrier can be attributed to steric congestion between the B(pin) group and the phenyl group of the substrate.

Figure 1. Proposed reaction mechanism for selective defluorination using the copper(I)/diboron system.



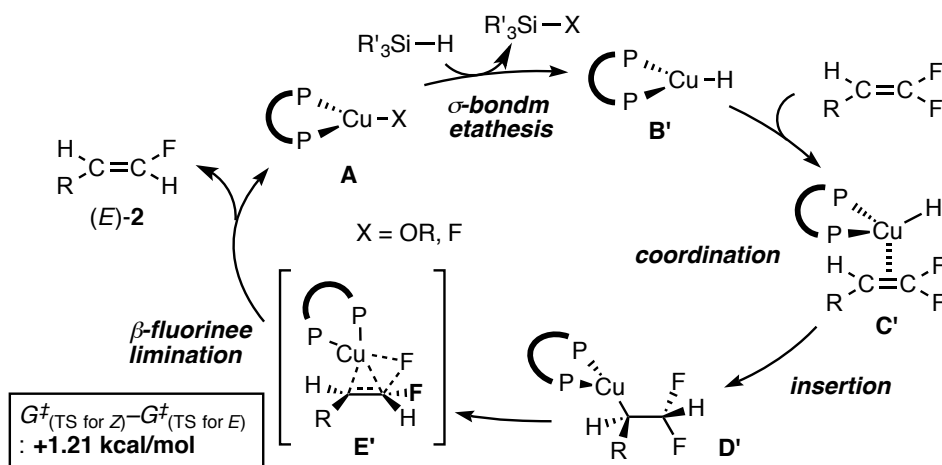
We also conducted an additional mechanistic experiment to support the proposed reaction mechanism. The *E*-selective defluorination reaction with use of PhMe_2SiD instead of PhMe_2SiH provided the corresponding β-deuterated product, (*E*)-**2a'** with excellent regio- and *E*-selectivity (Scheme 4). This suggests that the current defluorination proceeds via the regioselective addition of copper(I)-hydride to the substrate, followed by β-fluorine elimination of the alkylcopper(I) intermediate.

Scheme 4. Deuterium labelling experiment for the *E*-selective synthesis.



We have postulated a reaction mechanism for the defluorination using the copper(I)/hydrosilane system, which is shown in Figure 2. In this case, the copper(I)-hydride species **B'** would be produced initially, and subsequent insertion would give the alkylcopper(I) intermediate **D'**, which is similar to that suggested in the copper(I)/diboron system. The β -fluorine elimination of **D'** via transition state **E'** would proceed to give the defluorinated product (*E*)-**2** as well as generating the copper(I) fluoride **A**. DFT calculations ($\omega\text{B97XD/cc-pVDZ}$) (Figure S2, p. S23 in SI) showed that the activation barrier for the transition state for the *E*-isomer is +1.21 kcal/mol lower in energy than that for the *Z*-isomer.

Figure 2. Proposed reaction mechanism for selective defluorination using the copper(I)/hydrosilane system.



Summary

In summary, we have developed a novel stereodivergent hydrodefluorination of *gem*-difluoroalkenes for the preparation of (*Z*)- and (*E*)-terminal monofluoroalkenes using borylcopper(I) and copper(I)-hydride species with excellent selectivities. This reaction involves the regioselective boryl- or hydrocupration of *gem*-difluoroalkenes, followed by stereoselective fluorine elimination from the resulting alkylcopper(I) intermediates. Our study is the first example of the stereodivergent synthesis of (*Z*)- and (*E*)-terminal monofluoroalkenes from the same starting material. Further studies directed toward the reaction of alkyl *gem*-difluoroalkenes are currently underway.

Experimental

General.

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents (Tetrahydrofuran, dehydrated –super–, 41001-05, Kanto Chemical Co., Inc.) for reactions were purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieve (MS 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^1H : 392 or 396 MHz, ^{13}C : 99 or 100 MHz and ^{19}F : 373 MHz). Tetramethylsilane (^1H), CDCl_3 (^{13}C) and Fluorobenzene (^{19}F , δ –113.60) were employed as external standards, respectively. Multiplicity was recorded as follows: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, o = octet, m = multiplet. CuCl (ReagentPlus® grade, 224332-25G, $\geq 99\%$) was purchased from Sigma-Aldrich Co., and CuOAc was purchased from Wako Pure Chemical Industries Ltd, and used as received. Dimethyl terephthalate and 1,1,2,2-tetrachloroethane were used as an internal standard to determine NMR yields. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. Medium-pressure column chromatography was carried out on a Biotage Flash Purification System Isolera, which is equipped with a UV detector. Recycle preparative gel permeation chromatography (GPC) was conducted with a JAI LC-9101 using CHCl_3 as the eluent. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

Preparation of Substrates.

All *gem*-difluoroalkenes were known compounds and synthesized according to the procedure in the literatures. The *gem*-difluoroalkenes **1a**, **1f**, **1j**, **1k** and **1l** were synthesized through direct difluoromethylenation from corresponding aldehydes using TMSCF_3 .¹ The *gem*-difluoroalkenes **1b–1e**, **1g** and **1i** were synthesized through difluoromethylation of corresponding aldehydes using 2,2-difluoro-2-(fluorosulfonyl)acetate.² The *gem*-difluoroalkenes **1h** was synthesized through decarboxylative Wittig reaction of difluoromethylene phosphobetaine with aldehydes.³ The synthesized *gem*-difluoroalkenes were

subjected to purification by Kugelrohr distillation prior to use.

General Defluorination Procedures.

Procedure for the copper(I)-catalyzed *Z*-selective defluorination of *gem*-difluoroalkenes **1a** (Table 1).

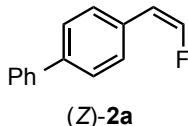
Copper chloride (2.7 mg, 0.027 mmol), Xantphos (14.4 mg, 0.025 mmol), bis(pinacolato)diboron (154.0 mg, 0.61 mmol) and **1a** (107.1 mg, 0.50 mmol) were placed in an oven-dried reaction vial. And then, the vial was transferred to the glove box and Na(*O-t*-Bu) (48.0 mg, 0.50 mmol) was added to the vial under argon atmosphere. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, the vial was removed from the glove box and connected to a vacuum/nitrogen manifold through a needle. After dry THF (1 mL) was added to the reaction mixture, MeOH (22 μ L, 0.54 mmol) was added dropwise to the reaction mixture at 30 °C. After the reaction was complete, the mixture was passed through a short silica gel eluting with Et₂O. The crude material was purified by medium-pressure column chromatography (SiO₂, hexane) to give the corresponding defluorination product (*Z*)-**2a** (81.1 mg, 0.41 mmol, 83%) as a white solid.

Procedure for the copper(I)-catalyzed *E*-selective defluorination of *gem*-difluoroalkenes **1a** (Table 3).

Dppp (10.4 mg, 0.025 mmol) and **1a** (106.9 mg, 0.5 mmol) were placed in an oven-dried reaction vial. And then, the vial was transferred to the glove box and copper acetate (3.1 mg, 0.025 mmol) and NaOTMS (123.2 mg, 1.0 mmol) were added to the vial under argon atmosphere. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, the vial was removed from the glove box and connected to a vacuum/nitrogen manifold through a needle. After dry THF (500 μ L) was added to the mixture, dimethylphenylsilane (155 μ L, 1.0 mmol) was added dropwise to the reaction mixture at -20 °C. After the reaction was complete, the mixture was passed through a short silica gel eluting with Et₂O. The crude material was purified by medium-pressure column chromatography (SiO₂, hexane) to give the corresponding defluorination product (*E*)-**2a** (71.5 mg, 0.36 mmol, 73%) as a white solid.

Characterization of Defluorination Products.

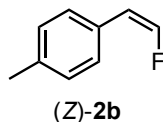
(Z)-4-(2-Fluorovinyl)-1,1'-biphenyl [(Z)-2a].



The reaction was conducted with 107.1 mg (0.495 mmol) of **1a**. The product (Z)-**2a** was obtained in 83% yield (81.1 mg, 0.409 mmol) as a white solid (m.p. = 83–85°C). The stereoselectivity of (Z)-**2a** was determined by ^1H NMR analysis (*E/Z* 1:>99).

^1H NMR (396 MHz, CDCl_3 , δ): 5.66 (dd, $J = 5.2, 44.7$ Hz, 1H), 6.69 (dd, $J = 5.2, 82.7$ Hz, 1H), 7.32–7.38 (m, 1H), 7.41–7.48 (m, 2H), 7.57–7.63 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 110.4 (CH), 126.9 (CH), 127.1 (CH), 127.4 (CH), 128.8 (CH), 129.2 (d, $J_{\text{C-F}} = 6.7$ Hz, CH), 131.6 (C), 140.2 (d, $J_{\text{C-F}} = 1.9$ Hz, CH), 140.6 (C), 148.3 (d, $J_{\text{C-F}} = 270.9$ Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): -122.3 (dd, $J = 45.8, 79.7$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{11}\text{F}$, 198.0845; found, 198.0848.

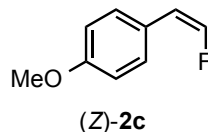
(Z)-1-(2-Fluorovinyl)-4-methylbenzene [(Z)-2b].



The reaction was conducted with 77.5 mg (0.503 mmol) of **1b**. The product (Z)-**2b** was obtained in 69% yield (47.3 mg, 0.347 mmol) as an oil. The stereoselectivity of (Z)-**2b** was determined by ^1H NMR analysis (*E/Z* 1:>99).

^1H NMR (392 MHz, CDCl_3 , δ): 2.34 (s, 3H), 5.58 (dd, $J = 5.5, 45.4$ Hz, 1H), 6.62 (dd, $J = 5.5, 83.1$ Hz, 1H), 7.15 (d, $J = 7.8$ Hz, 2H), 7.41 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 21.2 (CH_3), 110.6 (CH), 128.7 (d, $J_{\text{C-F}} = 6.6$ Hz, CH), 129.2 (CH), 129.7 (C), 137.3 (C), 147.7 (d, $J_{\text{C-F}} = 268.6$ Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): -123.8 (dd, $J = 45.4, 79.7$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_9\text{H}_9\text{F}$, 136.0688; found, 136.0685.

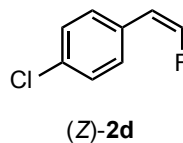
(Z)-1-(2-Fluorovinyl)-4-methoxybenzene [(Z)-2c].



The reaction was conducted with 86.0 mg (0.505 mmol) of **1c**. The product (Z)-**2c** was obtained in 51% yield (39.3 mg, 0.258 mmol) as an oil. The stereoselectivity of (Z)-**2c** was determined by ^1H NMR analysis (*E/Z* 1:>99).

^1H NMR (392 MHz, CDCl_3 , δ): 3.81 (s, 3H), 5.55 (dd, $J = 5.5, 45.5$ Hz, 1H), 6.59 (dd, $J = 5.3, 82.9$ Hz, 1H), 6.87 (d, $J = 8.6$ Hz, 2H), 7.45 (d, $J = 9.0$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 55.2 (CH_3), 110.2 (CH), 113.8 (CH), 125.3 (C), 130.1 (d, $J_{\text{C-F}} = 6.6$ Hz, CH), 147.0 (d, $J_{\text{C-F}} = 267.8$ Hz, CH), 158.8 (d, $J_{\text{C-F}} = 2.9$ Hz, C). ^{19}F NMR (373 MHz, CDCl_3 , δ): -125.8 (dd, $J = 45.4, 79.7$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_9\text{H}_9\text{FO}$, 152.0637; found, 152.0641.

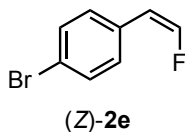
(Z)-1-Chloro-4-(2-fluorovinyl)benzene [(Z)-2d].



The reaction was conducted with 87.7 mg (0.502 mmol) of **1d**. The product (Z)-**2d** was obtained in 52% yield (40.7 mg, 0.260 mmol) as an oil. The stereoselectivity of (Z)-**2d** was determined by ^1H NMR analysis (*E/Z* 1:>99).

^1H NMR (392 MHz, CDCl_3 , δ): 5.58 (dd, $J = 5.5, 44.7$ Hz, 1H), 6.66 (dd, $J = 5.5, 82.7$ Hz, 1H), 7.28–7.37 (m, 2H), 7.40–7.48 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 109.8 (CH), 128.6 (CH), 130.0 (d, $J_{\text{C-F}} = 7.5$ Hz, CH), 131.0 (C), 133.1 (d, $J_{\text{C-F}} = 2.8$ Hz, C), 148.6 (d, $J_{\text{C-F}} = 270.6$ Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): -121.9 (dd, $J = 45.4, 79.7$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_8\text{H}_6\text{ClF}$, 156.0142; found, 156.0146.

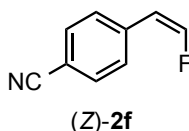
(Z)-1-Bromo-4-(2-fluorovinyl)benzene [(Z)-2e].



The reaction was conducted with 108.7 mg (0.496 mmol) of **1e**. The product (Z)-**2e** was obtained in 82% yield (81.8 mg, 0.407 mmol) as an oil. The stereoselectivity of (Z)-**2e** was determined by ^1H NMR analysis (*E/Z* 1:>99).

^1H NMR (392 MHz, CDCl_3 , δ): 5.57 (dd, $J = 5.3, 43.7$ Hz, 1H), 6.67 (dd, $J = 5.5, 81.5$ Hz, 1H), 7.34–7.41 (m, 2H), 7.43–7.49 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 109.8 (CH), 121.3 (d, $J_{\text{C-F}} = 3.9$ Hz, C), 130.3 (d, $J_{\text{C-F}} = 7.6$ Hz, CH), 131.4 (C), 131.6 (CH), 148.6 (d, $J_{\text{C-F}} = 272.8$ Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): -121.5 (dd, $J = 45.8, 79.7$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_8\text{H}_6\text{BrF}$, 199.9637; found, 199.9635.

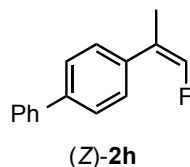
(Z)-4-(2-Fluorovinyl)benzonitrile [(Z)-2f].



The reaction was conducted with 81.7 mg (0.495 mmol) of **1f**. The product (Z)-**2f** was obtained in 28% yield (20.7 mg, 0.141 mmol) as an oil. The stereoselectivity of (Z)-**2f** was determined by ^1H NMR analysis (*E/Z* 1:>99).

^1H NMR (392 MHz, CDCl_3 , δ): 5.67 (dd, $J = 5.1, 43.1$ Hz, 1H), 6.76 (dd, $J = 5.3, 81.7$ Hz, 1H), 7.57–7.66 (m, 4H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 109.7 (CH), 110.8 (C), 118.8 (C), 129.2 (d, $J_{\text{C-F}} = 7.6$ Hz, CH), 132.2 (CH), 137.0 (C), 150.4 (d, $J_{\text{C-F}} = 275.3$ Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): -117.1 (dd, $J = 45.4, 79.7$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_9\text{H}_6\text{FN}$, 147.0484; found, 147.0483.

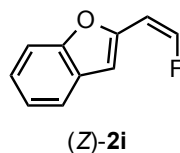
(Z)-4-(1-Fluoroprop-1-en-2-yl)-1,1'-biphenyl [(Z)-2h].



The reaction was conducted with 115.8 mg (0.503 mmol) of **1h**. The product (Z)-**2h** was obtained in 16% yield (16.8 mg, 0.0791 mmol) as a white solid (m.p. = 52–54°C). The stereoselectivity of (Z)-**2h** was determined by ¹H NMR analysis (*E/Z* 1:>99). Borylated product **3h** was obtained in moderate yield (45% NMR yield) and unreacted substrate **1h** was recovered in low yield (20% NMR yield) except for (Z)-**2h**.

¹H NMR (392 MHz, CDCl₃, δ): 1.95 (dd, *J* = 1.4, 4.9 Hz, 3H), 6.70 (dd, *J* = 1.2, 84.2 Hz, 1H), 7.31–7.39 (m, 1H), 7.40–7.49 (m, 2H), 7.55–7.65 (m, 6H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.9 (d, *J*_{C-F} = 7.6 Hz, CH₃), 116.5 (C), 126.9 (CH), 127.0 (CH), 127.3 (CH), 128.1 (d, *J*_{C-F} = 6.6 Hz, CH), 128.8 (CH), 134.7 (C), 140.1 (C), 140.7 (C), 144.4 (d, *J*_{C-F} = 264.0 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): –128.8 (d, *J* = 79.7 Hz, 1F). HRMS-EI (*m/z*): [M]⁺ calcd for C₁₅H₁₃F, 212.1001; found, 212.1000.

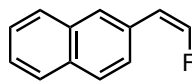
(Z)-2-(2-Fluorovinyl)benzofuran [(Z)-2i].



The reaction was conducted with 90.1 mg (0.500 mmol) of **1i**. The product (Z)-**2i** was obtained in 55% yield (44.4 mg, 0.274 mmol) as an oil. The stereoselectivity of (Z)-**2i** was determined by ¹H NMR analysis (*E/Z* 1:>99).

¹H NMR (396 MHz, CDCl₃, δ): 5.88 (dd, *J* = 5.1, 41.6 Hz, 1H), 6.76 (dd, *J* = 4.9, 80.2 Hz, 1H), 6.94 (s, 1H), 7.19–7.31 (m, 2H), 7.42–7.48 (m, 1H), 7.53–7.59 (m, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 101.8 (CH), 106.8 (d, *J*_{C-F} = 10.5 Hz, CH), 111.0 (CH), 121.0 (CH), 122.9 (CH), 124.5 (CH), 128.8 (C), 149.32 (C), 149.34 (d, *J*_{C-F} = 274.7 Hz, CH), 154.0 (C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –115.6 (dd, *J* = 45.4, 79.7 Hz, 1F). HRMS-EI (*m/z*): [M]⁺ calcd for C₁₀H₇FO, 162.0481; found, 162.0481.

(Z)-2-(2-Fluorovinyl)naphthalene [(Z)-2j].

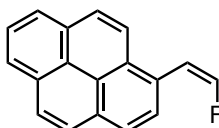


(Z)-2j

The reaction was conducted with 95.9 mg (0.504 mmol) of **1j**. The product (Z)-**2j** was obtained in 73% yield (63.5 mg, 0.369 mmol) as a white solid (m.p. = 60–62°C). The stereoselectivity of (Z)-**2j** was determined by ¹H NMR analysis (*E/Z* 1:>99).

¹H NMR (392 MHz, CDCl₃, δ): 5.78 (dd, *J* = 5.3, 44.9 Hz, 1H), 6.74 (dd, *J* = 5.5, 83.1 Hz, 1H), 7.43–7.51 (m, 2H), 7.69 (dd, *J* = 1.6, 8.6 Hz, 1H), 7.77–7.85 (m, 3H), 7.93 (s, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 110.9 (CH), 126.1 (CH), 126.2 (CH), 126.6 (d, *J*_{C-F} = 7.6 Hz, CH), 127.5 (CH), 127.9 (d, *J*_{C-F} = 6.6 Hz, CH), 128.02 (CH), 128.04 (CH), 130.1 (C), 132.5 (C), 133.3 (C), 148.4 (d, *J*_{C-F} = 270.5 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): –122.2 (dd, *J* = 45.4, 79.7 Hz, 1F). HRMS-EI (*m/z*): [M]⁺ calcd for C₁₂H₉F, 172.0688; found, 172.0689.

(Z)-1-(2-Fluorovinyl)pyrene [(Z)-2k].

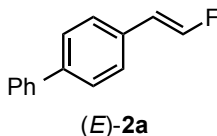


(Z)-2k

The reaction was conducted with 133.4 mg (0.505 mmol) of **1k**. The product (Z)-**2k** was obtained in 63% yield (77.9 mg, 0.316 mmol) as a white solid (m.p. = 125–126°C). The stereoselectivity of (Z)-**2k** was determined by ¹H NMR analysis (*E/Z* 1:>99).

¹H NMR (392 MHz, CDCl₃, δ): 6.60 (dd, *J* = 5.1, 43.1 Hz, 1H), 7.00 (dd, *J* = 5.7, 83.3 Hz, 1H), 7.98–8.23 (m, 7H), 8.26 (d, *J* = 9.4 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 107.9 (CH), 123.1 (CH), 124.57 (C), 124.65 (CH), 125.0 (CH), 125.3 (CH), 125.8 (CH), 126.0 (C), 127.26 (CH), 127.36 (CH), 127.44 (CH), 127.6 (CH), 128.2 (C), 130.6 (C), 131.2 (C), 148.7 (d, *J*_{C-F} = 270.6 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): –123.9 (dd, *J* = 45.4, 79.7 Hz, 1F). HRMS-EI (*m/z*): [M]⁺ calcd for C₁₈H₁₁F, 246.0845; found, 246.0836.

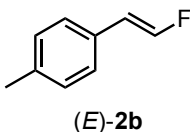
(E)-4-(2-Fluorovinyl)-1,1'-biphenyl [(E)-2a].



The reaction was conducted with 106.9 mg (0.494 mmol) of **1a**. The stereoselectivity of the crude material was determined by GLC analysis (*E/Z* 95:5) as a white solid (m.p. = 108–116°C). The product (E)-**2a** was obtained in 73% yield (71.5 mg, 0.361 mmol, *E/Z* 90:10) determined by ¹H NMR analysis.

¹H NMR (392 MHz, CDCl₃, δ): 6.43 (dd, *J* = 11.2, 19.4 Hz, 1H), 7.09–7.38 (m, 4H), 7.41–7.47 (m, 2H), 7.52–7.63 (m, 4H). ¹³C NMR (99 MHz, CDCl₃, δ): 113.5 (d, *J*_{C-F} = 16.0 Hz, CH), 126.5 (d, *J*_{C-F} = 2.8 Hz, CH), 126.9 (CH), 127.38 (CH), 127.42 (CH), 128.8 (CH), 131.6 (d, *J*_{C-F} = 11.3 Hz, C), 140.3 (d, *J*_{C-F} = 1.9 Hz, C), 140.5 (C), 150.2 (d, *J*_{C-F} = 259.4 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): –130.1 (dd, *J* = 22.7, 79.7 Hz, 1F). HRMS-EI (*m/z*): [M]⁺ calcd for C₁₄H₁₁F, 198.0845; found, 198.0845.

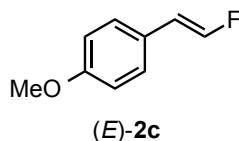
(E)-1-(2-Fluorovinyl)-4-methylbenzene [(E)-2b].



The reaction was conducted with 77.0 mg (0.499 mmol) of **1b**. After the reaction was complete, the crude material was dissolved in THF (1.0 mL) and TBAF (1.0 M, 800 μL) was added to the mixture at 0 °C to remove byproducts. The resultant solution was stirred for 3 h at 0 °C. After that, the mixture was added to the H₂O, then extracted with Et₂O. The organic layer was washed with water two times. The combined organic layer was then dried over MgSO₄ followed by evaporation. The crude material was purified by medium-pressure column chromatography (SiO₂, pentane) to give the product (E)-**2b** in 27% yield (18.2 mg, 0.134 mmol) as an oil. The stereoselectivity of (E)-**2b** was determined by ¹H NMR analysis of the crude material (*E/Z* 95:5).

¹H NMR (396 MHz, CDCl₃, δ): 2.33 (s, 3H), 6.36 (dd, *J* = 11.5, 19.4 Hz, 1H), 7.08–7.18 (m, 4H), 7.14 (dd, *J* = 11.5, 72.4 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 21.1 (CH₃), 113.6 (d, *J*_{C-F} = 16.0 Hz, CH), 126.0 (d, *J*_{C-F} = 2.8 Hz, CH), 129.4 (CH), 129.6 (d, *J*_{C-F} = 12.2 Hz, C), 137.3 (C), 149.6 (d, *J*_{C-F} = 257.4 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): –131.9 (dd, *J* = 22.7, 79.7 Hz, 1F). HRMS-EI (*m/z*): [M]⁺ calcd for C₉H₉F, 136.0688; found, 136.0689.

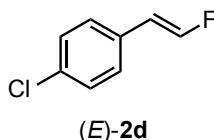
(E)-1-(2-Fluorovinyl)-4-methoxybenzene [(E)-2c].



The reaction was conducted with 83.6 mg (0.491 mmol) of **1c**. The product **(E)-2c** was obtained in 94% yield (70 mg, 0.460 mmol) as an oil. The stereoselectivity of **(E)-2c** was determined by ^1H NMR analysis of the crude material (*E/Z* 95:5).

^1H NMR (396 MHz, CDCl_3 , δ): 3.80 (s, 3H), 6.35 (dd, $J = 11.3, 19.6$ Hz, 1H), 6.82–6.89 (m, 2H), 7.09 (dd, $J = 11.5, 83.9$ Hz, 1H), 7.15–7.20 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 55.2 (CH_3), 113.2 (d, $J_{\text{C-F}} = 16.0$ Hz, CH), 114.2 (CH), 125.0 (d, $J_{\text{C-F}} = 12.2$ Hz, C), 127.2 (d, $J_{\text{C-F}} = 2.8$ Hz, CH), 148.9 (d, $J_{\text{C-F}} = 256.5$ Hz, CH), 159.0 (C). ^{19}F NMR (373 MHz, CDCl_3 , δ): -131.9 (dd, $J = 28.3, 74.1$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_9\text{H}_9\text{FO}$, 152.0637; found, 152.0643.

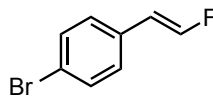
(E)-1-Chloro-4-(2-fluorovinyl)benzene [(E)-2d].



The reaction was conducted with 87.1 mg (0.499 mmol) of **1d**. The product **(E)-2d** was obtained in 13% yield (10.0 mg, 0.0639 mmol) as an oil. The stereoselectivity of **(E)-2d** was determined by ^1H NMR analysis of the crude material (*E/Z* 90:10).

^1H NMR (392 MHz, CDCl_3 , δ): 6.35 (dd, $J = 11.4, 19.2$ Hz, 1H), 7.15 (dd, $J = 11.0, 82.3$ Hz, 1H), 7.18 (d, $J = 8.6$ Hz, 2H), 7.23–7.32 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 112.9 (d, $J_{\text{C-F}} = 16.9$ Hz, CH), 127.3 (d, $J_{\text{C-F}} = 2.8$ Hz, CH), 128.9 (CH), 131.1 (d, $J_{\text{C-F}} = 12.2$ Hz, C), 133.1 (d, $J_{\text{C-F}} = 1.9$ Hz, C), 150.4 (d, $J_{\text{C-F}} = 260.3$ Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): -129.2 (dd, $J = 23.1, 79.7$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_8\text{H}_6\text{ClF}$, 156.0142; found, 156.0148.

(E)-1-Bromo-4-(2-fluorovinyl)benzene [(E)-2e].

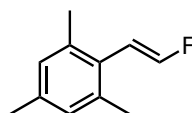


(E)-2e

The reaction was conducted with 107.9 mg (0.493 mmol) of **1e**. The product **(E)-2e** was obtained in 14% yield (14.3 mg, 0.071 mmol) as an oil. The stereoselectivity of **(E)-2e** was determined by ^1H NMR analysis ($E/Z >99:1$).

^1H NMR (396 MHz, CDCl_3 , δ): 6.34 (dd, $J = 11.1, 19.0$ Hz, 1H), 7.09–7.15 (m, 2H), 7.17 (dd, $J = 11.5, 82.3$ Hz, 1H), 7.41–7.47 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 113.0 (d, $J_{\text{C-F}} = 16.9$ Hz, CH), 121.2 (d, $J_{\text{C-F}} = 1.9$ Hz, C), 127.6 (d, $J_{\text{C-F}} = 2.8$ Hz, CH), 131.6 (d, $J_{\text{C-F}} = 12.2$ Hz, C), 131.9 (CH), 150.4 (d, $J_{\text{C-F}} = 260.3$ Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): -128.9 (dd, $J = 22.7, 79.7$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_8\text{H}_6\text{BrF}$, 199.9637; found, 199.9640.

(E)-2-(2-Fluorovinyl)-1,3,5-trimethylbenzene [(E)-2g].

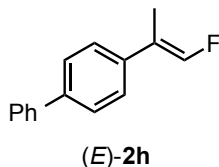


(E)-2g

The reaction was conducted with 90.8 mg (0.498 mmol) of **1g**. The product **(E)-2g** was obtained in 20% NMR yield. The stereoselectivity of **(E)-2g** was determined by ^1H NMR analysis ($E/Z >99:1$). **(E)-2g** contains inseparable impurities.

^1H NMR (396 MHz, CDCl_3 , δ): 2.27 (s, 9H), 6.29 (dd, $J = 11.7, 20.4$ Hz, 1H), 6.66 (dd, $J = 11.5, 85.9$ Hz, 1H), 6.88 (s, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 20.9 (CH_3), 21.0 (CH_3), 110.0 (d, $J_{\text{C-F}} = 14.1$ Hz, CH), 127.4 (d, $J_{\text{C-F}} = 12.2$ Hz, C), 128.5 (CH), 136.8 (d, $J_{\text{C-F}} = 2.9$ Hz, C), 140.1 (C), 151.3 (d, $J_{\text{C-F}} = 259.3$ Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): -123.7 (dd, $J = 22.9, 91.1$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{11}\text{H}_{13}\text{F}$, 164.1001; found, 164.1003.

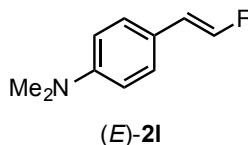
(E)-4-(1-Fluoroprop-1-en-2-yl)-1,1'-biphenyl [(E)-2h].



The reaction was conducted with 114.4 mg (0.497 mmol) of **1h**. The product (**E**)-**2h** was obtained in 77% yield (81.2 mg, 0.383 mmol) as a white solid (m.p. = 102–109°C). The stereoselectivity of (**E**)-**2h** was determined by ¹H NMR analysis (*E/Z* >99:1). No byproducts could be observed.

¹H NMR (392 MHz, CDCl₃, δ): 2.08 (dd, *J* = 1.6, 3.9 Hz, 3H), 6.98 (dq, *J* = 1.5, 84.9 Hz, 1H), 7.32–7.41 (m, 3H), 7.41–7.48 (m, 2H), 7.54–7.63 (m, 4H). ¹³C NMR (99 MHz, CDCl₃, δ): 12.1 (d, *J*_{C-F} = 5.7 Hz, CH₃), 119.6 (d, *J*_{C-F} = 10.3 Hz, C), 126.1 (d, *J*_{C-F} = 2.9 Hz, CH), 127.1 (CH), 127.4 (CH), 127.5 (CH), 129.0 (CH), 136.4 (d, *J*_{C-F} = 9.4 Hz, C), 140.4 (C), 140.7 (C), 146.0 (d, *J*_{C-F} = 258.4 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): –131.5 (d, *J* = 79.7 Hz, 1F). HRMS-EI (*m/z*): [M]⁺ calcd for C₁₅H₁₃F, 212.1001; found, 212.1000.

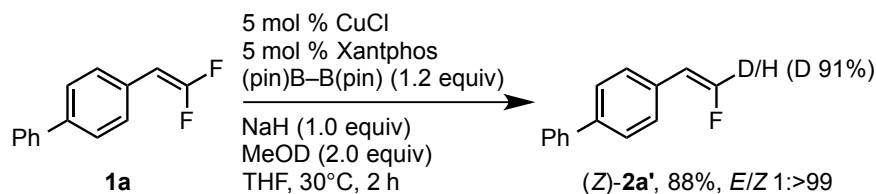
(E)-4-(2-Fluorovinyl)-*N,N*-dimethylaniline [(E)-2l].



The reaction was conducted with 92.4 mg (0.504 mmol) of **1l**. The product (**E**)-**2l** was obtained in 80% yield (66.6 mg, 0.403 mmol) as a white solid (m.p. = 62–64°C). The stereoselectivity of (**E**)-**2l** was determined by ¹H NMR analysis of the crude material (*E/Z* 94:6).

¹H NMR (392 MHz, CDCl₃, δ): 2.94 (s, 6H), 6.32 (dd, *J* = 11.4, 20.0 Hz, 1H), 6.67 (d, *J* = 8.6 Hz, 2H), 7.08 (dd, *J* = 11.2, 84.4 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 40.5 (CH₃), 112.6 (CH), 113.5 (d, *J*_{C-F} = 16.0 Hz, CH), 120.4 (d, *J*_{C-F} = 11.2 Hz, C), 127.0 (d, *J*_{C-F} = 2.9 Hz, CH), 148.0 (d, *J*_{C-F} = 253.7 Hz, CH), 149.9 (C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –136.0 (dd, *J* = 22.9, 91.1 Hz, 1F). HRMS-ESI (*m/z*): [M+H]⁺ calcd for C₁₀H₁₃NF, 166.1027; found, 166.1028.

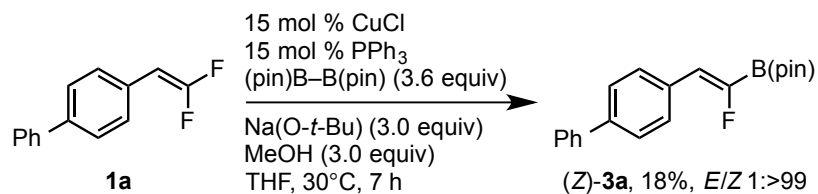
Deuterium Labelling Experiment about Z-selective Synthesis.



The defluorination of **1a** under optimized conditions using NaH/MeOD instead Na(O-*t*-Bu)/MeOH gave **(Z)-2a'** bearing a deuterium label at its β-position (D 91%), with perfect *Z* selectivity (*E/Z* 1:>99) determined by ^1H NMR analysis. **(Z)-2a'** was obtained as a white solid (m.p. = 82–83°C).

^1H NMR (392 MHz, CDCl_3 , δ): 5.66 (d, J = 44.7 Hz, 1H), 6.69 (dd, J = 5.5, 83.1 Hz, 0.09H), 7.32–7.38 (m, 1H), 7.42–7.48 (m, 2H), 7.56–7.64 (m, 6H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 110.2 (CH), 126.9 (CH), 127.1 (CH), 127.3 (CH), 128.8 (CH), 129.2 (d, $J_{\text{C-F}}$ = 7.5 Hz, CH), 131.6 (C), 140.1 (d, $J_{\text{C-F}}$ = 1.9 Hz, C), 140.5 (C), 148.0 (dt, J = 29.6, 269.7 Hz, C). ^{19}F NMR (373 MHz, CDCl_3 , δ): –122.6– –123.1 (m, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{10}\text{DF}$, 199.0908; found, 199.0903.

Synthesis of Monofluoroalkenyl Boronate Ester (Z)-3a.

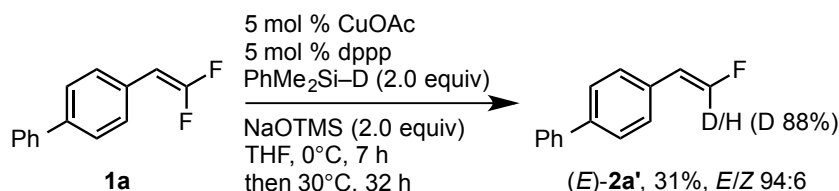


The product **(Z)-3a** was synthesized through the borylation with a copper(I)/ PPh_3 complex catalyst system. The crude mixture was purified by flash column chromatography (SiO_2 , ethyl acetate/hexane, 0:100–3:97) followed by GPC to give the corresponding borylation product **(Z)-3a** (58.1 mg, 0.18 mmol, 18%) as a white solid (m.p. = 90–93°C). The stereoselectivity of **(Z)-3a** was determined by ^1H NMR analysis (*E/Z* 1:>99).

^1H NMR (392 MHz, CDCl_3 , δ): 1.35 (s, 12H), 6.43 (d, J = 47.4 Hz, 1H), 7.32–7.39 (m, 1H), 7.41–7.48 (m, 2H), 7.57–7.64 (m, 4H), 7.70 (d, J = 8.2 Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 24.7 (CH_3), 84.8 (C), 123.4 (CH), 127.0 (CH), 127.1 (CH), 127.5 (CH), 128.8 (CH), 130.3 (d, $J_{\text{C-F}}$ = 8.5 Hz, CH), 131.9 (C), 140.5 (C), 141.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.^{4,5} ^{19}F NMR (373 MHz, CDCl_3 , δ): –123.8 (d, J = 45.4 Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{20}\text{H}_{22}^{10}\text{BFO}_2$, 323.1733; found,

323.1731.

Deuterium Labelling Experiment about *E*-Selective Synthesis.



PhMe₂Si-D was synthesized according to the literature procedure.⁶ The defluorination of **1a** at 30°C using PhMe₂Si-D instead of PhMe₂Si-H gave (*E*)-**2a'** bearing a deuterium label at its β-position (D 94%), with high *E* selectivity (*E/Z* 90:10) determined by ¹H NMR analysis. (*E*)-**2a'** was obtained as a white solid (m.p. = 117°C).

¹H NMR (392 MHz, CDCl₃, δ): 5.66 (d, *J* = 45.1 Hz, 0.06H), 6.43 (d, *J* = 19.2 Hz, 1H), 7.29–7.39 (m, 3H), 7.41–7.48 (m, 2H), 7.52–7.63 (m, 4H). ¹³C NMR (99 MHz, CDCl₃, δ): 113.3 (d, *J*_{C-F} = 16.0 Hz, CH), 126.5 (d, *J*_{C-F} = 2.8 Hz, CH), 126.9 (CH), 127.38 (CH), 127.43 (CH), 128.8 (CH), 131.6 (d, *J*_{C-F} = 11.3 Hz, C), 140.3 (d, *J*_{C-F} = 1.9 Hz, C), 140.5 (C), 149.9 (dt, *J* = 30.3, 258.1 Hz, C). ¹⁹F NMR (373 MHz, CDCl₃, δ): -130.5– -130.8 (m, 1F). HRMS-EI (*m/z*): [*M*]⁺ calcd for C₁₄H₁₀DF, 199.0908; found, 199.0905.

Details of the DFT Calculations.

All calculations were performed with the Gaussian 09W (revision C.01) program package.⁷ Geometry optimizations were performed with ωB97XD/cc-PVDZ in the gas-phase. The frequency calculations were conducted on gas-phase optimized geometries to check the all the stationary points as either minima or transition states. The intrinsic reaction coordinate (IRC) was calculated for the transition states to confirm that the structures were indeed connected by two relevant minimas.

TS1

C	2.716600	3.068300	-0.228600
C	1.545700	3.642500	0.087500
H	3.604800	3.694800	-0.384800
H	1.482000	4.734200	0.188900

Cu	0.754700	0.503800	0.139900
P	0.022200	2.637300	0.352500
P	2.856500	1.241100	-0.421200
C	-0.774300	3.500500	1.770500
H	-0.898500	4.579100	1.587400
H	-1.760600	3.041800	1.933600
H	-0.170200	3.348000	2.676000
C	-1.039000	3.154900	-1.061800
H	-2.026700	2.690300	-0.925900
H	-1.149200	4.247200	-1.136800
H	-0.604400	2.754200	-1.988000
C	4.324900	0.816100	0.599200
H	4.518700	-0.260400	0.470600
H	5.216600	1.394500	0.311900
H	4.091000	0.995300	1.658000
C	3.504600	1.069700	-2.135100
H	4.423600	1.652800	-2.298100
H	3.712400	0.002300	-2.301600
H	2.729200	1.385700	-2.846700
C	0.412900	-1.513300	0.622600
H	-0.029700	-1.421300	1.620800
C	-0.566500	-1.652700	-0.404400
F	-0.426800	-2.668500	-1.288500
C	1.754600	-2.119400	0.561200
C	2.471900	-2.353400	1.749500
C	2.414700	-2.406500	-0.652600
C	3.777400	-2.836700	1.732900
H	1.988800	-2.140900	2.706900
C	3.718800	-2.892500	-0.666100
H	1.894000	-2.235500	-1.595200
C	4.417700	-3.108800	0.523700
H	4.299600	-3.004300	2.678000
H	4.197800	-3.107300	-1.624800
H	5.439400	-3.492500	0.507900
C	-3.865900	-0.251100	0.798000
C	-4.249000	-0.891500	-0.581800

B	-2.060100	-1.219100	-0.163100
O	-2.421700	-0.253400	0.745300
O	-3.117500	-1.750800	-0.843400
C	-4.293800	0.127600	-1.721100
H	-4.366900	-0.411400	-2.675900
H	-5.158400	0.801700	-1.632000
H	-3.370900	0.725800	-1.748300
C	-5.514600	-1.734000	-0.567700
H	-6.386000	-1.118700	-0.294600
H	-5.690100	-2.153400	-1.568400
H	-5.436300	-2.568600	0.140100
C	-4.348100	1.178300	0.992800
H	-5.446600	1.227700	0.941000
H	-4.037400	1.544900	1.982300
H	-3.934400	1.851700	0.231000
C	-4.268200	-1.113800	1.993800
H	-3.783200	-0.718000	2.897500
H	-5.356800	-1.107500	2.150400
H	-3.938800	-2.154100	1.858300
F	-0.389500	-0.391400	-1.536100

Zero-point correction=	0.488068 (Hartree/Particle)
Thermal correction to Energy=	0.521651
Thermal correction to Enthalpy=	0.522595
Thermal correction to Gibbs Free Energy=	0.423241
Sum of electronic and zero-point Energies=	-3479.077535
Sum of electronic and thermal Energies=	-3479.043953
Sum of electronic and thermal Enthalpies=	-3479.043009
Sum of electronic and thermal Free Energies=	-3479.142363

TS2

C	-4.425800	-1.123000	0.927100
C	-4.120800	0.035600	1.528700
H	-5.384800	-1.615000	1.138600
H	-4.833300	0.486000	2.232800
Cu	-1.493400	-0.511000	-0.321300
P	-2.533500	0.905100	1.182400

P	-3.270700	-1.928300	-0.261700
C	-3.124700	2.528000	0.547600
H	-3.831700	3.010000	1.240400
H	-2.249400	3.177100	0.393700
H	-3.609000	2.371500	-0.426400
C	-1.946700	1.337200	2.873100
H	-1.062900	1.982800	2.764000
H	-2.714300	1.865900	3.458900
H	-1.644500	0.420000	3.397900
C	-4.398900	-2.310000	-1.668300
H	-3.847200	-2.915000	-2.402600
H	-5.295100	-2.860500	-1.342800
H	-4.701000	-1.370900	-2.153000
C	-3.039300	-3.585400	0.509100
H	-3.998100	-4.085900	0.713700
H	-2.436900	-4.205400	-0.170500
H	-2.477400	-3.462200	1.445500
C	0.014100	0.302100	-1.576500
C	0.977300	-0.686400	-1.195200
F	0.981000	-1.727300	-2.062100
C	3.960400	-0.237000	1.100700
C	4.574400	-1.024800	-0.108100
B	2.383000	-0.591700	-0.475300
O	2.724400	0.261000	0.540700
O	3.397700	-1.432600	-0.839100
H	-0.350600	0.104300	-2.590900
C	0.071700	1.734700	-1.225200
C	-0.460700	2.679400	-2.124700
C	0.549900	2.229400	0.005800
C	-0.506400	4.037200	-1.821900
H	-0.850600	2.330100	-3.084600
C	0.519600	3.590100	0.299500
H	0.954100	1.533600	0.739600
C	-0.012600	4.510200	-0.605700
H	-0.927400	4.735800	-2.549200
H	0.914100	3.936300	1.258700

H	-0.039800	5.575500	-0.369700
C	5.394900	-0.138400	-1.045000
H	6.349200	0.159000	-0.586200
H	5.609300	-0.697200	-1.966900
H	4.838700	0.769700	-1.320000
C	5.364800	-2.266400	0.276400
H	5.753000	-2.753600	-0.629300
H	6.220300	-1.997600	0.915400
H	4.737800	-2.991200	0.810400
C	3.576500	-1.139800	2.273300
H	4.465200	-1.523300	2.795600
H	2.975600	-0.556800	2.985700
H	2.964700	-1.987700	1.933600
C	4.789400	0.943100	1.583000
H	4.286600	1.428500	2.431900
H	5.781000	0.604800	1.921700
H	4.921200	1.693500	0.793500
F	0.399100	-1.512600	0.192000

Zero-point correction=	0.487694 (Hartree/Particle)
Thermal correction to Energy=	0.521477
Thermal correction to Enthalpy=	0.522422
Thermal correction to Gibbs Free Energy=	0.420948
Sum of electronic and zero-point Energies=	-3479.070791
Sum of electronic and thermal Energies=	-3479.037008
Sum of electronic and thermal Enthalpies=	-3479.036063
Sum of electronic and thermal Free Energies=	-3479.137537

TS3

C	1.730300	-2.523400	-0.094600
C	2.791300	-1.813500	0.313600
H	1.811800	-3.614300	-0.192100
H	3.734900	-2.324200	0.548400
Cu	0.623500	0.519600	-0.219500
P	2.723500	0.018900	0.495700
P	0.121800	-1.712200	-0.478500
C	3.346700	0.234100	2.218100

H	4.305000	-0.283600	2.378200
H	3.479400	1.308800	2.411100
H	2.597700	-0.153800	2.923000
C	4.180800	0.539400	-0.504500
H	4.330600	1.620300	-0.367800
H	5.097500	0.002700	-0.215200
H	3.963300	0.357200	-1.566200
C	-1.015700	-2.570400	0.685600
H	-2.044900	-2.250500	0.463600
H	-0.939000	-3.665400	0.601000
H	-0.777100	-2.260300	1.712500
C	-0.327600	-2.477300	-2.091500
H	-0.291200	-3.577000	-2.059100
H	-1.349100	-2.153700	-2.340500
H	0.353100	-2.104200	-2.869500
C	-1.062900	1.803900	0.531400
H	-0.661500	2.093300	1.506100
C	-0.801500	2.678100	-0.519200
H	-1.502800	2.858400	-1.337000
F	-0.030500	3.734500	-0.265500
C	-2.219100	0.901400	0.489200
C	-2.817900	0.448300	1.678900
C	-2.757000	0.426400	-0.725800
C	-3.907300	-0.418100	1.659700
H	-2.418700	0.793900	2.635900
C	-3.855400	-0.428800	-0.742100
H	-2.281900	0.711700	-1.667600
C	-4.440500	-0.862900	0.449100
H	-4.348700	-0.747600	2.603100
H	-4.252900	-0.771900	-1.700600
H	-5.296700	-1.539200	0.433900
F	0.326500	1.866200	-1.721100

Zero-point correction=	0.316136 (Hartree/Particle)
Thermal correction to Energy=	0.339838
Thermal correction to Enthalpy=	0.340782
Thermal correction to Gibbs Free Energy=	0.261954

Sum of electronic and zero-point Energies=	-3068.652769
Sum of electronic and thermal Energies=	-3068.629067
Sum of electronic and thermal Enthalpies=	-3068.628123
Sum of electronic and thermal Free Energies=	-3068.706951

TS4

C	1.945800	-2.306800	-0.502000
C	2.965000	-1.616400	0.027700
H	2.094600	-3.354000	-0.797400
H	3.942900	-2.098000	0.163000
Cu	0.650600	0.634700	-0.086700
P	2.779100	0.139300	0.552100
P	0.280800	-1.548900	-0.717400
C	3.395700	0.059100	2.288900
H	4.387200	-0.414900	2.355200
H	3.456900	1.081200	2.690600
H	2.678500	-0.509400	2.897800
C	4.193500	0.935700	-0.319600
H	4.281100	1.974900	0.029500
H	5.143500	0.409100	-0.140500
H	3.977000	0.955700	-1.396900
C	-0.761400	-2.663200	0.310800
H	-1.816800	-2.396400	0.151300
H	-0.602000	-3.723100	0.059500
H	-0.526100	-2.493700	1.370700
C	-0.169200	-2.061400	-2.426500
H	-0.049500	-3.144000	-2.585500
H	-1.220300	-1.782000	-2.591700
H	0.451800	-1.507100	-3.144000
C	-1.120000	1.699200	0.762900
H	-0.705900	1.897900	1.755600
C	-0.887800	2.716200	-0.161000
C	-2.205100	0.711500	0.679700
C	-2.630000	0.050300	1.847000
C	-2.831800	0.347500	-0.530500
C	-3.636800	-0.910300	1.816700

H	-2.157100	0.303800	2.799500
C	-3.841700	-0.610300	-0.556600
H	-2.519000	0.825400	-1.458500
C	-4.255500	-1.250000	0.613500
H	-3.942500	-1.398200	2.745100
H	-4.314200	-0.860000	-1.509800
H	-5.048500	-1.999200	0.587900
F	-1.802600	3.016700	-1.086100
H	-0.284200	3.581100	0.121100
F	0.362700	2.181300	-1.382200

Zero-point correction=	0.316763 (Hartree/Particle)
Thermal correction to Energy=	0.340319
Thermal correction to Enthalpy=	0.341263
Thermal correction to Gibbs Free Energy=	0.263042
Sum of electronic and zero-point Energies=	-3068.651299
Sum of electronic and thermal Energies=	-3068.627743
Sum of electronic and thermal Enthalpies=	-3068.626798
Sum of electronic and thermal Free Energies=	-3068.705020

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Chapter 2.

Copper(I)-Catalyzed Enantioselective γ -Boryl Substitution of Trifluoromethyl Alkenes

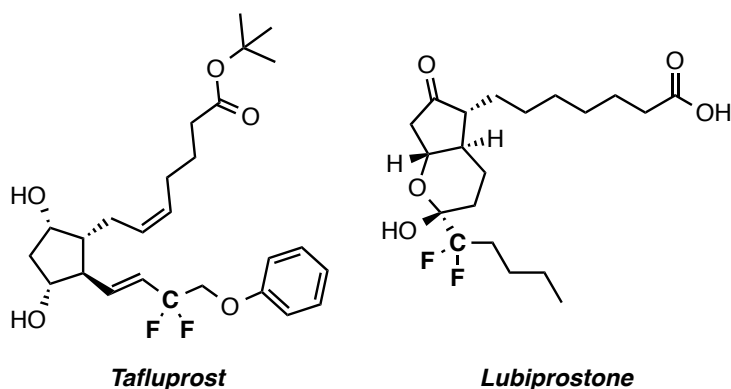
Abstract

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.

Introduction

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 ($-\text{CF}_3$), the introduction of the difluoromethylene ($-\text{CF}_2-$) 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 the development of optically active difluoromethylation methods has increased commensurately.

Figure 1. Representative bioactive *gem*-difluoromethylene-containing molecules.

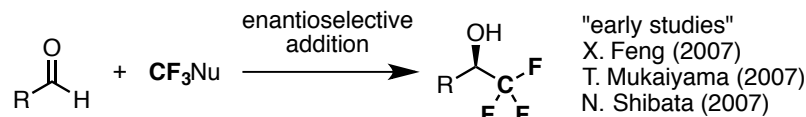


The enantioselective addition of fluorinated nucleophiles to carbonyl compounds is a powerful approach, as the introduction of a fluorinated unit and the generation of a chiral center can be conducted at same time (Scheme 1a and b). Early studies on the enantioselective addition of trifluoromethyl nucleophiles (CF_3Nu) to carbonyl compounds have been reported by e.g. Feng,³ Mukaiyama,⁴ and Shibata⁵ (Scheme 1a), and there are many other examples.⁶ Conversely, the enantioselective addition of difluoromethyl nucleophiles (CHF_2Nu) to carbonyl compounds is limited to one case that proceeded in moderate enantioselectivity, reported by Hu and co-workers (Scheme 2b; up to 64% ee),⁷ while examples for the addition of difluoroalkyl nucleophiles (RCF_2Nu) to carbonyl compounds remain elusive. To achieve such an enantioselective difluoroalkylation of carbonyl groups, we focused on optically active γ,γ -*gem*-difluoroallylboronates with a stereogenic C–B bond (Scheme 1c). The allylboration of aldehydes with enantio-enriched allylboronates generally proceeds in a highly stereospecific manner.⁸ We synthesized such γ,γ -*gem*-difluoroallylboronates with a chiral C–B bond with high optical purity, and when these showed similar stereoselectivity to known allylboronates, we hypothesized that this reaction may offer an efficient pathway to stereodefined b,b-difluoro homoallylic alcohols.

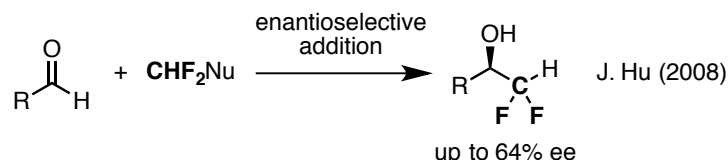
In 2011, Hoveyda and co-workers reported *N*-heterocyclic carbene/copper(I)-catalyzed borylations of an α -(trifluoromethyl)styrene derivative that produce an achiral β,β -difluorostyrene derivative, wherein the β -fluorine elimination is involved in the catalytic cycle.^{9–11} Recently, Zhou and co-workers have reported the synthesis of γ,γ -*gem*-difluoroallylboronates via iron-catalyzed boryl substitutions.^{12,13} However, to the best of our knowledge, examples for the enantioselective synthesis of *gem*-difluoroallylboronates have not yet been reported. 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 provide optically active *gem*-difluoroallylboronates. Subsequently, these boronates can be converted into the corresponding difluoromethylene-containing homoallylic alcohols via allylation reactions (Scheme 2).

Scheme 1. Enantioselective fluoroalkylation of carbonyl compounds.

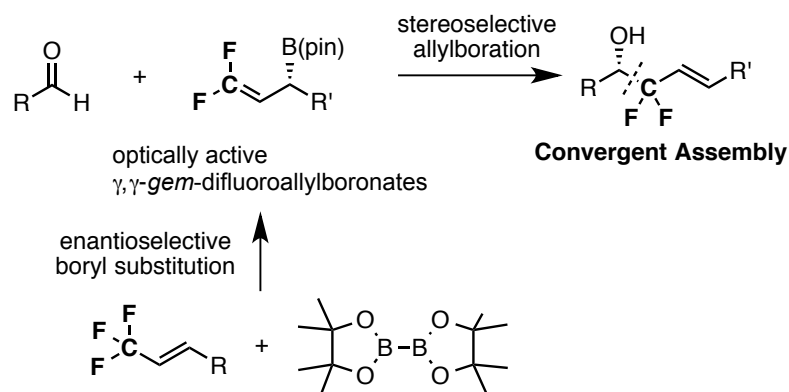
a. Enantioselective addition of trifluoromethyl nucleophiles



b. Enantioselective addition of difluoromethyl nucleophiles



c. Enantioselective borylation/stereoselective allylboration assembly
(This work)

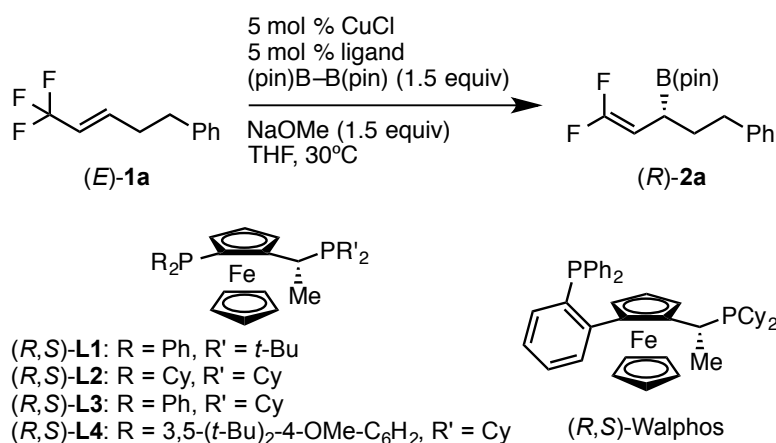


Results and Discussion

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 the desired product (*R*)-**2a** in high yield (91%) and excellent enantioselectivity (97% ee) (Table 1, entry 1). Upon increasing the amount of NaOMe to 10 mol %, the boryl substitution scarcely proceeded (Table 1, entry 2). 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 reactions 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 (Table 1, entries 8–11). The use of

(*R,R*)-BenzP* and (*R,R*)-QuinoxP*, which are effective for the enantioselective allylic boryl substitution,¹⁴ 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 ee (Table 1, entry 12).

Table 1. Optimization of the reaction conditions for the copper(I)-catalyzed enantioselective boryl substitution of CF₃-substituted alkene (*E*)-**1a**.^a

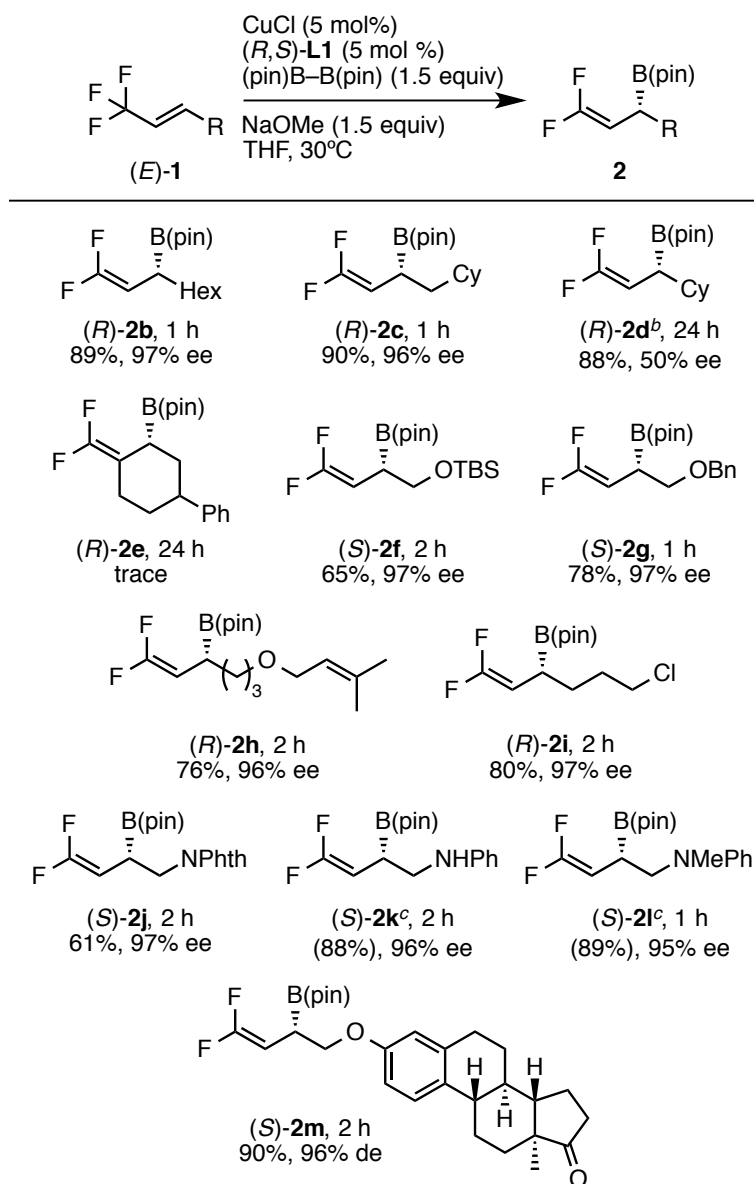


entry	chiral ligand	time (h)	yield (%) ^b	ee (%) ^c
1 ^d	(<i>R,S</i>)- L1	2	91 (85)	97
2 ^e	(<i>R,S</i>)- L1	24	<5	–
3 ^f	(<i>R,S</i>)- L1	4	84	97
4	(<i>R,S</i>)- L2	2	94	46
5	(<i>R,S</i>)- L3	2	91	96
6	(<i>R,S</i>)- L4	2	89	93
7	(<i>R,S</i>)-Walphos	1	91	–5
8	(<i>R,R</i>)-BenzP*	1	90	–84
9	(<i>R,R</i>)-QuinoxP*	21	80	84
10	(<i>R</i>)-Segphos	1	92	50
11	(<i>R,R</i>)-Me-DuPhos	8	92	40
12 ^g	(<i>R,S</i>)- L1	2	97	–61

^aReagents 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°C. ^bNMR yield. The isolated yield is shown in parentheses. ^cThe ee value of (*R*)-**2a** was determined by HPLC analysis of the alcohol derived from the obtained boronate. ^d0.5 mmol scale. ^e10 mol % of NaOMe. ^fT = 0°C. ^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*)-**2b**: 89% yield, 97% ee; (*R*)-**2c**: 90% yield, 96% ee]. A branched CF₃-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 CF₃-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 and side-products were not detected [(*R*)-**2i**: 80% yield, 97% ee].¹⁵ CF₃-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).

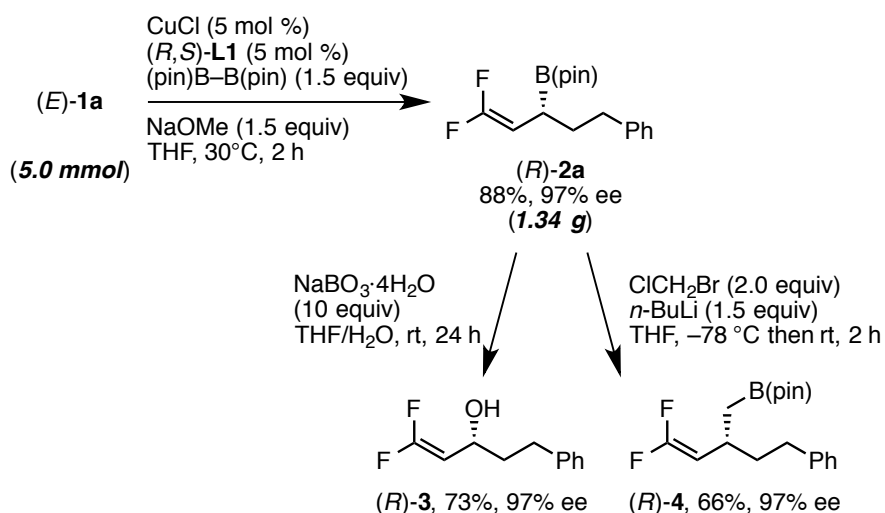
Table 2. Substrate scope of the copper(I)-catalyzed enantioselective boryl substitution of CF₃-substituted alkene (*E*)-**1**.^a



^aReagents 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. ^bT = 50°C. ^cNMR 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.

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 NaBO₃ or to a homologation with a halomethyl lithium reagent.^{16,17} These reactions afforded the corresponding alcohol (*R*)-**3** (73%, 96% ee) and homoallylboronate (*R*)-**4** (66%, 97% ee), respectively.

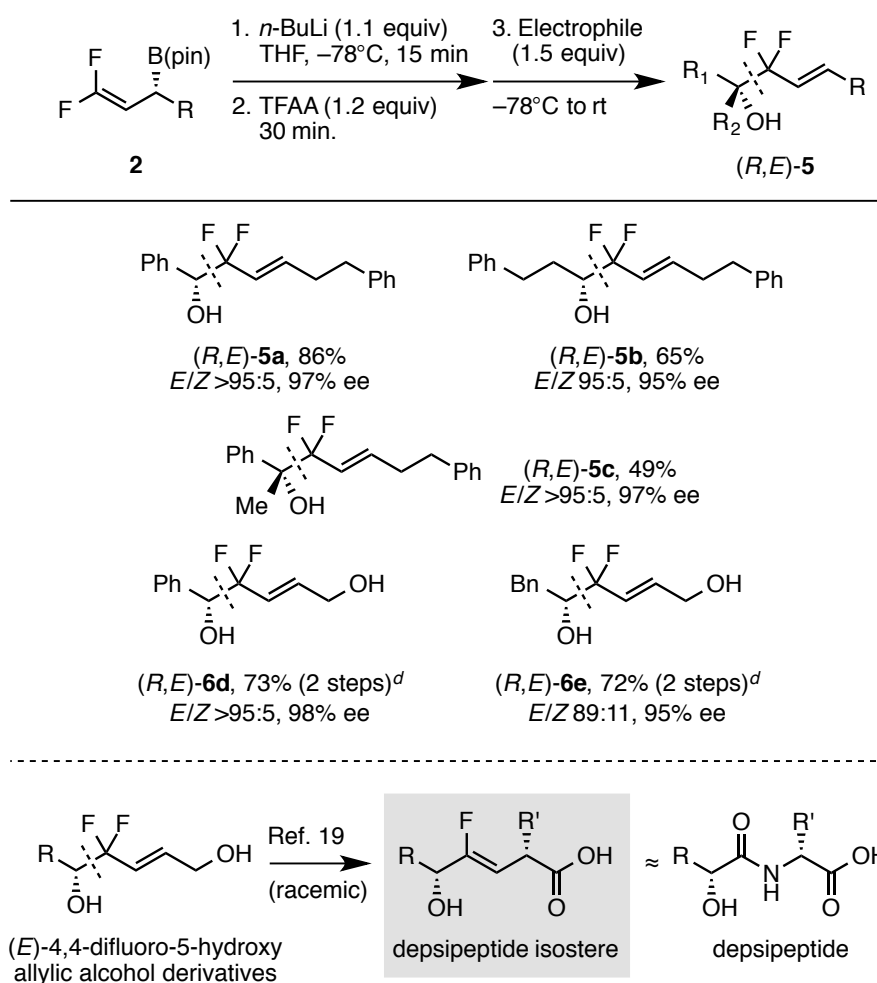
Scheme 2. Gram-scale synthesis of enantioenriched chiral *gem*-difluoroallylboronates and their subsequent derivatization.



We then investigated the allylation of carbonyl compounds with *gem*-difluoroallylboronate **2** (Table 3). The reaction of (*R*)-**2a** with benzaldehyde, 3-phenylpropionaldehyde, acetaldehyde, and acetophenone using Aggarwal's carbonyl allylation conditions¹⁸ afforded the corresponding homoallylic alcohols in high stereoselectivity and stereospecificity (*R,E*)-**5a–c**). 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.¹⁹ 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}

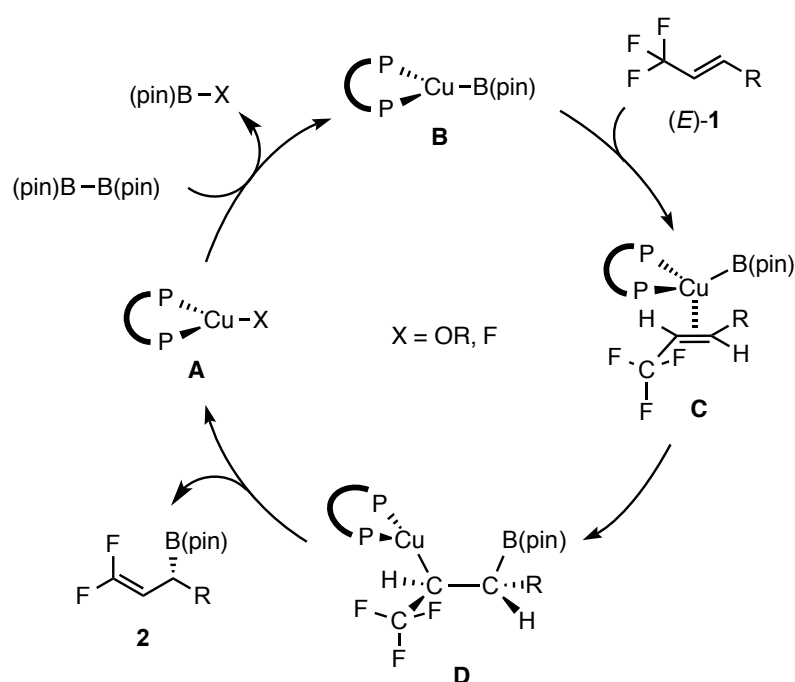


^aReagents and conditions: **2** (0.25 mmol), *n*-BuLi (0.28 mmol), TFAA (0.30 mmol), electrophile (0.38 mmol), in THF (2.5 mL); T = $-78^{\circ}\text{C} \rightarrow \text{rt}$. ^bThe *E/Z* ratio of the products was determined by ^1H NMR spectroscopy and HPLC. ^cIsolated product yields. The ee values of the products were determined by HPLC. ^dThe product was isolated after treatment with TBAF/THF. TFAA = trifluoroacetic anhydride. TBAF = tetrabutylammonium fluoride.

We have postulated a reaction mechanism for the enantioselective γ -boryl substitution, which is shown in Figure 2. Copper(I) alkoxide **A** would initially

react with diboron to afford the borylcopper(I) species **B**. The coordination of the trifluoromethyl alkene (*E*)-**1** to species **B** would result in the formation of the π -complex **C**, which would undergo an insertion reaction to give the alkylcopper(I) intermediate **D**. Then, β -fluorine elimination from this intermediate **D** would proceed to give the product **2** as well as generating the copper(I) fluoride **A**.

Figure 2. Proposed reaction mechanism for enantioselective γ -boryl substitution of trifluoromethyl-substituted alkenes.



Summary

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

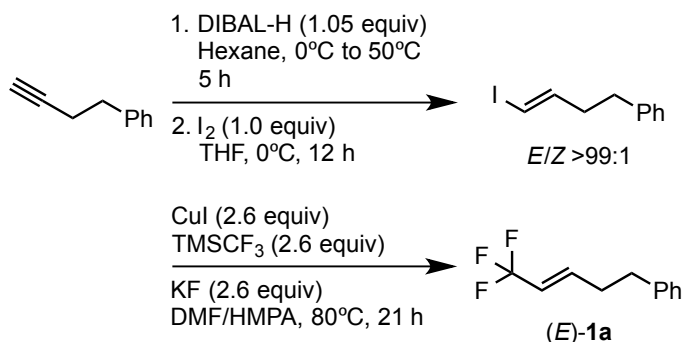
Experimental

General.

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^1H : 400 MHz, ^{13}C : 100 MHz and ^{19}F : 373 MHz). Tetramethylsilane (^1H), CDCl_3 (^{13}C) and Fluorobenzene (^{19}F , δ -113.60) were employed as the external standards, respectively. Mesitylene was used as an internal standard to determine NMR yield. Multiplicity was recorded as follows: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, o = octet, m = multiplet. CuCl (ReagentPlus® grade, 224332-25G, $\geq 99\%$) were purchased from Sigma-Aldrich Co. and used as received. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with a ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. HPLC analyses with chiral stationary phase were carried out using a Hitachi LaChrome Elite HPLC system with a L-2400 UV detector. Specific optical rotations were measured with HORIBA SEPA-300. Medium-pressure column chromatography was carried out on a Biotage Flash Purification System Isolera, which is equipped with a UV detector. Recycle preparative gel permeation chromatography (GPC) was conducted with a JAI LC-9101 using CHCl_3 as the eluent. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

Preparation of Substrates.

Preparation of (*E*)-(5,5,5-trifluoropent-3-en-1-yl)benzene [(*E*)-1a].²⁰



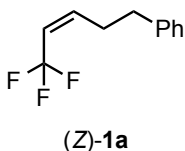
In a vacuum dried 100 mL round bottomed flask, DIBAL-H (1.0 M hexane solution, 27.3 mL) was added dropwise to the mixture of 3-butyne-1-ylbenzene (5.0 g, 26.0 mmol) and dry THF (30.0 mL) at 0°C under a nitrogen atmosphere. The reaction is then heated to 50°C for 5 hours and then cooled to 0°C. Iodine (6.60 g, 27.3 mmol) in THF (20.0 mL) was added dropwise and stirred for 12 hours. The reaction mixture was quenched by 6M HCl at 0°C and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, Hexane only). The resultant product was submitted to the subsequent reaction without further purification.

In a vacuum dried 200 mL round bottomed flask, mixture of potassium fluoride (3.23 g, 55.6 mmol) and copper iodide (10.59 g, 55.6 mmol) was heated under reduced pressure until a greenish color appeared, and after cooling to room temperature, the alkenyl compound (5.84 g, 21.4 mmol) in DMF/HMPA (50.0 mL each) and TMSCF₃ (8.15 mL, 55.6 mmol) were added to this flask successively. The mixture was stirred for 12 hours at 60°C. After quenching with saturated aqueous NH₄Cl solution, The reaction mixture was filtrated by celite. The resulting mixture then extracted with Et₂O three times. The combined organic layer was the dried over MgSO₄. After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, Hexane only). (*E*)-1a was obtained in 70% yield over 2 steps (3.63 g, 18.1 mmol) as a colorless oil.

¹H NMR (401 MHz, CDCl₃, δ): 2.43–2.55 (m, 2H), 2.76 (t, *J* = 7.8 Hz, 2H), 5.59–5.69 (m, 1H), 6.42 (dtq, *J* = 2.3, 6.8, 15.8 Hz, 1H), 7.15–7.34 (m, 5H). ¹³C NMR (100

MHz, CDCl₃, δ): 33.1 (CH₂), 34.2 (CH₂), 118.9 (q, J = 33.2 Hz, CH), 123.1 (q, J = 270.8 Hz, C), 126.3 (CH), 128.3 (CH), 128.5 (CH), 139.70 (q, J = 6.4 Hz, CH), 140.6 (C). ¹⁹F NMR (373 MHz, CDCl₃, δ): -64.5 (s, 3F). HRMS–EI (m/z): [M]⁺ calcd for C₁₁H₁₁F₃, 200.0813; found, 200.0803.

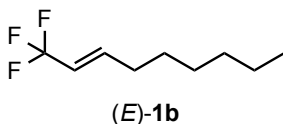
(Z)-(5,5,5-Trifluoropent-3-en-1-yl)benzene [(Z)-1a].



(Z)-1a was prepared from the corresponding aldehyde through Wittig reaction according to the literature followed by copper(I)-mediated trifluoromethylation described above.²¹

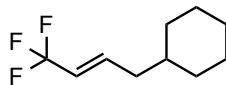
¹H NMR (401 MHz, CDCl₃, δ): 2.59–2.67 (m, 2H), 2.72–2.78 (m, 2H), 5.61 (dqt, J = 1.7, 8.7, 11.8 Hz, 1H), 6.01 (dt, J = 7.6, 11.0 Hz, 1H), 7.17–7.33 (m, 5H). ¹³C NMR (100 MHz, CDCl₃, δ): 29.9 (CH₂), 35.0 (CH₂), 118.9 (q, J = 33.5 Hz, CH), 123.3 (q, J = 272.7 Hz, C), 126.24 (CH), 128.4 (CH), 128.5 (CH), 140.6 (C), 141.8 (q, J = 5.4 Hz, C). ¹⁹F NMR (373 MHz, CDCl₃, δ): -58.73 (s, 3F). HRMS–EI (m/z): [M]⁺ calcd for C₁₁H₁₁F₃, 200.08128; found, 200.08025.

(E)-1,1,1-Trifluoronon-2-ene [(E)-1b].



¹H NMR (401 MHz, CDCl₃, δ): 0.89 (t, J = 7.0 Hz, 3H), 1.23–1.36 (m, 6H), 1.39–1.48 (m, 2H), 2.11–2.19 (m, 2H), 5.60 (dqt, J = 1.6, 6.4, 15.7 Hz, 1H), 6.38 (dtq, J = 2.2, 6.7, 15.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 14.0 (CH₃), 22.6 (CH₂), 28.0 (CH₂), 28.8 (CH₂), 31.5 (CH₂), 31.7 (CH₂), 118.4 (q, J = 33.1 Hz, CH), 123.2 (q, J = 268.9 Hz, C), 140.8 (q, J = 6.4 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): -64.4 (s, 3F). HRMS–EI (m/z): [M]⁺ calcd for C₉H₁₅F₃, 180.1126; found, 180.1131.

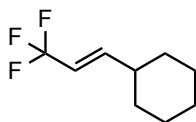
(E)-(4,4,4-Trifluorobut-2-en-1-yl)cyclohexane [(E)-1c].



(E)-1c

^1H NMR (399 MHz, CDCl_3 , δ): 0.86–1.00 (m, 2H), 1.08–1.30 (m, 3H), 1.33–1.46 (m, 1H), 1.62–1.76 (m, 5H), 2.01–2.07 (m, 2H), 5.59 (dtq, J = 1.4, 6.4, 15.8 Hz, 1H), 6.35 (dtq, J = 2.5, 7.6, 15.5 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 26.2 (CH_2), 26.3 (CH_2), 33.0 (CH_2), 37.1 (CH), 39.4 (CH_2), 119.3 (q, J = 32.9 Hz, CH), 123.1 (q, J = 270.2 Hz, C), 139.5 (t, J = 6.7 Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): –64.3 (s, 3F). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_{15}\text{F}$, 192.1126; found, 192.1124.

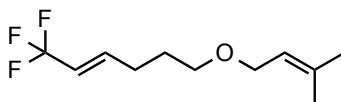
(E)-(3,3,3-Trifluoroprop-1-en-1-yl)cyclohexane [(E)-1d].



(E)-1d

^1H NMR (401 MHz, CDCl_3 , δ): 1.05–1.36 (m, 5H), 1.64–1.72 (m, 1H), 1.73–1.81 (m, 4H), 2.02–2.14 (m, 1H), 5.54 (dq, J = 1.5, 6.4, 15.9 Hz, 1H), 6.32 (ddq, J = 2.1, 6.5, 15.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 25.7 (CH_2), 25.9 (CH_2), 31.7 (CH_2), 39.7 (CH), 116.2 (q, J = 33.2 Hz, CH), 123.6 (q, J = 270.2 Hz, C), 145.8 (q, J = 6.4 Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): –64.2 (s, 3F). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_9\text{H}_{13}\text{F}_3$, 178.0969; found, 178.0973.

(E)-1,1,1-Trifluoro-4-[(3-methylbut-2-en-1-yl)oxy]but-2-ene [(E)-1h].

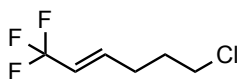


(E)-1h

(E)-**1h** was prepared through the reactions of the corresponding terminal alkyne and HZrCp₂Cl according to the literature followed by copper(I)-mediated trifluoromethylation described above.²²

¹H NMR (392 MHz, CDCl₃, δ): 1.68 (s, 3H), 1.68–1.74 (m, 2H), 1.75 (s, 3H), 2.22–2.29 (m, 2H), 3.43 (t, *J* = 6.3 Hz, 2H), 3.94 (d, *J* = 7.4 Hz, 2H), 5.34 (tsept, *J* = 1.4, 6.9 Hz, 1H), 5.63 (dtq, *J* = 1.6, 6.4, 15.8 Hz, 1H), 6.39 (dtq, *J* = 2.3, 6.8, 15.7 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 17.7 (CH₃), 25.5 (CH₃), 28.0 (CH₂), 28.1 (CH₂), 67.1 (CH₂), 68.5 (CH₂), 118.6 (q, *J* = 33.2 Hz, CH), 121.0 (CH), 123.0 (q, *J* = 268.7 Hz, C), 136.8 (C), 140.0 (q, *J* = 6.6 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): –64.5 (s, 3F). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₁H₁₇F₃O₁, 222.1232; found, 222.1236.

(E)-6-Chloro-1,1,1-trifluorohex-2-ene [(E)-1i].

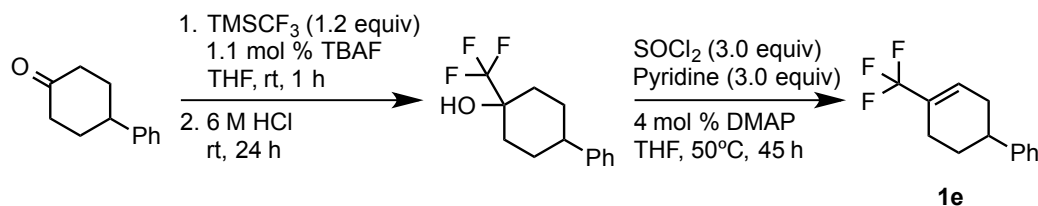


(E)-1i

(E)-**1i** was prepared from the corresponding alkyne according to the procedure described above.

¹H NMR (401 MHz, CDCl₃, δ): 1.89–1.97 (m, 2H), 2.31–2.39 (m, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 5.68 (dtq, *J* = 1.6, 6.3, 15.8 Hz, 1H), 6.36 (dqt, *J* = 2.3, 6.8, 15.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 28.5 (CH₂), 30.6 (CH₂), 43.7 (CH₂), 119.6 (q, *J* = 33.5 Hz, CH), 128.9 (q, *J* = 270.2 Hz, C), 138.8 (q, *J* = 6.4 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): –64.6 (s, 3F). HRMS–EI (*m/z*): [M]⁺ calcd for C₆H₈ClF₃, 172.0267; found, 172.0270.

Preparation of 4-(trifluoromethyl)-1,2,3,6-tetrahydro-1,1'-biphenyl (**1e**).²³

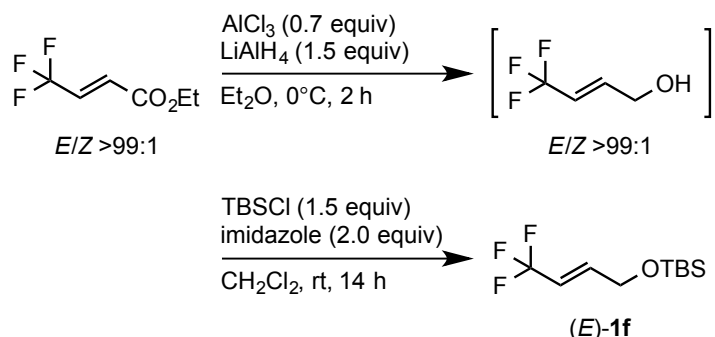


In a vacuum dried 50 mL round bottomed flask, TMSCF_3 (3.56 mL, 24.0 mmol) was added dropwise to the mixture of 4-phenylcyclohexanone (3.48 g, 20.0 mmol) and dry THF (20.0 mL) under a nitrogen atmosphere. Then, the catalytic amount of TBAF (1.0 M in THF, 0.22 mmol) was added dropwise. The reaction mixture was stirred for 1 hours and then aqueous 6M HCl was added and stirred for 24 hours. The reaction mixture was extracted with Et_2O three times. The combined organic layer was dried over MgSO_4 . After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , EtOAc/Hexane 0:100–30:70). The resultant product was submitted to the subsequent reaction without further purification.

In a vacuum dried 50 mL round bottomed flask, pyridine (2.42 mL, 30.0 mmol) and SOCl_2 (2.18 mL, 30.0 mmol) were added to the solution of alcohol (2.44 g, 10.0 mmol) and dry THF (10.0 mL) with 50 mg of DMAP under a nitrogen atmosphere. The mixture was stirred for 45 hours at 50°C. After quenching with saturated aqueous NH_4Cl solution, the mixture was extracted with Et_2O three times and the combined organic layer was dried over MgSO_4 . After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , Hexane only). **1e** was obtained in 87% yield (1.97 g, 8.7 mmol) as a white solid.

^1H NMR (401 MHz, CDCl_3 , δ): 1.74–1.86 (m, 1H), 2.02–2.11 (m, 1H), 2.19–2.37 (m, 3H), 2.41–2.52 (m, 1H), 2.76–2.86 (m, 1H), 6.41–6.46 (m, 1H), 7.20–7.28 (m, 3H), 7.30–7.39 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 22.7 (CH_2), 28.7 (CH_2), 32.3 (CH_2), 39.0 (CH), 124.1 (q, $J = 273.0$ Hz, C), 128.1 (q, $J = 30.6$ Hz, CH), 130.0 (q, $J = 5.7$ Hz, CH), 145.6 (C). ^{19}F NMR (373 MHz, CDCl_3 , δ): –69.8 (s, 3F). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3$, 226.0969; found, 226.0968.

Preparation of (*E*)-*tert*-butyldimethyl[(4,4,4-trifluorobut-2-en-1-yl)oxy]silane [(*E*)-1f].

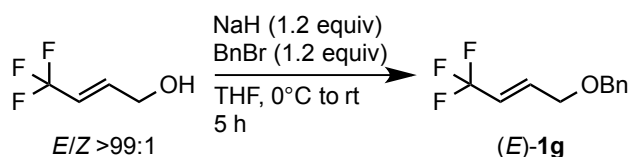


In a 50 mL round bottom flask, a solution of the ester (3.36 g, 20.0 mmol) in Et₂O (11 mL) was added to a slurry of LiAlH₄ (1.14 g, 30.0 mmol) and AlCl₃ (1.86 g, 14.0 mmol) in Et₂O (15.5 mL) dropwise at 0°C. After stirred for 2 hours, the reaction was quenched by addition of water and stirred until a white solid was formed. The mixture was filtered to remove the white precipitation, and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed by evaporation under reduced pressure at 0°C. The resultant product was submitted to the subsequent reaction without further purification.

The corresponding alcohol and imidazole (1.36 g, 20.0 mmol) were dissolved in dry CH₂Cl₂ (20.0 mL) under a nitrogen atmosphere. TBS chloride (2.26 mg, 15.0 mmol) was then added to the solution at room temperature. After stirred for 14 hours, the reaction mixture was quenched by addition of water and extracted with CH₂Cl₂ three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, hexane only) to afford (*E*)-1f (1.64 g, 6.8 mmol, 68%) as a colorless oil.

¹H NMR (401 MHz, CDCl₃, δ): 0.09 (s, 6H), 0.92 (s, 9H), 4.29 (qt, *J* = 3.3, 5.7 Hz, 2H), 5.93 (dtq, *J* = 2.2, 6.7, 15.6 Hz, 1H), 6.45 (dtq, *J* = 2.1, 3.2, 15.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): -5.6 (CH₃), 18.3 (C), 25.8 (CH₃), 61.2 (CH₂), 117.1 (q, *J* = 34.2 Hz, CH), 123.6 (q, *J* = 269.8 Hz, C), 139.4 (q, *J* = 6.1 Hz, CH). ¹⁹F NMR (373 MHz, CDCl₃, δ): -64.3 (s, 3F). HRMS–EI (*m/z*): [*M*]⁺ calcd for C₁₀H₁₉F₃OSi, 240.1157; found, 240.1164.

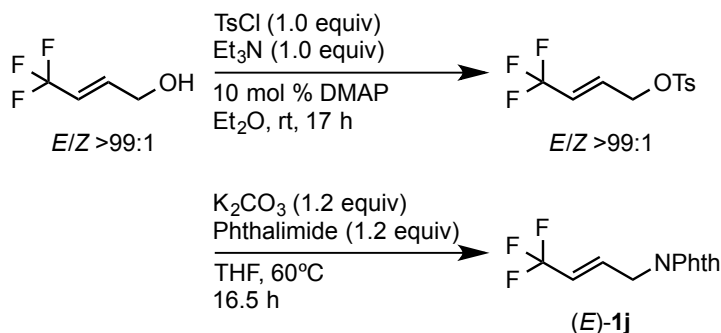
Preparation of (*E*)-[[(4,4,4-trifluorobut-2-en-1-yl)oxy]methyl]benzene [(*E*)-1g**].²⁴**



A solution of the allyl alcohol (1.74 g, 13.8 mmol) in THF (15.0 mL) was added to a suspension of NaH (60 wt.%, 0.656 mg, 16.4 mmol) in THF at 0°C. Benzyl bromide (2.31 mL, 19.5 mmol) was then added and the reaction mixture was stirred for 5 hours at room temperature. The reaction mixture was quenched by addition of water, extracted with Et₂O three times, The combined organic layer was dried over MgSO₄ followed by filtration. The crude mixture was purified by flash column chromatography (SiO₂, diethyl ether/hexane, 0:100–25:75) to afford (*E*)-**1g** (1.58 g, 7.31 mmol, 53%) as a colorless oil.

¹H NMR (401 MHz, CDCl₃, δ): 4.11–4.16 (m, 2H), 4.58 (s, 2H), 5.98 (dtq, *J* = 2.2, 6.6, 15.6 Hz, 1H), 6.44 (dtq, *J* = 2.1, 4.1, 15.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 67.6 (CH₂), 72.8 (CH₂), 118.4 (q, *J* = 34.2 Hz, CH), 123.2 (q, *J* = 270.2 Hz, C), 136.6 (q, *J* = 6.1 Hz, CH), 137.6 (C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –64.8 (s, 3F). HRMS–EI (*m/z*): [*M*]⁺ calcd for C₁₁H₁₁F₃O₁, 216.0762; found, 216.0770.

Preparation of (*E*)-2-(4,4,4-trifluorobut-2-en-1-yl)isoindoline-1,3-dione [(*E*)-1j].²⁴

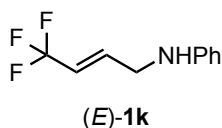


The corresponding alcohol (1.26 g, 10.0 mmol), Et₃N (1.39 mL, 10.0 mmol), and DMAP (122.17 mg, 1.0 mmol) were dissolved in dry Et₂O (25.0 mL) under a nitrogen atmosphere. Tosyl chloride (1.91 g, 10.0 mmol) was then added to the solution at room temperature. After stirred for 17 hours, the reaction mixture was quenched by addition of water and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, EtOAc/hexane, 0:100–25:75) to afford the corresponding tosyl ester (1.15 g, 4.1 mmol, 41%) as a white solid.

In a 50 mL round bottom flask, the corresponding tosyl ester (0.841 g, 3.0 mmol), and phthalimide (0.530 g, 3.0 mmol), were dissolved in dry THF (10.0 mL) under a nitrogen atmosphere. K₂CO₃ (0.498 g, 3.0 mmol) was then added to the solution at room temperature. The mixture was stirred for 16.5 hours at 60°C. The reaction mixture was then quenched by addition of water and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, EtOAc/hexane, 0:100–15:85) to afford (*E*)-1j (0.580 g, 2.28 mmol, 76%) as a white solid.

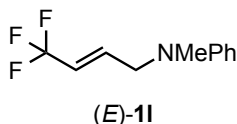
¹H NMR (396 MHz, CDCl₃, δ): 4.41 (dq, *J* = 2.1, 7.8 Hz, 2H), 5.81 (dqt, *J* = 1.7, 6.3, 15.9 Hz, 1H), 6.43 (dtq, *J* = 2.0, 5.9, 15.7 Hz, 1H), 7.74–7.80 (m, 2H), 7.87–7.92 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, δ): 37.5 (CH₂), 121.0 (q, *J* = 34.5 Hz, CH), 122.4 (q, *J* = 270.8 Hz, C), 123.5 (CH), 133.5 (q, *J* = 6.5 Hz, CH), 134.3 (CH), 167.4 (C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –65.0 (s, 3F). HRMS–EI (*m/z*): [*M*]⁺ calcd for C₁₂H₁₈F₃NO₂, 255.0507; found, 255.0507.

(E)-N-(4,4,4-Trifluorobut-2-en-1-yl)aniline [(E)-1k].²⁴



¹H NMR (392 MHz, CDCl₃, δ): 3.92 (br, 3H), 5.89 (dtq, *J* = 1.6, 6.6, 16.2 Hz, 1H), 6.50 (dtq, *J* = 2.2, 4.3, 16.0 Hz, 1H), 6.58–6.65 (m, 2H), 6.76 (tt, *J* = 0.9, 7.5 Hz, 1H), 7.17–7.24 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, δ): 44.1 (CH₂), 112.8 (CH₂), 118.1 (CH), 119.0 (q, *J* = 33.7 Hz, CH), 123.1 (q, *J* = 268.1 Hz, C), 129.3 (CH₂), 138.7 (q, *J* = 6.0 Hz, CH), 147.1 (C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –64.4 (s, 3F). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₀H₁₀F₃N, 201.0765; found, 201.0769.

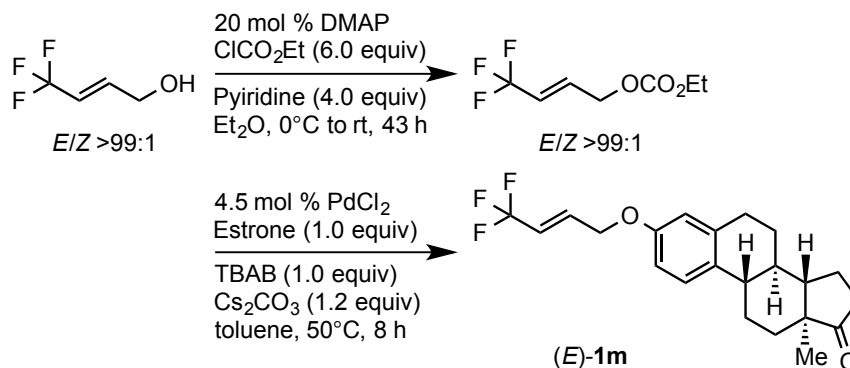
(E)-N-Methyl-N-(4,4,4-trifluorobut-2-en-1-yl)aniline [(E)-1l].²⁴



¹H NMR (401 MHz, CDCl₃, δ): 2.97 (s, 3H), 4.03 (tt, *J* = 2.4, 4.7 Hz, 2H), 5.76 (dq, *J* = 2.0, 6.5, 15.4 Hz, 1H), 6.42 (dtq, *J* = 2.0, 4.2, 15.7 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.76 (t, *J* = 7.2 Hz, 1H), 7.22–7.28 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, δ): 38.1 (CH₃), 53.2 (CH₂), 112.2 (CH₂), 117.1 (CH), 119.0 (q, *J* = 33.9 Hz, CH), 123.1 (q, *J* = 270.51 Hz, C), 129.2 (CH₂), 136.5 (q, *J* = 5.7 Hz, CH), 148.8 (C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –64.2 (s, 3F). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₁H₁₂F₃N, 215.0922; found, 215.0922.

Preparation of

(8*R*,9*S*,13*S*,14*S*)-13-Methyl-3-[[*(E)*-4,4,4-trifluorobut-2-en-1-yl]oxy}-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one [(*E*)-**1m**].²⁵



The ally alcohol (2.52 g, 20.0 mmol), pyridine (6.44 mL, 80.0 mmol), and DMAP (488.7 mg, 4.0 mmol) were dissolved in dry Et₂O (80.0 mL) under a nitrogen atmosphere. Ethyl chloroformate (11.4 mL, 120.0 mmol) was then added to the solution at 0°C. After stirred for 43 hours at room temperature, the reaction mixture was quenched by addition of water and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, Hexane only) to afford the corresponding ester (2.00 g, 10.1 mmol, 51%) as a colorless oil.

In a Schlenk flask, Estrone (540.7 mg, 2.0 mmol), TBAB (644.7 mg, 2.0 mmol), Cs₂CO₃ (644.7 mg, 2.0 mmol), PdCl₂ (16.0 mg, 0.09 mmol) were dissolved in dry toluene (4.0 mL) under a nitrogen atmosphere. The corresponding ether (396.3 mg, 2.0 mmol) was then added to the solution at room temperature. The mixture was stirred for 10 hours at 85°C. The reaction mixture was then quenched by addition of water and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, EtOAc/hexane, 10:90–25:75) to afford the corresponding ether (*E*)-**1m** (290.1 mg, 0.77 mmol, 38%) as a white solid.

¹H, ¹³C and ¹⁹F NMR were in agreement with those in the literature.²⁵

¹H NMR (401 MHz, CDCl₃, δ): 0.92 (s, 3H), 1.39–1.69 (m, 10H), 1.93–2.20 (m, 4H), 2.22–2.30 (m, 1H), 2.39–2.43 (m, 1H), 2.51 (dd, *J* = 8.4, 18.8 Hz, 1H), 2.87–2.93 (m, 2H), 4.62 (td, *J* = 2.9, 5.7 Hz, 2H), 6.06 (dqt, *J* = 2.2, 6.6, 15.4 Hz, 1H), 6.55

(dtq, $J = 1.9, 3.8, 15.8$ Hz, 1H), 6.66 (d, $J = 2.8$ Hz, 1H), 6.72 (dd, $J = 2.8, 8.8$ Hz, 1H), 7.22 (d, $J = 8.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 13.7 (CH_3), 21.5 (CH_2), 25.8 (CH_2), 26.4 (CH_2), 29.5 (CH_2), 31.5 (CH_2), 35.8 (CH_2), 38.2 (CH), 43.9 (CH), 47.9 (C), 50.3 (CH), 65.5 (CH_2), 112.0 (CH), 114.6 (CH), 119.0 (q, $J = 34.5$ Hz, CH), 122.9 (q, $J = 269.9$ Hz, C), 126.4 (CH), 132.9 (C), 135.2 (q, $J = 6.1$ Hz, CH), 137.9 (C), 155.8 (C), 220.8 (C). ^{19}F NMR (373 MHz, CDCl_3 , δ): -64.9 (s, 3F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{22}\text{H}_{25}\text{F}_3\text{O}_2$, 378.1807; found, 378.1806.

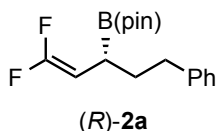
General Borylation Procedure.

Procedure for the copper(I)-catalyzed enantioselective boryl substitution of (*E*)-**1a** (Table 1, Entry 1).

Copper chloride (2.50 mg, 0.0250 mmol) and bis(pinacolato)diboron (190 mg, 0.75 mmol), (*R,S*)-**L1** (13.6 mg, 0.0250 mmol) were placed in an oven-dried reaction vial and put into an argon-filled glovebox. NaOMe (40.7 mg, 0.75 mmol) was placed in a reaction vial. Then the flask was capped with a rubber septum and removed from the glovebox and dry THF (1.00 mL) were added in the vial through the rubber septum using a syringe. After stirring for 30 min at 30°C, (*E*)-**1a** (100 mg, 0.500 mmol) was added to the mixture at 30°C. After the reaction was complete, the reaction mixture was passed through a short silica gel column (Φ : 10 mm, height of the silica- gel column: 30 mm) eluting with Et_2O . The crude material was purified by flash column chromatography (SiO_2 , Et_2O /hexane, typically 0:100–5:95) to give the corresponding borylation product (*R*)-**2a** as a white solid.

Borylation Product Characterizations.

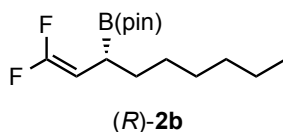
(R)-2-(1,1-Difluoro-5-phenylpent-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(R)-2a].



The reaction was conducted with 100.1 mg (0.50 mmol) of (*E*)-**1a**. The product (*R*)-**2a** was obtained in 85% yield (131.6 mg) with 97% ee.

¹H NMR (392 MHz, CDCl₃, δ): 1.24 (s, 12H), 1.60–1.72 (m, 1H), 1.82–1.93 (m, 2H), 2.51–2.71 (m, 2H), 4.19 (ddd, *J* = 2.7, 10.1, 25.8 Hz, 1H), 7.14–7.20 (m, 3H), 7.24–7.30 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 18.2 (br, B–CH), 24.6 (CH₃), 33.0 (CH₂), 35.1 (CH₂), 78.8 (t, *J* = 21.9 Hz, CH), 83.5 (C), 125.7 (CH), 128.3 (CH), 128.4 (CH), 142.1 (C), 156.1 (t, *J* = 289.9 Hz, C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –89.6 (d, *J* = 57.1 Hz, 1F), –91.8 (dd, *J* = 22.8, 45.5 Hz, 1F). HRMS–EI (*m/z*): [*M*]⁺ calcd for C₁₇H₂₃O₂BF₂, 307.1796; found, 307.1802. [*α*]_D²⁵ +3.5 (*c* 1.70, CHCl₃). The ee value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, *R* isomer: *t*_R = 8.81 min., *S* isomer: *t*_S = 9.80 min.

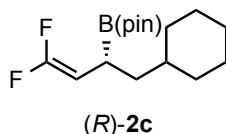
(R)-2-(1,1-Difluoronon-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(R)-2b].



The reaction was conducted with 90.0 mg (0.50 mmol) of (*E*)-**1b**. The product (*R*)-**2b** was obtained in 89% yield (128.3 mg) with 97% ee.

^1H NMR (396 MHz, CDCl_3 , δ): 0.87 (t, J = 6.7 Hz, 3H), 1.17–1.40 (m, 21H), 1.48–1.57 (m, 1H), 1.82 (q, J = 8.3 Hz, 1H), 4.12 (ddd, J = 2.8, 10.7, 25.9 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 14.0 (CH_3), 18.0 (br, B–CH), 22.6 (CH_2), 24.6 (CH_3), 28.7 (C), 29.1 (CH_2), 31.0 (CH_2), 31.7 (CH_2), 79.1 (t, J = 21.1 Hz, CH), 83.4 (C), 156.0 (t, J = 286.4 Hz, C). ^{19}F NMR (373 MHz, CDCl_3 , δ): –90.2 (d, J = 57.1 Hz, 1F), –92.6 (dd, J = 26.6, 51.3 Hz, 1F). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{27}\text{O}_2\text{BF}_2$, 287.2109; found, 287.2100. $[\alpha]_{\text{D}}^{25}$ –8.3 (c 1.02, CHCl_3). The ee value was determined by HPLC analysis of the corresponding ester after oxidation of the boryl group and esterification with *p*-nitrobenzoyl chloride. Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, *R* isomer: t_{R} = 21.30 min., *S* isomer: t_{S} = 20.29 min.

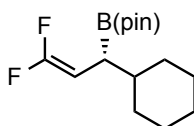
(R)-2-(1-Cyclohexyl-4,4-difluorobut-3-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(R)-2c].



The reaction was conducted with 96.7 mg (0.50 mmol) of (*E*)-**1c**. The product (*R*)-**2c** was obtained in 90% yield (135.1 mg) with 96% ee.

^1H NMR (399 MHz, CDCl_3 , δ): 0.73–0.94 (m, 2H), 1.07–1.42 (m, 6H), 1.24 (s, 12H), 1.60–1.78 (m, 5H), 1.95 (q, $J = 8.6$ Hz, 1H), 4.08 (ddd, $J = 2.8, 10.5, 26.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 15.1 (br, B–CH), 24.58 (CH_3), 24.62 (CH_3), 26.3 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 32.4 (CH_2), 33.7 (CH_2), 36.2 (CH), 38.3 (CH_2), 79.3 (t, $J = 21.1$ Hz, CH), 83.4 (C), 155.9 (t, $J = 286.5$ Hz, C). ^{19}F NMR (373 MHz, CDCl_3 , δ): –90.2 (d, $J = 57.1$ Hz, 1F), –92.6 (dd, $J = 26.6, 51.3$ Hz, 1F). HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{28}\text{O}_2\text{BF}_2$, 300.2181; found, 300.2187. $[\alpha]_{\text{D}}^{26} -23.9$ (c 0.94, CHCl_3). The ee value was determined by HPLC analysis of the corresponding ester after oxidation of the boryl group and esterification with *p*-nitrobenzoyl chloride. Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 2.0/98.0, 0.5 mL/min, 40 °C, *R* isomer: $t_{\text{R}} = 10.33$ min., *S* isomer: $t_{\text{S}} = 9.81$ min.

(R)-2-(1-Cyclohexyl-3,3-difluoroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(R)-2d].

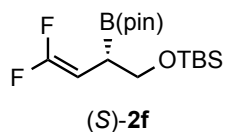


(R)-2d

The reaction was conducted with 89.1 mg (0.50 mmol) of (*E*)-**1d**. The product (*R*)-**2d** was obtained in 88% yield (125.8 mg) with 50% ee.

¹H NMR (399 MHz, CDCl₃, δ): 0.86–1.31 (m, 5H), 1.25 (s, 12H), 1.39–1.52 (m, 1H), 1.58–1.75 (m, 6H), 4.13 (ddd, *J* = 3.1, 11.0, 25.5 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 24.7 (CH₃), 26.3 (CH₂), 26.38 (CH₂), 26.42 (CH₂), 31.8 (CH), 32.8 (CH), 39.3 (CH), 77.3 (t, *J* = 21.5 Hz, CH), 83.3 (C), 156.1 (t, *J* = 289.5 Hz, C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –89.6 (d, *J* = 45.9 Hz, 1F), –92.6 (dd, *J* = 22.8, 45.5 Hz, 1F). HRMS–EI (*m/z*): [M+H]⁺ calcd for C₁₅H₂₅O₂BF₂, 285.1952; found, 285.1941. [α]_D²⁶ –4.2 (*c* 1.07, CHCl₃). The ee value was determined by HPLC analysis of the corresponding ester after oxidation of the boryl group and esterification with *p*-nitrobenzoyl chloride. Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 2.0/98.0, 0.5 mL/min, 40 °C, *R* isomer: *t*_R = 14.55 min., *S* isomer: *t*_S = 15.42 min.

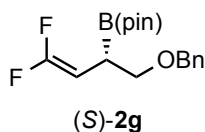
(S)-tert-Butyl{[4,4-difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl]oxy}dimethylsilane [(S)-2f].



The reaction was conducted with 120.2 mg (0.50 mmol) of (*E*)-**1f**. The product (*S*)-**2f** was obtained in 65% yield (113.9 mg) with 97% ee.

¹H NMR (392 MHz, CDCl₃, δ): 0.03 (s, 6H), 0.88 (s, 9H), 1.24 (s, 12H), 2.08 (dt, *J* = 5.8, 11.1 Hz, 1H), 3.64–3.73 (m, 2H), 4.25 (ddd, *J* = 2.5, 10.3, 26.4 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): –5.5 (CH₃), 18.2 (C), 23.1 (br, B–CH), 24.7 (CH₃), 24.7 (CH₃), 25.8 (CH₃), 64.1 (CH₂), 76.7 (t, *J* = 22.0 Hz, CH), 83.6 (C), 156.2 (t, *J* = 284.8 Hz, C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –89.5 (d, *J* = 45.9 Hz, 1F), –91.6 (dd, *J* = 22.9, 45.7 Hz, 1F). HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₆H₃₁O₃BF₂SiNa, 370.2032; found, 370.2038. [α]_D²⁵ +3.6 (*c* 0.97, CHCl₃). The ee value was determined by HPLC analysis of the corresponding ester after oxidation of the boryl group and esterification with *p*-nitrobenzoyl chloride. Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = 0.75/99.25, 0.5 mL/min, 40 °C, *R* isomer: *t*_R = 9.36 min., *S* isomer: *t*_S = 10.08 min.

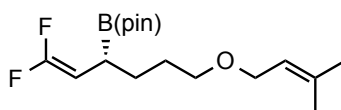
(S)-2-[1-(Benzyloxy)-4,4-difluorobut-3-en-2-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(S)-2g].



The reaction was conducted with 108.1 mg (0.50 mmol) of (*E*)-**1g**. The product (*S*)-**2g** was obtained in 78% yield (126.1 mg) with 97% ee.

^1H NMR (396 MHz, CDCl_3 , δ): 1.24 (s, 12H), 2.24 (dt, $J = 6.8, 9.6$ Hz, 1H), 3.57 (d, $J = 6.3$ Hz, 2H), 4.29 (ddd, $J = 2.5, 10.1, 26.1$ Hz, 1H), 4.51 (d, $J = 4.0$ Hz, 2H), 7.24–7.36 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 20.3 (br, B–CH), 24.6 (CH_3), 24.6 (CH_3), 71.1 (CH_2), 72.7 (CH_2), 76.8 (t, $J = 21.1$ Hz, CH), 83.7 (C), 127.4 (CH_2), 128.2 (CH_2), 138.4 (C), 156.1 (t, $J = 286.9$ Hz, C). ^{19}F NMR (373 MHz, CDCl_3 , δ): –89.1 (d, $J = 45.9$ Hz, 1F), –91.2 (dd, $J = 26.6, 51.3$ Hz, 1F). HRMS–ESI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{17}\text{H}_{23}\text{O}_3\text{BF}_2$, 323.1745; found, 323.1748. $[\alpha]_{\text{D}}^{25}$ –0.4 (c 1.12, CHCl_3). The ee value was determined by HPLC analysis of the corresponding ester after oxidation of the boryl group and esterification with *p*-nitrobenzoyl chloride. Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = 5.0/95.0, 0.5 mL/min, 40 °C, *R* isomer: $t_{\text{R}} = 15.31$ min., *S* isomer: $t_{\text{S}} = 15.78$ min.

(R)-2-{1,1-Difluoro-6-[(3-methylbut-2-en-1-yl)oxy]hex-1-en-3-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(R)-2h].

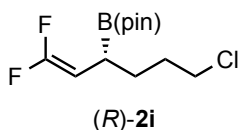


(R)-2h

The reaction was conducted with 111.4 mg (0.501 mmol) of (*E*)-**1h**. The product (*S*)-**2h** was obtained in 76% yield (125.5 mg, 0.380 mmol) with 96% ee.

^1H NMR (392 MHz, CDCl_3 , δ): 1.24 (s, 12H), 1.33–1.48 (m, 1H), 1.49–1.66 (m, 3H), 1.67 (s, 3H), 1.74 (s, 3H), 1.77–1.88 (m, 1H), 3.35–3.44 (m, 2H), 3.39 (d, $J = 6.7$ Hz, 2H), 4.13 (ddd, $J = 2.7, 10.6, 25.5$ Hz, 1H), 5.34 (tsept, $J = 1.4, 6.7$ Hz, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 17.9 (CH_3), 18.1 (br, B–CH), 24.6 (CH_3), 25.7 (CH_3), 27.4 (CH_2), 28.9 (CH_2), 67.1 (CH_2), 69.9 (CH_2), 78.8 (t, $J = 21.1$ Hz, CH), 83.4 (C), 121.2 (CH), 136.5 (C), 156.0 (t, $J = 285.1$ Hz, C). ^{19}F NMR (373 MHz, CDCl_3 , δ): –92.4 (dd, $J = 30.0, 53.9$ Hz, 1F), –89.8 (d, $J = 47.8$ Hz, 1F). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{16}\text{H}_{26}\text{O}_3\text{BF}_2$, 314.1979; found, 314.1976. $[\alpha]_{\text{D}}^{22} -12.4$ (c 0.97, CHCl_3). The ee value was determined by HPLC analysis of the corresponding ester after oxidation of the boryl group and esterification with *p*-nitrobenzoyl chloride. Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 3.0/97.0, 0.5 mL/min, 40 °C, *R* isomer: $t_{\text{R}} = 14.16$ min., *S* isomer: $t_{\text{S}} = 13.00$ min.

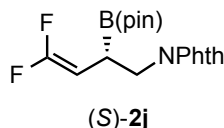
(R)-2-(6-Chloro-1,1-difluorohex-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(R)-2i].



The reaction was conducted with 85.9 mg (0.50 mmol) of (*E*)-**1i**. The product (*S*)-**2i** was obtained in 80% yield (112.0 mg) with 97% ee.

¹H NMR (396 MHz, CDCl₃, δ): 1.25 (s, 12H), 1.40–1.54 (m, 1H), 1.65–1.89 (m, 4H), 3.52 (t, *J* = 6.1 Hz, 2H), 4.13 (ddd, *J* = 2.8, 10.9, 25.5 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 17.6 (br, B–CH), 24.6 (CH₃), 28.2 (CH₂), 31.7 (CH₂), 44.7 (CH₂), 78.5 (t, *J* = 21.1 Hz, CH), 83.6 (C), 156.1 (t, *J* = 287.4 Hz, C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –89.4 (d, *J* = 45.9 Hz, 1F), –91.9 (dd, *J* = 26.6, 51.3 Hz, 1F). HRMS–ESI (*m/z*): [M+H]⁺ calcd for C₁₂H₂₁O₂BClF₂, 280.1322; found, 280.1323. [α]_D²⁶ –12.7 (c 1.18, CHCl₃). The ee value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 2.0/98.0, 0.5 mL/min, 40 °C, *R* isomer: *t*_R = 17.04 min., *S* isomer: *t*_S = 15.93 min.

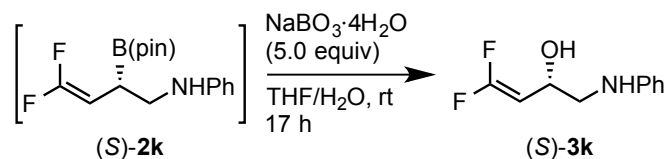
(S)-2-[4,4-Difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl]isoindoline-1,3-dione [(S)-2j].



The reaction was conducted with 127.6 mg (0.50 mmol) of (*E*)-**1j**. The product (*S*)-**2j** was obtained in 61% yield (110.3 mg) with 97% ee.

¹H NMR (392 MHz, CDCl₃, δ): 1.229 (s, 6H), 1.233 (s, 6H), 2.53 (q, *J* = 9.3 Hz, 1H), 3.78–3.85 (m, 2H), 4.20 (ddd, *J* = 1.4, 11.2, 25.3 Hz, 1H), 7.69–7.75 (m, 2H), 7.82–7.87 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, δ): 18.7 (br, B–CH), 24.6 (CH₃), 24.7 (CH₃), 76.2 (t, *J* = 22.0 Hz, CH), 84.0 (C), 123.2 (CH), 132.0 (C), 133.8 (CH), 156.8 (t, *J* = 286.6 Hz, C), 168.3 (C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –91.1 (dd, *J* = 33.9 Hz, 1F), –91.1 (dd, *J* = 22.8, 45.5 Hz, 1F). HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₈H₂₀O₄NBF₂Na, 385.1382; found, 385.1389. [α]_D²⁶ –55.1 (c 0.99, CHCl₃). The ee value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 7.0/93.0, 0.5 mL/min, 40 °C, *R* isomer: *t*_R = 24.64 min., *S* isomer: *t*_S = 25.81 min.

(S)-4,4-Difluoro-1-(phenylamino)but-3-en-2-ol [(S)-3k].

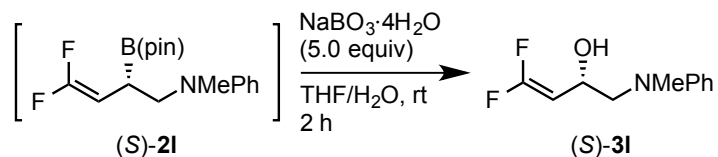


The reaction was conducted with 100.6 mg (0.50 mmol) of (*E*)-**1k**. The NMR yield of (*S*)-**2k** was determined by ¹H NMR analysis (88%) of crude material and the product of borylation product was submitted to the subsequent oxidation without further purification.

In a reaction vial, the crude material of above reaction was dissolved in THF/H₂O (1:1, 1.00 mL). NaBO₃·4H₂O (384.6 mg, 2.50 mmol) was then added at room temperature. After stirred for 17 hours, the reaction mixture was extracted with Et₂O. The organic layer was dried over MgSO₄. After filtration, the crude mixture was purified by flash column chromatography (SiO₂, EtOAc/hexane, 5:95–20:20) to afford the corresponding alcohol [(*S*)-**3k**] (77.9 mg, 0.39 mmol, 78%, 2 steps) as a colorless oil with 96% ee.

¹H NMR (392 MHz, CDCl₃, δ): 2.14 (br, 1H), 3.14–3.23 (m, 1H), 3.29–3.35 (m, 1H), 4.01 (br, 1H), 4.45 (ddd, *J* = 2.6, 9.1, 24.2 Hz, 1H), 4.60–4.68 (m, 1H), 6.65–6.70 (m, 2H), 6.74–6.80 (m, 1H), 7.17–7.24 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, δ): 49.8 (CH₃), 63.8 (d, *J* = 7.7 Hz, CH), 80.2 (dd, *J* = 17.7, 20.6 Hz, CH), 113.3 (CH), 118.3 (CH), 129.3 (CH), 147.5 (C), 156.9 (t, *J* = 292.7 Hz, C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –85.1 (d, *J* = 33.9 Hz, 1F), –85.4 (dd, *J* = 28.5, 1F). HRMS–EI (*m/z*): [*M*]⁺ calcd for C₁₀H₁₁ONF₂, 199.0807; found, 199.0842. [α]_D²⁶ +38.1 (*c* 1.05, CHCl₃). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = 7.0/93.0, 0.5 mL/min, 40 °C, *R* isomer: *t*_R = 27.25 min., *S* isomer: *t*_S = 29.59 min.

(S)-4,4-Difluoro-1-(phenylamino)but-3-en-2-ol [(S)-31].

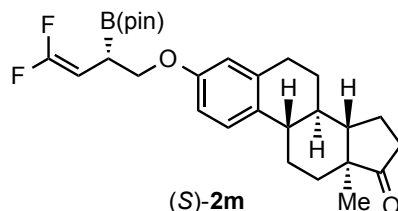


The reaction was conducted with 107.5 mg (0.50 mmol) of (*E*)-**11**. The NMR yield of (*S*)-**21** was determined by ^1H NMR analysis (89%) of crude material and the product of borylation was submitted to the subsequent oxidation without further purification.

In a reaction vial, the crude material of above reaction was dissolved in THF/ H_2O (1:1, 1.00 mL). $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (384.6 mg, 2.50 mmol) was then added at room temperature. After stirred for 2 hours, the reaction mixture was extracted with Et_2O . The organic layer was dried over MgSO_4 . After filtration, the crude mixture was purified by flash column chromatography (SiO_2 , ethyl acetate/hexane, 5:95–15:85) to afford the corresponding alcohol [(*S*)-**31**] (75 mg, 0.350 mmol, 70%, 2 steps) as a colorless oil with 95% ee.

^1H NMR (401 MHz, CDCl_3 , δ): 2.28 (s, 1H), 2.99 (s, 3H), 3.29–3.41 (m, 2H), 4.34–4.44 (m, 1H), 4.65–4.74 (m, 1H), 6.76–6.84 (m, 3H), 7.22–7.29 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 59.6 (CH_2), 63.2 (CH), 80.1 (t, $J = 19.7$ Hz, CH), 80.2 (q, $J = 12.1$ Hz, CH_3), 113.1 (d, $J = 7.7$ Hz, CH), 117.6 (d, $J = 6.7$ Hz, CH), 129.2 (d, $J = 12.5$ Hz, CH), 149.7 (C), 156.8 (t, $J = 292.2$ Hz, C). ^{19}F NMR (373 MHz, CDCl_3 , δ): –85.0 (d, $J = 33.9$ Hz, 1F), –85.6 (dd, $J = 28.5$, 1F). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{11}\text{H}_{13}\text{NF}_2\text{O}$, 213.0965; found, 213.0955. $[\alpha]_{\text{D}}^{26} +4.6$ (c 1.09, CHCl_3). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 5.0/95.0, 0.5 mL/min, 40 °C, *R* isomer: $t_{\text{R}} = 9.82$ min., *S* isomer: $t_{\text{S}} = 9.23$ min.

(8*R*,9*S*,13*S*,14*S*)-3-[[*(S)*-4,4-Difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl]oxy]-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one [(*S*)-**2m**].



The reaction was conducted with 189.2 mg (0.50 mmol) of (*E*)-**1m**. The product (*S*)-**2m** was obtained in 90% yield (219.2 mg) with 96% de.

¹H NMR (399 MHz, CDCl₃, δ): 0.90 (s, 3H), 1.256 (s, 6H), 1.261 (s, 6H), 1.36–1.68 (m, 6H), 1.88–2.19 (m, 4H), 2.20–2.29 (m, 1H), 2.31–2.42 (m, 2H), 2.45–2.55 (m, 2H), 4.01 (d, *J* = 6.0 Hz, 2H), 4.36 (ddd, *J* = 2.4, 10.0, 25.9 Hz, 1H), 6.63 (d, *J* = 2.8 Hz, 1H), 6.70 (dd, *J* = 2.6, 8.6 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 13.7 (CH₃), 19.8 (br, B–CH), 21.4 (CH₂), 24.5 (CH₃), 24.5 (CH₃), 25.8 (CH₂), 26.4 (CH₂), 29.5 (CH₂), 31.4 (CH₂), 35.7 (CH₂), 38.2 (CH), 43.8 (CH), 47.8 (C), 50.2 (CH), 68.8 (CH₂), 76.2–77.2 (m, CH), 83.8 (C), 112.1 (CH), 114.4 (CH), 126.1 (CH), 131.9 (C), 137.5 (C), 156.1 (t, *J* = 287.5 Hz, C), 156.7 (C), 220.7 (C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –88.7 (d, *J* = 45.9 Hz, 1F), –90.4– –90.6 (m, 1F). HRMS–EI (*m/z*): [M+H]⁺ calcd for C₂₈H₃₇O₄BF₂, 485.2789; found, 485.2786. The de value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® AY-3, 2-PrOH/Hexane = 75/25, 0.5 mL/min, 40 °C, *R* isomer: *t_R* = 25.01 min., *S* isomer: *t_S* = 28.88 min.

Single Crystal X-ray Structural Analysis.

The absolute configuration of the product was determined based on X-ray crystallographic analysis of the borylation product (*R*)-**2a**. The absolute configurations of other borylation products were deduced by this product. The details were summarized in Figure S1 and Table S1.

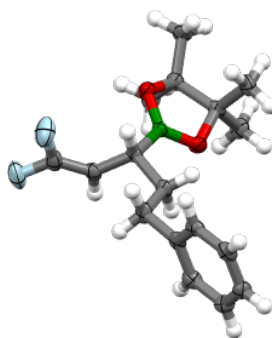


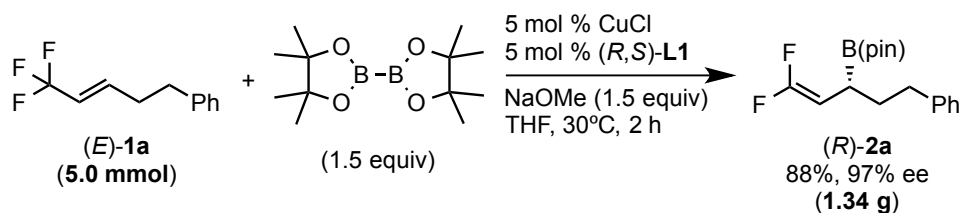
Figure S1. Molecular structure of (*R*)-**2a**. Thermal ellipsoids set at 50% probability.

Table S1. Summary of X-ray crystallographic data for (*R*)-**2a**.

CCDC	1830542
Empirical formula	C ₁₇ H ₂₃ BF ₂ O ₂
Formula weight	308.16
Temperature/K	123
Crystal system	triclinic
Space group	<i>P</i> 1
<i>a</i> / Å	8.4411(3)
<i>b</i> / Å	8.8976(3)
<i>c</i> / Å	11.9567(5)
α /°	102.491(3)
β /°	95.879(3)
γ /°	104.175
Volume/Å ³	838.53(6)
<i>Z</i>	2
ρ_{calc} g/cm ³	1.221
μ /mm ⁻¹	0.761

F(000)	328.0
Crystal size/mm ³	0.1×0.08×0.07
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.678 to 147.216
Index ranges	-10 ≤ h ≤ 10, -10 ≤ k ≤ 11, -14 ≤ l ≤ 14
Reflections collected	15568
Independent reflections	5735 [<i>R</i> _{int} = 0.0469, <i>R</i> _{sigma} = 0.0299]
Data/restraints/parameters	5735/3/405
Goodness-of-fit on F ²	1.071
Final <i>R</i> indexes [<i>I</i> ≥ 2σ (<i>I</i>)]	<i>R</i> ₁ = 0.0471, <i>wR</i> ₂ = 0.1255
Final <i>R</i> indexes [all data]	<i>R</i> ₁ = 0.0480, <i>wR</i> ₂ = 0.1266
Largest diff. peak/hole / e Å ⁻³	0.36/−0.22
Flack parameter	0.09(8)

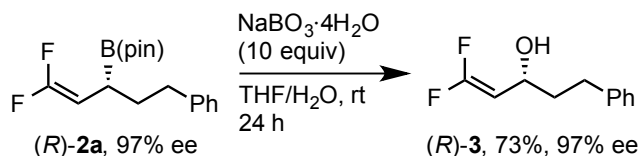
Large Scale Reaction.



Copper chloride (24.8 mg, 0.25 mmol), bis(pinacolato)diboron (1.90 g, 7.5 mmol), (R,S)-L1 (135.6 mg, 0.25 mmol) and NaOMe (406.5 mg, 7.5 mmol) were placed in a round-bottomed flask under a nitrogen atmosphere. Dry THF (10.0 mL) was added in the flask through the rubber septum using a syringe. After stirring for 30 min at 30°C, (E)-1a (1.00 g, 5.0 mmol) was added to the mixture. After the reaction was complete, the reaction mixture was quenched by water and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvents were removed under a reduced pressure. The crude material was purified by flash column chromatography (SiO₂, Et₂O/hexane, 0:100–8:92) to give the corresponding borylation product (R)-2a (88%, 1.36 g, 4.4 mmol) as a colorless oil with 97% ee.

Derivatization of *gem*-Difluoroallylboronates.

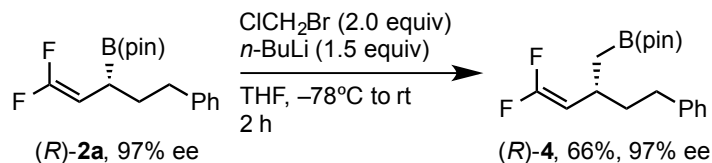
Experimental Procedure of Oxidation of (*R*)-2a.



In a reaction vial, (*R*)-2a (76.7 mg, 0.249 mmol) was dissolved in THF/H₂O (3:2, 5.00 mL). NaBO₃·4H₂O (383.7 mg, 2.49 mmol) was then added at room temperature. After stirred for 24 hours, the reaction mixture was extracted three times with EtOAc, dried over MgSO₄ and filtered. The crude mixture was purified by flash column chromatography (SiO₂, EtOAc/hexane 10:90–30:70) to give the corresponding alcohol (*R*)-3 (35.6 mg, 0.180 mmol, 73%) as a colorless oil with 97% ee.

¹H NMR (392 MHz, CDCl₃, δ): 1.60 (brs, 1H), 1.77–1.89 (m, 1H), 1.91–2.03 (m, 1H), 2.63–2.77 (m, 2H), 4.32–4.46 (m, 2H), 7.15–7.24 (m, 3H), 7.24–7.33 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 31.5 (CH₂), 39.0 (CH₂), 64.8 (d, *J* = 5.6 Hz, CH), 82.6 (t, *J* = 18.3 Hz, CH), 126.0 (CH), 128.3 (CH), 128.4 (CH), 141.2 (C), 156.7 (t, *J* = 290.4 Hz, C). ¹⁹F NMR (373 MHz, CDCl₃, δ): –86.8 (d, *J* = 33.9 Hz, 1F), –86.7 (d, *J* = 45.8 Hz, 1F). HRMS-EI (*m/z*): [*M*]⁺ calcd for C₁₁H₁₂F₂O, 198.0856; found, 198.0854. [*α*]_D²² +18.2 (*c* 0.99, CHCl₃). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, *R* isomer: *t*_R = 9.01 min., *S* isomer: *t*_S = 10.14 min.

Experimental Procedure of Homologation of (R)-2a.

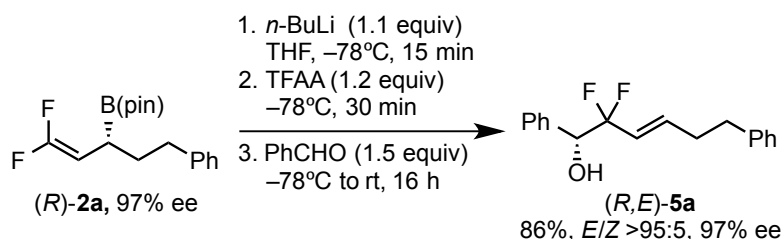


The homologation was performed according to the literature procedure.⁶ In an oven-dried reaction vial, (R)-2a (77.6 mg, 0.252 mmol) and bromochloromethane (34 μL , 0.507 mmol) were dissolved in dry THF (2.00 mL) in nitrogen atmosphere. After the mixture was cooled to -78°C , a solution of *n*-BuLi in hexane (1.55 M, 245 μL , 0.380 mmol) was added dropwise. The mixture was stirred at room temperature for 1.5 hours. The mixture was then quenched by addition of saturated aqueous NH_4Cl solution and extracted three times with Et_2O . The combined organic layer was washed with brine, dried over MgSO_4 followed by filtration. The crude material was purified by medium-pressure column chromatography (SiO_2 , EtOAc/hexane , 0:100–10:90) to give the corresponding (R)-4 (53.8 mg, 0.167 mmol, 86%) as a colorless oil with 97% ee.

^1H NMR (392 MHz, CDCl_3 , δ): 0.93 (ddd, $J = 7.2, 15.5, 41.9$ Hz, 2H), 1.23 (s, 6H), 1.24 (s, 6H), 1.49–1.62 (m, 1H), 1.69–1.81 (m, 1H), 2.44–2.70 (m, 3H), 4.08 (ddd, $J = 3.9, 10.6, 24.7$ Hz, 1H), 7.13–7.22 (m, 3H), 7.22–7.32 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 18.7 (br, B– CH_2), 24.7 (CH_3), 24.8 (CH_3), 29.7 (d, $J = 3.7$ Hz, CH), 33.7 (CH_2), 39.7 (CH_2), 83.1 (C), 83.5 (t, $J = 19.7$ Hz, CH), 125.7 (CH), 128.26 (CH), 128.30 (CH), 142.2 (C), 156.0 (t, $J = 286.1$ Hz, C). ^{19}F NMR (373 MHz, CDCl_3 , δ): -90.8 (q, $J = 22.7$ Hz, 1F), -90.4 (d, $J = 57.0$ Hz, 1F). HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{18}\text{H}_{25}\text{BF}_2\text{O}_2$, 321.1952; found, 321.1937. $[\alpha]_{\text{D}}^{22} -7.9$ (c 1.01, CHCl_3). The ee value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IC-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40°C , *R* isomer: $t_{\text{R}} = 11.22$ min., *S* isomer: $t_{\text{S}} = 12.22$ min.

Allylation of Carbonyl Compounds with *gem*-Difluoroallylboronates

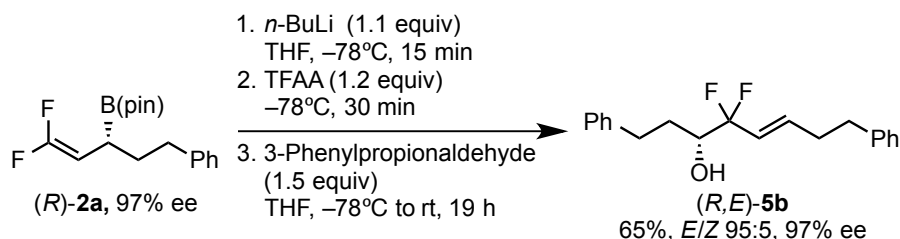
Experimental procedures of allylation reaction between (R)-2a and benzaldehyde.¹⁸



In an oven-dried reaction vial, a solution of difluoroallylboronate (R)-2a (77.8 mg, 0.252 mmol) in THF (2.5 mL) was treated with *n*-BuLi in hexane (1.55 M, 185 μL , 0.287 mmol) at -78°C and the solution was stirred for 15 min. Trifluoroacetic anhydride (42 μL , 0.3 mmol) was added dropwise to this mixture and the reaction was stirred for a further 30 min at -78°C . Benzaldehyde (38 μL , 0.375 mmol) was then added at -78°C and the mixture was allowed to warm up to room temperature. After 16 hours, the reaction was quenched by addition of saturated aqueous NH_4Cl solution and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over MgSO_4 followed by filtration. The crude material was purified by flash column chromatography (SiO_2 , EtOAc/hexane, 0:100–30:70) to give the corresponding (R,E)-5a (62.5 mg, 0.217 mmol, 86%) as a colorless oil with 97% ee. The stereoselectivity of (R,E)-5a was determined by ^1H NMR analysis (*E/Z* >95:5).

^1H NMR (392 MHz, CDCl_3 , δ): 2.05–2.48 (m, 3H), 2.68 (t, $J = 7.6$ Hz, 2H), 4.83 (t, $J = 9.4$ Hz, 1H), 5.40–5.53 (m, 1H), 6.05 (dt, $J = 7.1, 15.7$ Hz, 1H), 7.13 (d, $J = 8.2$ Hz, 2H), 7.21 (t, $J = 7.2$ Hz, 1H), 7.24–7.37 (m, 7H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 33.6 (CH_2), 34.7 (CH_2), 76.0 (t, $J = 30.5$ Hz, CH), 119.7 (t, $J = 245.2$ Hz, C), 121.9 (t, $J = 24.9$ Hz, CH), 126.1 (CH), 127.6 (CH), 128.1 (CH), 128.38 (CH), 128.41 (CH), 128.6 (CH), 136.1 (C), 137.5 (t, $J = 8.9$ Hz, CH), 140.9 (C). ^{19}F NMR (373 MHz, CDCl_3 , δ): -107.6 (d, $J = 239.1$ Hz, 1F), -106.2 (d, $J = 239.1$ Hz, 1F). HRMS-ACPI (m/z): $[\text{M}-\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{OF}_2$, 287.1253; found, 287.1256. $[\alpha]_{\text{D}}^{21} -30.8$ (c 0.99, CHCl_3). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OZ-3, 2-PrOH/hexane = 5:95, 0.5 mL/min, 40°C , *R* isomer: $t_{\text{R}} = 13.79$ min., *S* isomer: $t_{\text{S}} = 11.44$ min.

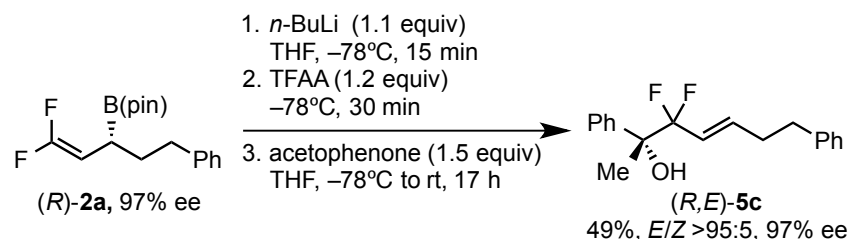
Allylation reaction between (*R*)-**2a** and 3-phenylpropionaldehyde.



The reaction was conducted with 77.4 mg (0.251 mmol) of (*R*)-**2a**. The title compound was purified by flash column chromatography (SiO_2 , EtOAc/hexane, 10:90–20:80). The compound (*R,E*)-**5b** was obtained in 65% isolated yield (52.0 mg, 0.164 mmol) with 97% ee as a white solid. The stereoselectivity of (*R,E*)-**5b** was determined by ^1H NMR analysis (*E/Z* 95:5).

^1H NMR (392 MHz, CDCl_3 , * indicates signals of the minor isomer, δ): 1.59–1.71 (m, 1H), 1.78–1.88 (m, 2H), 2.39–2.50 (m, 2H), 2.60–2.70 (m, 1H), 2.74 (t, J = 7.6 Hz, 2H), 2.82–2.93 (m, 1H), 3.60–3.74 (m, 1H), 5.42–5.61 (m, 1H), 5.86* (ddt, J = 2.1, 6.8, 15.1 Hz, 0.05H), 6.14 (ddt, J = 2.3, 6.8, 15.9 Hz, 0.95H), 7.11–7.35 (m, 10H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 31.5 (CH_2), 31.6 (CH_2), 33.7 (CH_2), 34.7 (CH_2), 72.8 (t, J = 30.0 Hz, CH), 120.4 (t, J = 244.3 Hz, C), 122.2 (t, J = 25.4 Hz, CH), 126.0 (CH), 126.1 (CH), 128.40 (CH), 128.43 (CH), 128.5 (CH), 137.1 (t, J = 8.9 Hz, CH), 140.9 (C), 141.2 (C). ^{19}F NMR (373 MHz, CDCl_3 , * indicates signals of the minor isomer, δ): -110.0 (d, J = 250.7 Hz, 1F), -106.8 (d, J = 250.3 Hz, 1F), -105.1^* (d, J = 262.2 Hz, 1F), -103.6^* (d, J = 250.3 Hz, 1F). HRMS-APCI (m/z): $[\text{M}-\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{21}\text{OF}_2$, 315.1566; found, 315.1573. $[\alpha]_{\text{D}}^{23} +10.4$ (c 1.01, CHCl_3). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OJ-3, 2-PrOH/hexane = 5:95, 0.5 mL/min, 40°C , *R* isomer: t_{R} = 48.04 min., *S* isomer: t_{S} = 55.28 min.

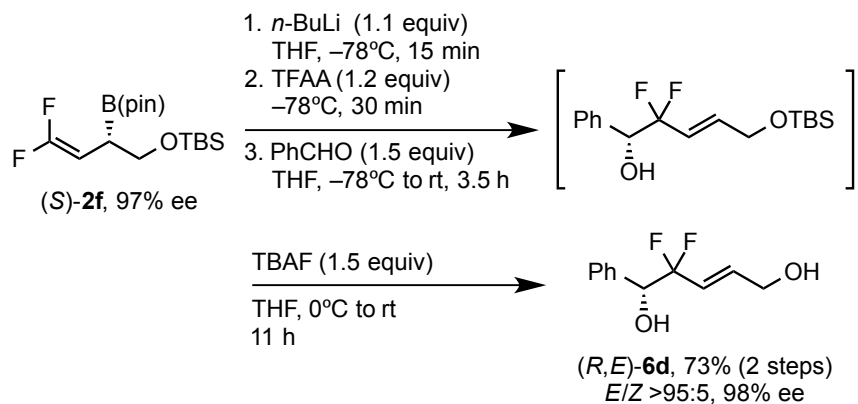
Allylation reaction between (*R*)-**2a** and acetophenone.



The reaction was conducted with 76.4 mg (0.248 mmol) of (*R*)-**2a**. The title compound was purified by flash column chromatography (SiO_2 , EtOAc/hexane, 0:100–30:70) and gel-permeation chromatography. The compound (*R,E*)-**5c** was obtained in 49% isolated yield (36.6 mg, 0.121 mmol) with 97% ee as a colorless oi. The stereoselectivity of (*R,E*)-**5c** was determined by ^1H NMR analysis (*E/Z* > 95:5).

^1H NMR (392 MHz, CDCl_3 , δ): 1.63 (s, 3H), 2.14 (s, 1H), 2.29–2.41 (m, 2H), 2.57–2.70 (m, 2H), 5.33–5.47 (m, 1H), 5.98 (dtt, $J = 2.3, 6.8, 15.8$ Hz, 1H), 7.07–7.14 (m, 2H), 7.17–7.24 (m, 1H), 7.24–7.35 (m, 5H), 7.37–7.43 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 23.5 (CH_3), 33.6 (CH_2), 34.7 (CH_2), 76.4 (t, $J = 27.2$ Hz, C), 120.7 (t, $J = 248.5$ Hz, C), 122.2 (t, $J = 25.4$ Hz, CH), 126.1 (CH), 126.3 (CH), 127.6 (CH), 127.8 (CH), 128.38 (CH), 128.42 (CH), 137.1 (t, $J = 8.4$ Hz, CH), 140.8 (C), 141.0 (C). ^{19}F NMR (373 MHz, CDCl_3 , δ): -110.8 (d, $J = 250.3$ Hz, 1F), -108.1 (d, $J = 239.1$ Hz, 1F). HRMS-ACPI (m/z): $[\text{M}-\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{OF}_2$, 301.1409; found, 301.1411. $[\alpha]_{\text{D}}^{21} -18.3$ (c 1.04, CHCl_3). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OZ-3, 2-PrOH/hexane = 5:95, 0.5 mL/min, 40°C , *R* isomer: $t_{\text{R}} = 9.20$ min., *S* isomer: $t_{\text{S}} = 8.50$ min.

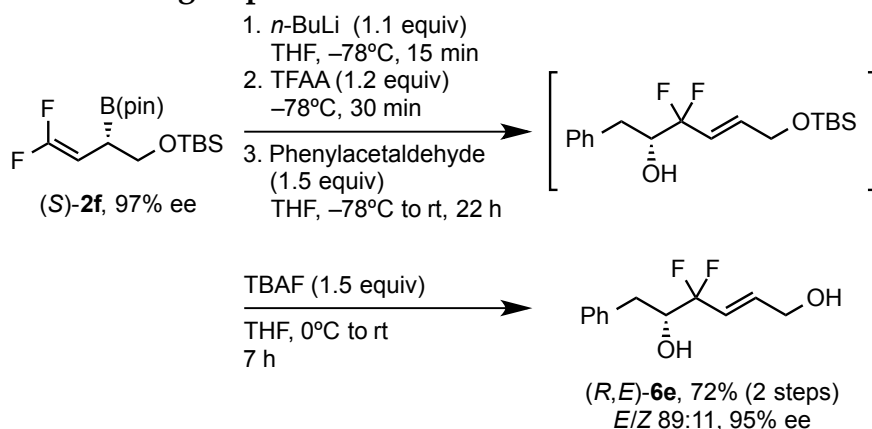
Allylation reaction between (S)-2f and benzaldehyde followed by deprotection of TBS group.



The reaction was conducted with 87.1 mg (0.25 mmol) of (S)-2f. The title compound was submitted to the subsequent deprotection without further purification. In a reaction vial, the crude material of the allylation reaction was dissolved in THF (2.0 mL). TBAF (1.0 M in THF solution, 375 μ L, 0.375 mmol) was then added at 0°C. After stirred for 11 hours at room temperature, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution and extracted three times with Et_2O . The combined organic layer was washed with brine, dried over MgSO_4 followed by filtration. The crude material was purified by flash column chromatography (SiO_2 , EtOAc /hexane, 0:100–50:50) to give the corresponding (R,E)-6d (38.9 mg, 0.181 mmol, 73% over 2 steps) as a colorless oil with 98% ee. The stereoselectivity of (R,E)-6d was determined by ^1H NMR analysis ($E/Z >95:5$).

^1H NMR (392 MHz, CDCl_3 , δ): 1.40–1.63 (br, 1H), 2.46–2.61 (br, 1H), 4.21 (br, 2H), 4.92 (t, $J = 9.4$ Hz, 1H), 5.75–5.88 (m, 1H), 6.31 (dt, $J = 2.2, 4.3, 16.2$ Hz, 1H), 7.31–7.46 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 61.7 (CH_2), 75.9 (t, $J = 30.2$ Hz, CH), 119.7 (t, $J = 245.8$ Hz, CH), 121.3 (t, $J = 25.4$ Hz, CH), 127.6 (CH), 128.2 (CH), 128.7 (CH), 136.1 (C), 136.6 (t, $J = 8.7$ Hz, CH). ^{19}F NMR (373 MHz, CDCl_3 , δ): -107.8 (d, $J = 251.0$ Hz, 1F), -106.0 (d, $J = 251.0$ Hz, 1F). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{F}_2\text{Na}$, 237.0697; found, 237.0700. $[\alpha]_{\text{D}}^{24} -23.4$ (c 0.94, CHCl_3). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® AY-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, R isomer: $t_{\text{R}} = 20.13$ min., S isomer: $t_{\text{S}} = 19.33$ min.

Allylation reaction between (S)-2f and phenylacetaldehyde followed by deprotection of TBS group.



The reaction was conducted with 87.1 mg (0.25 mmol) of (S)-2f. The title compound was submitted to the subsequent deprotection without further purification. In a reaction vial, the crude material of the allylation reaction was dissolved in THF (2.0 mL). TBAF (1.0 M in THF solution, 375 μ L, 0.375 mmol) was then added at 0°C. After stirred for 22 hours at room temperature, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution and extracted three times with Et_2O . The combined organic layer was washed with brine, dried over MgSO_4 followed by filtration. The crude material was purified by flash column chromatography (SiO_2 , EtOAc /hexane, 0:100–50:50) to give the corresponding (R,E)-6e (41.2 mg, 0.181 mmol, 72% over 2 steps) as a colorless oil with 95% ee. The stereoselectivity of (R,E)-6e was determined by ^1H NMR analysis (E/Z 89:11).

^1H NMR (401 MHz, CDCl_3 , δ): 2.01 (br, 1H), 2.46 (br, 1H), 2.67 (dd, $J = 10.6, 14.2$ Hz, 1H), 3.0 (d, $J = 14.4$ Hz, 1H), 3.97 (dt, $J = 9.6, 18.8$ Hz, 1H), 4.21–4.28 (m, 1.78H), 4.34–4.40* (m, 0.22H), 5.56–5.69* (m, 0.11H), 5.87–6.00 (m, 0.89H), 6.03–6.13* (m, 0.11H), 6.31 (dtq, $J = 2.3, 4.4, 15.7$ Hz, 0.89H), 7.19–7.36 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 36.4 (CH_2), 61.6 (CH_2), 74.6 (t, $J = 30.7$ Hz, CH), 120.1 (t, $J = 244.8$ Hz, CH), 121.6 (t, $J = 25.4$ Hz, CH), 126.7 (CH), 128.5 (CH), 129.3 (CH), 136.3 (t, $J = 8.6$ Hz, CH), 137.3 (C). ^{19}F NMR (373 MHz, CDCl_3 , δ): -110.8 (d, $J = 251.0$ Hz, 1F), -106.2 (d, $J = 250.7$, 1F). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2\text{F}_2\text{Na}$, 251.0854; found, 251.0856. $[\alpha]_{\text{D}}^{24} +27.7$ (c 0.94, CHCl_3). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 20/80, 0.5 mL/min, 40 °C, R isomer: $t_{\text{R}} = 16.69$ min., S isomer: $t_{\text{S}} = 10.19$ min.

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Chapter 3.

Copper(I)-Catalyzed Diastereoselective Borylative

***Exo*-Cyclization of Alkenyl Aryl Ketones**

Abstract

Copper(I)-catalyzed diastereoselective borylative *exo*-cyclization of alkenyl ketones with bis(pinacolato)diboron is reported. The reaction of alkenyl aryl ketones under a CuCl/Xantphos catalyst system provides four- or five-membered-ring *syn*-2-(borylmethyl)cycloalkanol derivatives in good yields with high *syn* selectivities. The utility of this method is demonstrated by further transformations of the cyclic products.

Introduction

Borylation of multiple bonds with concomitant C–C bond formation can provide rapid access to complex organoboron compounds,^{1–6} which are regarded as useful building blocks in organic synthesis.⁷ Recently, copper-catalyzed borylation has emerged as a useful method for synthesizing organoboron compounds.^{8,9} Our research group is interested in the efficient synthesis of small-ring carbocyclic organoboron compounds such as cyclopropyl- or cyclobutylboronates, and have reported several copper(I)-catalyzed borylative cyclization reactions of alkenes bearing a good leaving group (Scheme 1a).¹⁰ In this reaction, the *in situ* generated borylcopper species preferably reacts with the alkene moiety to afford the alkylcopper species. Then, subsequent intramolecular substitution leads to *exo*-cyclization products (Scheme 1a).

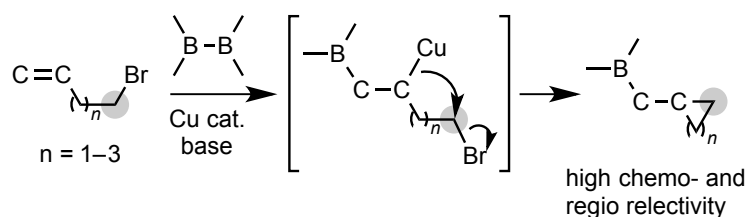
Looking to extend our borylative cyclization strategy, we envisioned a copper(I)-catalyzed borylative cyclization of γ -alkenyl ketones to provide 2-(borylmethyl)cyclobutanol derivatives containing two adjacent congested stereocenters (Scheme 1c). Cyclobutanols are an important structural motif in organic chemistry because they are often found in natural products,¹¹ and are used as versatile building blocks through various transformations with concomitant C–C bond activation driven by the relief of the ring strain.¹² However, the routes to access stereodefined cyclobutanols containing multiple stereogenic centers are still relatively limited compared with those for three-, five- and six-membered carbocyclic compounds.^{12a,13} The borylative cyclization of γ -alkenyl ketones is a novel and efficient route for the synthesis of 2-(borylmethyl)cyclobutanol derivatives. Clark and co-workers have already reported that carbonyl borylation proceeds exclusively over alkene borylation

in the presence of a CuCl/N-heterocyclic carbene (NHC) catalyst when the two groups are present in the same molecule. To achieve the *exo*-borylative cyclization of alkenyl ketones, the chemoselectivity preference of the borylation must be switched from the ketone group to the alkene group using appropriate substrates, catalysts and reagents. (Scheme 1b).¹⁴

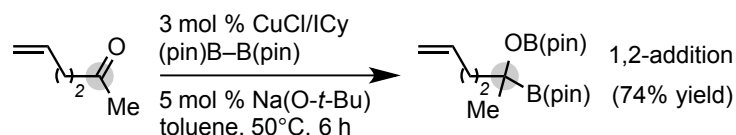
Scheme 1. Copper(I)-catalyzed borylative cyclization.

previous works

a. copper-catalyzed borylative *exo*-cyclization (Ito)

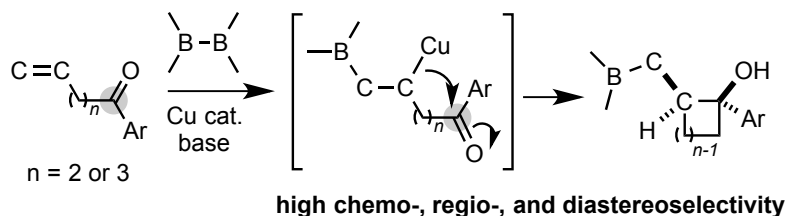


b. copper-catalyzed diboration of ketones (Clark)



this work

c. copper-catalyzed diastereoselective *exo*-cyclization



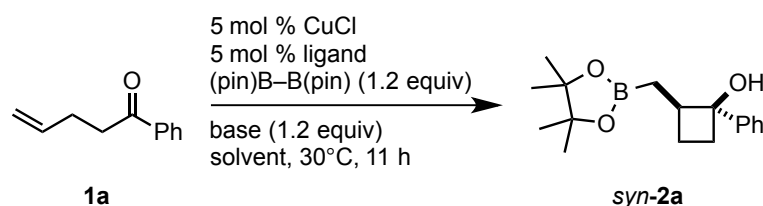
Herein, we report the diastereoselective *exo*-borylative cyclization of alkenyl aryl ketones catalyzed by a copper(I)/Xantphos catalyst system, which provides *syn*-1-aryl-2-(borylmethyl)cyclobutanol derivatives in high yields and with excellent diastereoselectivity. It is noteworthy that *syn*-selective synthesis of 1,2-substituted tertiary cyclobutanols has been scarcely reported.^{15,16} Furthermore, the reaction of δ -alkenyl aryl ketone also affords the corresponding five-membered-ring product.

Results and Discussion

First, we screened reaction conditions for the borylative cyclization of γ -alkenyl ketone **1a** with copper catalyst systems (Table 1). The boryl

cyclization of **1a** with CuCl/Xantphos (5 mol %), bis(pinacolato)diboron (1.2 equiv), and K(O-*t*-Bu) (1.2 equiv) in dimethoxyethane (DME) afforded the corresponding *syn*-2-(borylmethyl)cyclobutanol *syn*-**2a** in high yield (entry 1, 87% yield),¹⁷ and the corresponding diastereomer was not detected by ¹H and ¹³C NMR analyses of the crude reaction mixture. Using catalytic amount of K(O-*t*-Bu) (10 mol %) retarded the yield (66%, entry 2). The reaction of **1a** in the absence of the Xantphos ligand resulted in no reaction (entry 3). Product **2a** is unstable during purification using silica-gel chromatography. Thus, purification was conducted after esterification of the hydroxy group of the crude product **2a** (56% isolated yield, Table 1, entry 1).¹⁸ The relative configuration of the major product was unambiguously determined to be the *syn* configuration by X-ray crystallographic analysis of the boryl cyclization product after esterification (Figure S1). The reaction with monodentate PPh₃ provided no borylative cyclization product (entry 4), and bidentate phosphines afforded lower yields than Xantphos (entries 5–8). Clark et al. reported that selective diboration of the ketone moiety in γ -alkenyl methyl ketone using a borylcopper(I)/ICy complex and Na(O-*t*-Bu) gives the corresponding tertiary α -hydroxy boronate ester.¹⁴ In our case, the reaction with an NHC ligand precursor (ICy·HCl = 1,3-dicyclohexyl-imidazolium chloride) led to a complex mixture (entry 9). When the reaction was performed with Cu(O-*t*-Bu) (1 equiv), instead of the catalytic CuCl and stoichiometric K(O-*t*-Bu) conditions, no desired product was obtained (entry 10). Next, the effect of the base was investigated. Without base, the desired product was not formed (entry 11). The use of Na(O-*t*-Bu), KOMe or KOEt in DME, or the use of THF, Et₂O or toluene solvent with K(O-*t*-Bu) afforded inferior results compared with those using the standard conditions (entries 12–17).

Table 1. Optimization of the reaction conditions for copper(I)-catalyzed boryl cyclization.^a



entry	ligand	base	solvent	yield of <i>syn-2a</i> (%) ^{b,c}
1 ^d	Xantphos	K(O- <i>t</i> -Bu)	DME	87(56)
2 ^e	Xantphos	K(O- <i>t</i> -Bu)	DME	66
3	none	K(O- <i>t</i> -Bu)	DME	0
4	PPh ₃	K(O- <i>t</i> -Bu)	DME	0
5	dppe	K(O- <i>t</i> -Bu)	DME	25
6	dppp	K(O- <i>t</i> -Bu)	DME	34
7	dppb	K(O- <i>t</i> -Bu)	DME	12
8	dppf	K(O- <i>t</i> -Bu)	DME	10
9	ICy•HCl	K(O- <i>t</i> -Bu)	DME	0
10 ^f	Xantphos		DME	0
11	Xantphos	none	DME	0
12	Xantphos	Na(O- <i>t</i> -Bu)	DME	70
13	Xantphos	KOMe	DME	19
14	Xantphos	KOEt	DME	39
15	Xantphos	K(O- <i>t</i> -Bu)	THF	85
16	Xantphos	K(O- <i>t</i> -Bu)	Et ₂ O	87
17	Xantphos	K(O- <i>t</i> -Bu)	toluene	84

^aConditions: **1a** (0.5 mmol), (pin)B-B(pin) (0.6 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), and base (0.6 mmol) in a solvent (1 mL) at 30°C. ^bDetermined by ¹H NMR analysis.

^cIsolated yield after esterification of the hydroxy group in the product **2a** is shown in parentheses. For details, see supporting information. ^dThe dr of the crude reaction mixture was determined to be *syn/anti* = 97:3 based on the ¹H NMR analysis. The dr of the crude reaction mixtures with ligands except for Xantphos could not be determined because of overlapping signals. ^eAmount of base used was 10 mol %. ^fCu(O-*t*-Bu) (1 equiv) was used instead of CuCl/K(O-*t*-Bu).

With the optimized conditions in hand, the substrate scope for this boryl cyclization was investigated (Table 2). Alkenyl aryl ketones with 3,5-xylyl, 2-naphthyl, 4-bromo- or 4-methoxy phenyl groups provided the desired products in moderate to good yields (79%, 75%, 62%, 75%, respectively, Table 2, entries 1–4). Furthermore, the corresponding minor *anti*-isomers were not detected by ¹H NMR analysis. However, the isolated yields of derivatized products were generally low due to instability of **2** under the silica-gel purification conditions (32, 23, 21, 20%, respectively). Unfortunately, only

aromatic ketone substrates gave the desired products in this reaction. γ -Alkenyl ketones containing an alkyl-, alkenyl- or alkynyl moiety instead of an aromatic group resulted in complex mixtures. These results can be attributed to possible competitive side reactions including 1,2-diboration reaction of ketone, protoboration of carbon-carbon multiple bonds, and aldol reactions.

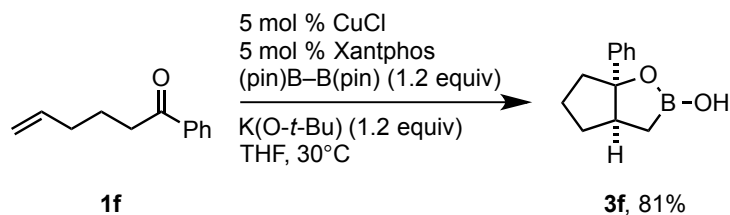
Table 2. Substrate scope for the copper(I)-catalyzed borylative cyclization of alkenyl aryl ketones.^a

entry	substrate (<i>R</i>)	product	yield (%)
1	1b (3,5-xylyl)	2b	79 (32)
2	1c (2-naphthyl)	2c	75 (23)
3	1d (4-BrC ₆ H ₄)	2d	62 (21)
4 ^b	1e (4-MeOC ₆ H ₄)	2e	75 (20)

^aReagents and conditions: Alkenyl ketone **1** (0.5 mmol), (pin)B–B(pin) (0.6 mmol), CuCl (0.025 mmol), Xantphos (0.025 mmol), and K(O-*t*-Bu) (0.6 mmol) in DME (1 mL) at 30°C. Yields were determined by ¹H NMR analysis of the crude product **2**, and isolated yields of the corresponding esterified products **4** are shown in parentheses. ^bIsolated yield of derivatized product from **2e** is shown in parentheses.

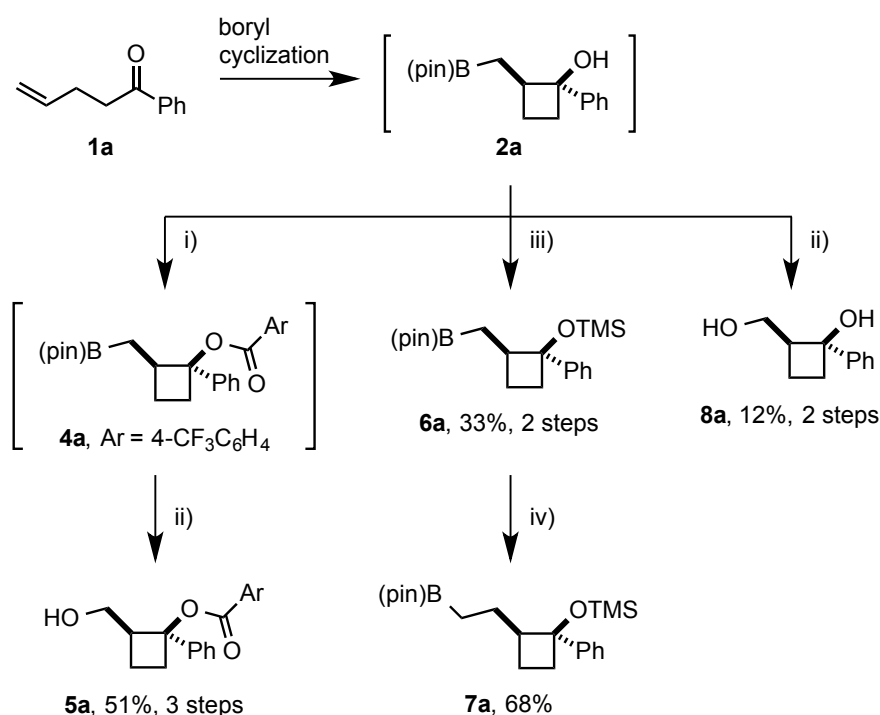
Reaction of δ -alkenyl phenyl ketone **1f** provided product **3f** bearing a bicyclic structure containing a 1,2-oxaborolane in high yield and with good diastereoselectivity (81%, Scheme 2).

Scheme 2. Reaction of δ -alkenyl phenyl ketone **1f**.



Further derivatization of the products from the crude mixtures was then investigated (Scheme 3). The crude product **4a** was subjected to NaBO₃ oxidation to afford the corresponding mono alcohol **5a** in good yield as a single isomer (51%, 3 steps). We also carried out TMS protection of the crude product **2a** to provide a 33% yield of the desired silylated product **6a** over 2 steps, followed by homologation to give **7a** in good yield (68%). Crude product **2a** also afforded the corresponding diol **8a** after NaBO₃ oxidation.

Scheme 3. Transformations of product **2a**.

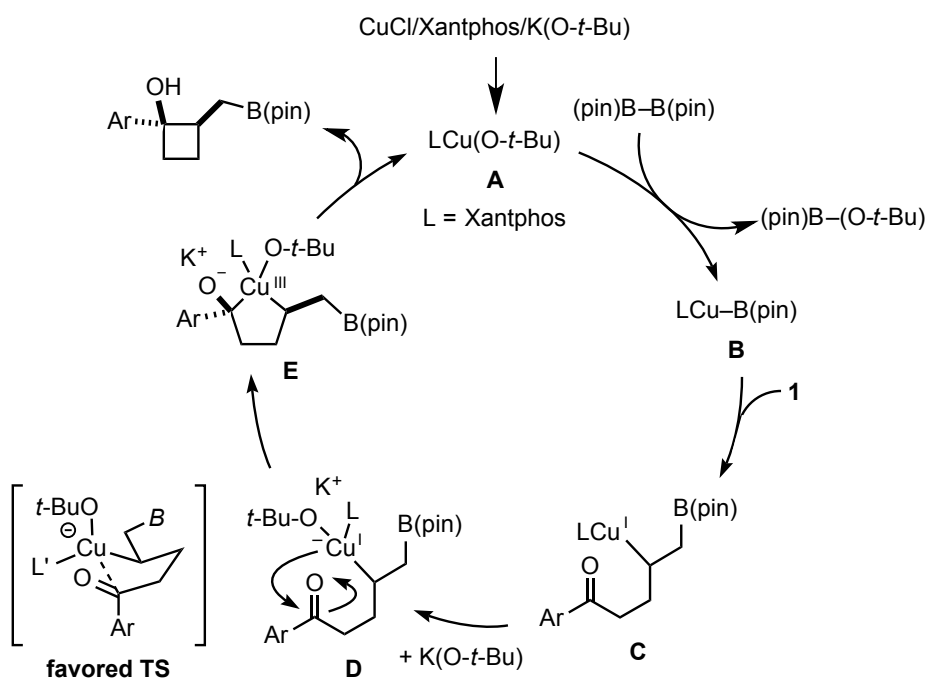


Reagents and conditions: (i) 4-(trifluoromethyl)benzoyl chloride (1.05 equiv), *i*-Pr₂NEt (1.05 equiv), DMAP (10 mol %), DME, 0°C, 3 h; (ii) NaBO₃·4H₂O (10 equiv), THF/H₂O, rt, 2 h; (iii) TMSOTf (5.0 equiv), 2,6-lutidine (10 equiv), CH₂Cl₂, 0°C, 3 h; (iv) ClCH₂Br (2.0 equiv), *n*-BuLi (1.5 equiv), THF, -78°C to rt, 19 h.

A proposed mechanism of the borylative cyclization is shown in Scheme 4. The reaction starts with the generation of Cu(O-*t*-Bu) complex **A** followed by σ -bond metathesis with a diboron species to form borylcopper(I) active species **B**. This then adds to the C-C double bond in **1** to form alkylcopper(I) species **C**. Subsequently, the *t*-butoxide base coordinates with the alkylcopper(I) species **C** to form a more nucleophilic *t*-butoxy(alkyl)cuprate **D**.¹⁹ This step would be facilitated by using strong base, which is compatible to the results shown in

Table 1, entries 10–14. In addition, Lewis acidity of the counter cations also might be involved in this step forming cuprate- π complex.¹⁹ Intramolecular nucleophilic attack of the copper(I) center on the carbonyl carbon would then occur, followed by reductive elimination of the resultant dialkylcopper(III) species **E** to lead to the formation of the boryl cyclization product. The high chemoselectivity with the Xantphos ligand may likely be attributed to the formation of a sterically congested borylcopper species.^{10d} This catalyst tuning would enable the preferential addition of intermediate **B** to the less sterically hindered alkene moiety over the more bulky aromatic ketone group. The high HOMO level of **B** with the Xantphos ligand is also important for alkene selectivity.^{10d} Regarding the origin of the *syn* selectivity, the favored transition state would go through less sterically hindered pathway, which leads to the observed high diastereoselectivity.

Scheme 4. Proposed mechanism of the borylative cyclization.



Summary

In conclusion, we have developed a novel method for preparing *syn*-1-aryl-2-(borylmethyl)cycloalkanols through a highly chemo-, regio-, and diastereoselective borylative cyclization of alkenyl ketones catalyzed by a copper(I)/Xantphos complex. This method provides rapid access to four- or five-membered-ring 2-(borylmethyl)cycloalkanols with high *syn* selectivity from simple starting materials. Although the isolation of the cyclized products is difficult, synthetic application should be possible using *in situ* transformations of the crude products. Development of effective transformations and further work toward an enantioselective synthesis are now ongoing in our group.

Experimental

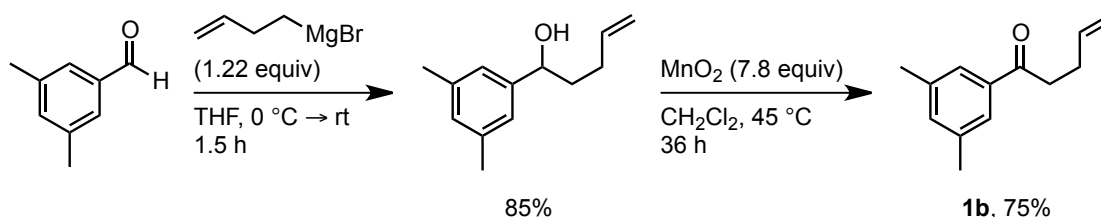
General.

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4A) prior to use. All reactions other than oxidation reaction were carried out in a nitrogen atmosphere. NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^1H : 392 MHz and ^{13}C : 99 MHz). Tetramethylsilane (^1H) and CDCl_3 (^{13}C) were employed as external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, $\geq 99\%$) and $\text{K}(\text{O}-t\text{-Bu})$ were respectively purchased from Sigma-Aldrich Co. and TCI, and used as received. Mesitylene was used as an internal standard to determine NMR yields. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. Recycle preparative gel permeation chromatography (GPC) was conducted with a JAI LC-9101 using CHCl_3 as the eluent. High-resolution mass spectra were recorded at the Center for Instrumental Analysis, Hokkaido University.

Preparation of Substrates.

Substrates were prepared from the corresponding aromatic aldehydes and Grignard reagents²⁰ and manganese dioxide oxidation²¹ according to the literature procedures.

1-(3,5-Dimethylphenyl)pent-4-en-1-one (**1b**).



Homoallylmagnesium bromide in THF (0.9 M, 40 mL, 36.5 mmol, 1.22 equiv) was added to 3,5-dimethylbenzaldehyde (4.03g, 30.1 mmol, 1.0 equiv) at 0 °C under a nitrogen atmosphere. After stirring for 1.5 h at room temperature, saturated NH₄Cl aq. was then added and the mixture was extracted with EtOAc three times and the combined organic layer was washed with brine and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, EtOAc/hexane, 0 : 100–10 : 90) to afford the corresponding alcohol (4.88 g, 25.6 mmol, 85%). This alcohol (4.88 g, 25.6 mmol, 1.0 equiv) was added to a solution of manganese oxide (17.3 g, 199.6 mmol, 7.8 equiv) in CH₂Cl₂ (50 mL) at room temperature. After stirring for 36 h at 45 °C, the mixture was filtered through Celite. The crude material was purified by flash column chromatography (SiO₂, EtOAc/hexane, 0 : 100–4 : 96) to afford the corresponding alkenyl ketone **1b** (3.63 g, 19.3 mmol, 75%) as a white solid.

¹H NMR of **1b** (392 MHz, CDCl₃, δ): 2.37 (s, 6H), 2.45–2.53 (m, 2H), 3.05 (t, *J* = 7.4 Hz, 2H), 5.01 (dd, *J* = 1.6, 10.2 Hz, 1H), 5.09 (dq, *J* = 1.6, 17.1 Hz, 1H), 5.90 (ddt, *J* = 6.7, 10.2, 16.9 Hz, 1H), 7.19 (s, 1H), 7.57 (s, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 21.2 (CH₃), 28.2 (CH₂), 37.8 (CH₂), 115.2 (CH₂), 125.8 (CH), 134.6 (CH), 137.0 (C), 137.4 (CH), 138.1 (C), 199.8 (C). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₃H₁₆O, 188.1201; found, 188.1197.

General Borylative Cyclization Procedures.

Procedures for Copper(I)-Catalyzed Diastereoselective Boryl Cyclization of **1a** (Table 1): Procedure A

Copper chloride (2.5 mg, 0.025 mmol, 5 mol %) and bis(pinacolato)diboron (152.2 mg, 0.60 mmol, 1.2 equiv), Xantphos (14.5 mg, 0.025 mmol, 5 mol %), K(O-*t*-Bu) (67.6 mg, 0.60 mmol, 1.2 equiv) were placed in an oven-dried reaction vial. K(O-*t*-Bu) was used in a glove box under argon atmosphere. After the vial was sealed with a screw cap containing a teflon-coated rubber septum, the vial was removed from the glove box and connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen three times. DME (1.0 mL) was added in the vial through the rubber septum using a syringe. After 30 minutes, **1a** (80.6 mg, 0.50 mmol, 1.0 equiv) was added to the mixture at 30 °C. After the reaction was complete, the reaction mixture was passed through a short silica gel column eluting with Et₂O. The residue was concentrated under reduced pressure. NMR yield was determined by ¹H NMR analysis of the crude reaction mixture (*syn*-**2a**; 87%) with mesitylene (31.6 mg, 0.26 mmol) was used as an internal standard.

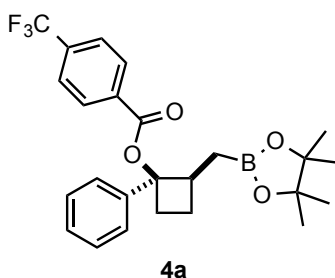
Procedures for Sequential Borylative Cyclization/Esterification of **1a** (Table 1, entry 1): Procedure B

Borylative cyclization reaction was performed according to the procedures described above. THF (1.0 mL) was used as a solvent instead of DME. After the reaction was complete, the reaction mixture was cooled to 0 °C. A solution of DMAP (5.6 mg, 0.05 mmol, 10 mol %) in THF (1.0 mL) and *i*-Pr₂NEt (67.2 mg, 0.52 mmol, 1.03 equiv) was added to the mixture. Then, 4-trifluoromethyl benzoyl chloride (110.5 mg, 0.53 mmol, 1.05 equiv) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column chromatography using florisil eluting with Et₂O. The crude material was purified by (SiO₂, EtOAc/Hex = 0 : 100–3 : 97) to give the corresponding esterification product *syn*-**4a** (129.7 mg, 0.282 mmol, 56% yield) as a white solid.

Characterization of Borylation Products.

In the case of substrate **1c** and **1d**, NMR yield was determined by ^1H NMR analysis of the reaction mixture. 1,3,5-Triisopropylbenzene was used as an internal standard.

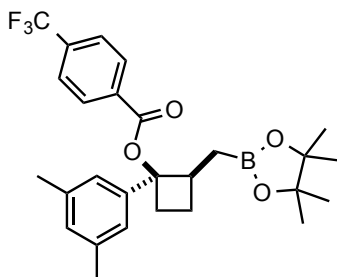
syn-1-Phenyl-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]cyclobutyl 4-(trifluoromethyl)benzoate (**4a**).



Alkenyl ketone **1a** (80.6 mg, 0.5 mmol, 1.0 equiv) was subjected to the borylation procedure described above. The crude material was purified by (SiO_2 , EtOAc/hexane = 0 : 100–3 : 97) to give the corresponding esterification product *syn*-**4a** [129.7 mg, 0.282 mmol, 56% yield, NMR yield of *syn*-**2a** in the crude reaction mixture; 87%] as a white solid.

^1H NMR (392 MHz, CDCl_3 , δ): 1.25 (s, 6H), 1.26 (s, 6H), 1.36 (dd, J = 10.0, 15.9 Hz, 1H), 1.46 (dd, J = 6.3, 15.7 Hz, 1H), 1.68–1.79 (m, 1H), 2.06–2.16 (m, 1H), 2.62–2.72 (m, 1H), 2.80–2.91 (m, 1H), 2.97–3.07 (m, 1H), 7.21–7.28 (m, 1H), 7.30–7.36 (m, 2H), 7.47–7.51 (m, 2H), 7.68 (d, J = 7.8 Hz, 2H), 8.20 (d, J = 7.8 Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 12.5 (br, B– CH_2), 23.0 (CH_2), 24.80 (CH_3), 24.86 (CH_3), 30.2 (CH_2), 44.0 (CH), 83.2 (C), 85.4 (C), 123.6 (q, $J_{\text{C-F}}$ = 273.8 Hz, C), 125.1 (CH), 125.2–152.4 (m, CH), 127.2 (CH), 128.3 (CH), 130.0 (CH), 134.23 (q, $J_{\text{C-F}}$ = 32.7 Hz, C), 134.28 (C), 143.1 (C), 163.8 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{28}\text{O}_4\text{BF}_3\text{Na}$, 482.1961; found, 482.1965.

syn-1-(3,5-Dimethylphenyl)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]cyclobutyl 4-(trifluoromethyl)benzoate (**4b**).

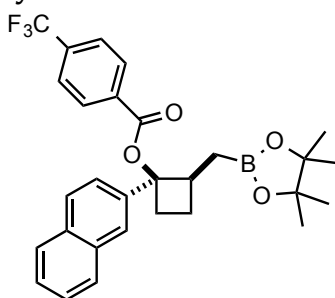


4b

Borylative cyclization reaction of **1b** was performed on 1.0 mmol scale. Alkenyl ketone **1b** (188.3 mg, 1.0 mmol, 1.0 equiv) was subjected to the borylation procedure described above. The crude material was purified by preparative thin-layer chromatography (preparative TLC, EtOAc/hexane 20 : 80, 1 h) to give the corresponding esterification product *syn*-**4b** [156.1 mg, 0.32 mmol, 32%, NMR yield of *syn*-**2b** in the crude reaction mixture; 79%] as a white solid.

^1H NMR (392 MHz, CDCl_3 , δ): 1.25 (s, 6H), 1.26 (s, 6H), 1.33 (dd, $J = 9.8, 15.7$ Hz, 1H), 1.45 (dd, $J = 6.3, 15.7$ Hz, 1H), 1.65–1.76 (m, 1H), 2.04–2.15 (m, 1H), 2.29 (s, 6H), 2.58–2.67 (m, 1H), 2.76–2.87 (m, 1H), 2.96–3.06 (m, 1H), 6.88 (s, 1H), 7.09 (s, 2H), 7.68 (d, $J = 7.8$ Hz, 2H), 8.21 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 12.5 (br, B– CH_2), 21.4 (CH_3), 23.0 (CH_2), 24.8 (CH_3), 24.9 (CH_3), 30.3 (CH_2), 44.0 (CH), 83.1 (C), 85.3 (C), 122.8 (CH), 123.6 (q, $J_{\text{C-F}} = 273.8$ Hz, C), 125.1–152.4 (m, CH), 129.0 (CH), 130.0 (CH), 134.1 (q, $J_{\text{C-F}} = 32.7$ Hz, C), 134.4 (C), 137.6 (C), 143.1 (C), 163.8 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{32}\text{O}_4\text{BF}_3\text{Na}$, 510.2274; found, 510.2281.

syn-1-(Naphthalen-2-yl)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]cyclobutyl 4-(trifluoromethyl)benzoate (**4c**).

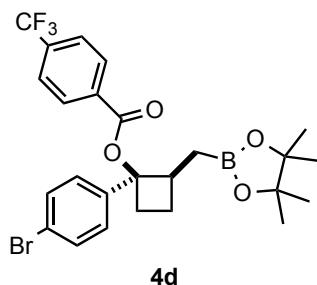


4c

Alkenyl ketone **1c** (104.8 mg, 0.5 mmol, 1.0 equiv) was subjected to the borylation procedure described above. The crude material was purified by preparative TLC (EtOAc/hexane 20 : 80, 1 h) to give the corresponding esterification product *syn*-**4c** (58.4 mg, 0.11 mmol, 23%, NMR yield of *syn*-**2c** in the crude reaction mixture; 75%) as a white solid.

^1H NMR (392 MHz, CDCl_3 , δ): 1.25 (s, 6H), 1.26 (s, 6H), 1.41 (dd, $J = 9.8, 15.7$ Hz, 1H), 1.54 (dd, $J = 6.3, 15.7$ Hz, 1H), 1.73–1.84 (m, 1H), 2.11–2.23 (m, 1H), 2.71–2.82 (m, 1H), 2.91–3.02 (m, 1H), 3.12–3.22 (m, 1H), 7.40–7.48 (m, 2H), 7.58–7.64 (m, 1H), 7.68 (d, $J = 8.2$ Hz, 2H), 7.75–7.87 (m, 3H), 7.99 (s, 1H), 8.21 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 12.7 (br, B- CH_2), 23.0 (CH_2), 24.8 (CH_3), 24.9 (CH_3), 30.4 (CH_2), 43.9 (CH), 83.2 (C), 85.3 (C), 123.55 (CH), 123.63 (q, $J_{\text{C-F}} = 273.8$ Hz, C), 124.0 (CH), 125.1–125.4 (m, CH), 125.9 (CH), 126.1 (CH), 127.5 (CH), 128.2 (CH), 130.0 (CH), 132.6 (C), 133.0 (C), 134.23 (C), 134.25 (q, $J_{\text{C-F}} = 32.7$ Hz, C), 140.3 (C), 163.9 (C). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{30}\text{O}_4\text{BF}_3\text{Na}$, 532.2118; found, 532.2133.

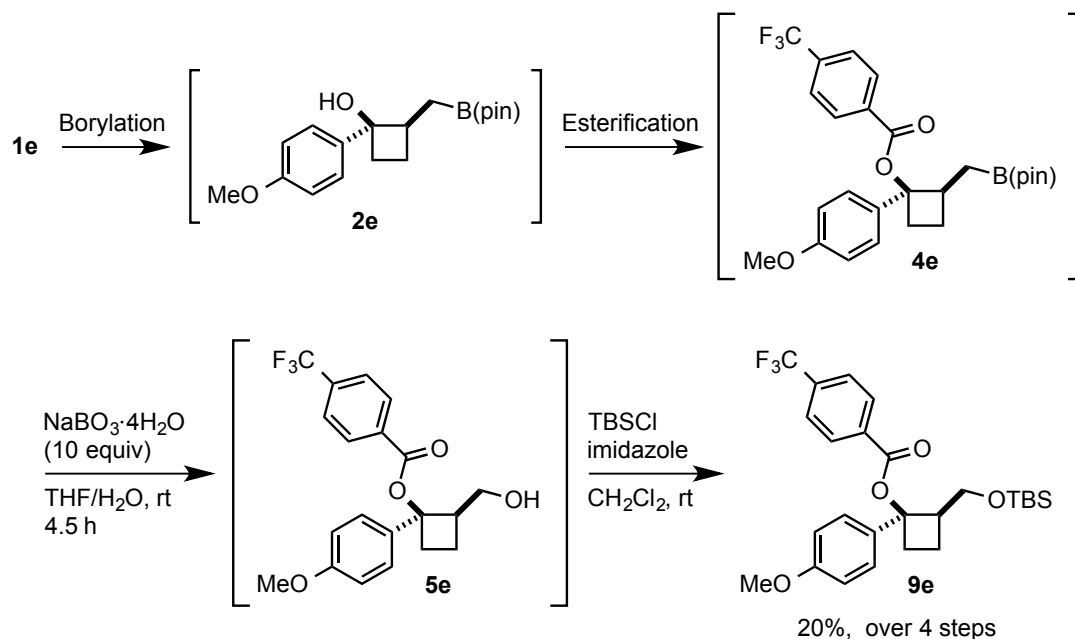
syn-1-(4-Bromophenyl)-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]cyclobutyl 4-(trifluoromethyl)benzoate (**4d**).



Alkenyl ketone **1d** (119.6 mg, 0.5 mmol, 1.0 equiv) was subjected to the borylation procedure described above. The crude material was purified by preparative TLC (EtOAc/hexane 20 : 80, 1 h) to give the corresponding esterification product *syn*-**4d** (57.2 mg, 0.11 mmol, 21%, NMR yield of *syn*-**2e** in the crude reaction mixture; 62%) as a white solid.

^1H NMR (392 MHz, CDCl_3 , δ): 1.25 (s, 6H), 1.26 (s, 6H), 1.33 (dd, $J = 9.6, 15.5$ Hz, 1H), 1.43 (dd, $J = 6.5, 15.5$ Hz, 1H), 1.68–1.79 (m, 1H), 2.04–2.15 (m, 1H), 2.61–2.71 (m, 1H), 2.78–2.88 (m, 1H), 2.91–3.00 (m, 1H), 7.35–7.40 (m, 2H), 7.43–7.48 (m, 2H), 7.69 (d, $J = 8.6$ Hz, 2H), 8.18 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 12.5 (br, B– CH_2), 23.0 (CH_2), 24.8 (CH_3), 24.9 (CH_3), 30.3 (CH_2), 43.8 (CH), 83.3 (C), 84.8 (C), 121.3 (C), 123.6 (q, $J_{\text{C-F}} = 273.8$ Hz, C), 125.2–152.5 (m, CH), 127.1 (CH), 130.0 (CH), 131.4 (CH), 134.0 (C), 134.4 (q, $J_{\text{C-F}} = 33.0$ Hz, C), 142.2 (C), 163.8 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{27}\text{O}_4\text{BBrF}_3\text{Na}$, 560.1066; found, 560.1072.

syn-2-[(*tert*-Butyldimethylsilyl)oxy]methyl]-1-(4-methoxyphenyl)cyclobutyl 4-(trifluoromethyl)benzoate (**9e**).

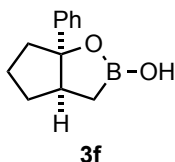


The borylation/esterification of **1e** was performed according to the procedure **B**. Alkenyl ketone **1e** (94.5 mg, 0.5 mmol, 1.0 equiv) was subjected to the borylative cyclization/esterification. Following NaBO_3 oxidation was performed according to the literature procedure.²² In a reaction vial, the crude mixture of **4e** was dissolved in THF/H₂O (3 : 2, 5 mL). $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (763.1 mg, 5.0 mmol, 10 equiv) was then added at room temperature. After stirred for 4.5 h, the reaction mixture was passed through a short silica gel column eluting with Et₂O. The crude material was purified by flash column chromatography (SiO₂, Et₃N/hexane 3 : 97, EtOAc/Hex 0 : 100–25 : 75, The eluent was dried over MgSO₄ for 1 h prior to use.) to obtain corresponding alcohol **5e** containing pinacol as an impurity (42.1 mg). The subsequent TBS protection of the crude material gave the corresponding product *syn*-**9e** [49.3 mg, 0.100 mmol, 20% yield, NMR yield of *syn*-**5e** in the crude reaction mixture; 75%].

¹H NMR (392 MHz, CDCl₃, δ): 0.092 (s, 3H), 0.13 (s, 3H), 0.93 (s, 9H), 1.82 (sep, J = 5.6 Hz, 1H), 1.88–1.99 (m, 1H), 2.69–2.80 (m, 1H), 2.83–2.92 (m, 1H), 2.97–3.06 (m, 1H), 3.79 (s, 3H), 3.91 (dd, J = 6.0, 10.3 Hz, 1H), 4.23 (dd, J = 8.1, 10.5 Hz, 1H), 6.87 (d, J = 9.1 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 8.13 (d, J = 8.2 Hz, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): –5.34 (CH₃), –5.31 (CH₃), 17.7 (CH₂), 18.3 (C), 25.9 (CH₃), 30.6 (CH₂), 48.8 (CH), 55.2 (CH₃), 62.6 (CH₂), 84.3 (C), 113.5 (CH), 125.2 (CH), 125.3 (CH), 126.2 (q, $J_{\text{C-F}}$ = 251.8 Hz, C), 127.7 (CH), 129.9 (CH),

134.2 (q, $J_{\text{C-F}} = 32.6$ Hz, C), 134.4 (C), 134.9 (C), 158.8 (C), 163.8 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{33}\text{O}_4\text{F}_3\text{NaSi}$, 517.1992; found, 517.1995.

Syn-3f.

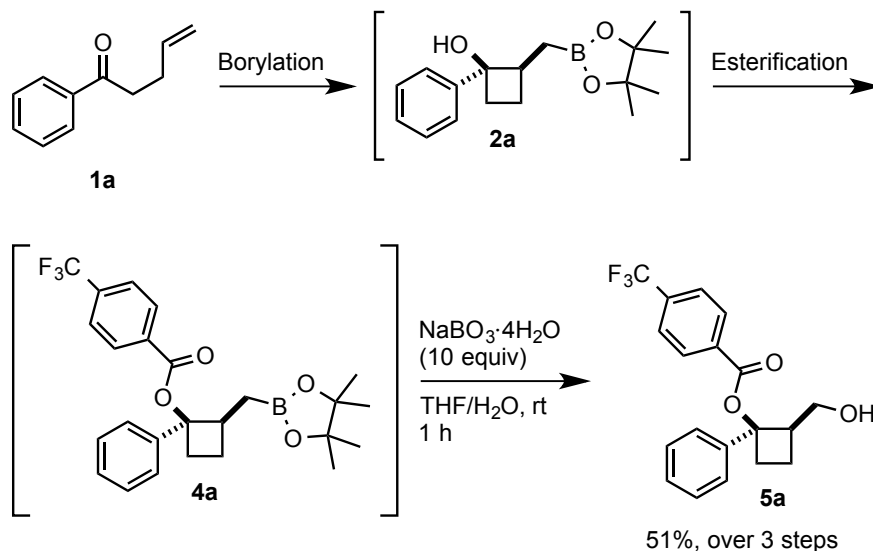


Alkenyl ketone **1f** (83.5 mg, 0.48 mmol, 1.0 equiv) was subjected to the borylation procedure described above. The crude material was purified by flash column chromatography (SiO_2 , EtOAc/hexane, 5 : 85–10 : 90) to give the corresponding oxaborolane *syn*-**3f** (78.1 mg, 0.39 mmol, 81%) as a colorless oil.

^1H NMR (396 MHz, $\text{CD}_3\text{CN}/\text{D}_2\text{O}$, δ): 0.50–0.61 (m, 1H), 0.86–1.00 (m, 2H), 1.20–1.32 (m, 1H), 1.50–1.67 (m, 2H), 1.71–1.94 (m, 2H), 2.36–2.48 (m, 1H), 6.98–7.07 (m, 1H), 7.08–7.21 (m, 4H). The proton directly attached to the oxygen atom was not detected. ^{13}C NMR (100 MHz, $\text{CD}_3\text{CN}/\text{D}_2\text{O}$, δ): 25.3 (CH_2), 36.1 (CH_2), 43.6 (CH_2), 49.8 (CH), 95.7 (C), 124.6 (CH), 126.7 (CH), 128.3 (CH), 147.6 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.^{24,25} HRMS–EI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2\text{B}$, 202.1274; found, 202.1277.

Procedures for Functionalization of Borylation Products.

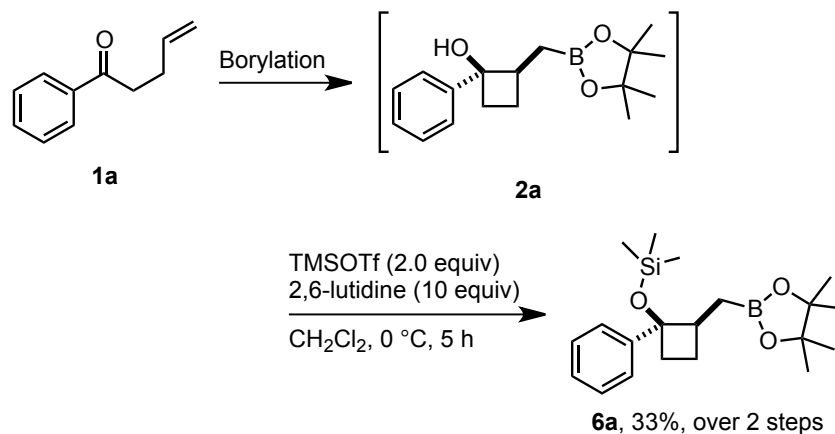
Procedure for the Synthesis of Mono Alcohol 5a through the Oxidation of 4a.



The borylation/esterification of **1a** was performed according to the procedure **B**. Alkenyl ketone **1a** (79.3 mg, 0.49 mmol, 1.0 equiv) was subjected to the borylation procedure described above. The NaBO_3 oxidation was performed according to the literature procedure.²² In a reaction vial, the crude mixture of **4a** (0.49 mmol scale, 87% NMR yield, 1.0 equiv) was dissolved in THF/ H_2O (3 : 2, 5 mL). $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (764.5 mg, 5.0 mmol, 10 equiv) was then added at room temperature. After stirred for 1 h, the reaction mixture was passed through a short silica gel column eluting with Et_2O . The crude material was purified by flash column chromatography (SiO_2 , Et_3N /hexane 3 : 97, EtOAc /Hex 0 : 100–15 : 85, Eluent was dried over MgSO_4 for 1 h prior to use.) to obtain corresponding alcohol **5a** (88.4 mg, 0.252 mmol, 51%) as a viscous oil.

^1H NMR (396 MHz, CDCl_3 , δ): 1.81–1.93 (m, 1H), 1.95–2.08 (m, 1H), 2.46 (brs, 1H), 2.68–2.80 (m, 1H), 2.83–2.95 (m, 1H), 3.17 (quintet, $J = 7.1$ Hz, 1H), 3.87 (dd, $J = 5.1, 11.5$ Hz, 1H), 3.99–4.09 (m, 1H), 7.24–7.32 (m, 1H), 7.37 (t, $J = 7.7$ Hz, 2H), 7.55 (d, $J = 7.9$ Hz, 2H), 7.70 (d, $J = 7.9$ Hz, 2H), 8.13 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 17.8 (CH_2), 32.0 (CH_2), 47.5 (CH), 62.7 (CH_2), 86.1 (C), 123.5 (q, $J_{\text{C-F}} = 274.0$ Hz, C), 125.4–125.6 (m, CH), 125.6 (CH), 127.7 (CH), 128.5 (CH), 130.0 (CH), 133.7 (C), 134.6 (q, $J_{\text{C-F}} = 32.9$ Hz, C), 142.3 (C), 164.5 (C). HRMS–ESI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{17}\text{O}_3\text{F}_3$, 350.1135; found, 350.1136.

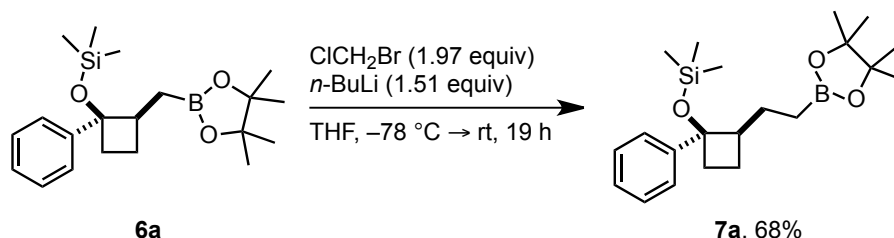
Procedure for the Synthesis of Silylated Product 6a through the Silyl Protection of 2a.



Alkenyl ketone **1a** (322.2 mg, 2.01 mmol, 1.0 equiv) was subjected to the borylation procedure described above. In an oven-dried reaction vial, the crude mixture of **2a** (77% NMR yield, 1.0 equiv) was placed in a reaction vial and then diluted with CH₂Cl₂ (20 mL) in a nitrogen atmosphere. 2,6-Lutidine (2.32 mL, 20 mmol, 10 equiv) was added to the solution and then TMSOTf (1.81 mL, 10 mmol, 5 equiv) was added dropwise at 0 °C. After stirred for 3 h, the mixture was passed through a short silica gel column eluting with Et₂O. The crude material was purified by flash column chromatography (SiO₂, EtOAc/hexane, 0 : 100–2 : 98) followed by GPC to give the corresponding silylated product **6a** (235.9 mg, 0.65 mmol, 33%) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): −0.06 (s, 9H), 1.09 (dd, *J* = 8.6, 16.1 Hz, 1H), 1.21 (dd, *J* = 7.8, 15.7 Hz, 1H), 1.24 (s, 12H), 1.50–1.60 (m, 1H), 1.84–1.94 (m, 1H), 2.28–2.38 (m, 1H), 2.52–2.62 (m, 1H), 2.62–2.71 (m, 1H), 7.18–7.24 (m, 1H), 7.27–7.34 (m, 2H), 7.46–7.51 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 1.6 (CH₃), 12.5 (br, B–CH₂), 22.3 (CH₂), 24.7 (CH₃), 25.0 (CH₃), 32.4 (CH₂), 45.3 (CH), 79.2 (C), 82.6 (C), 125.6 (CH), 126.4 (CH), 127.8 (CH), 147.5 (C). HRMS–EI (*m/z*): [*M*]⁺ calcd for C₂₀H₃₃BO₃Si, 360.2296; found, 360.2289.

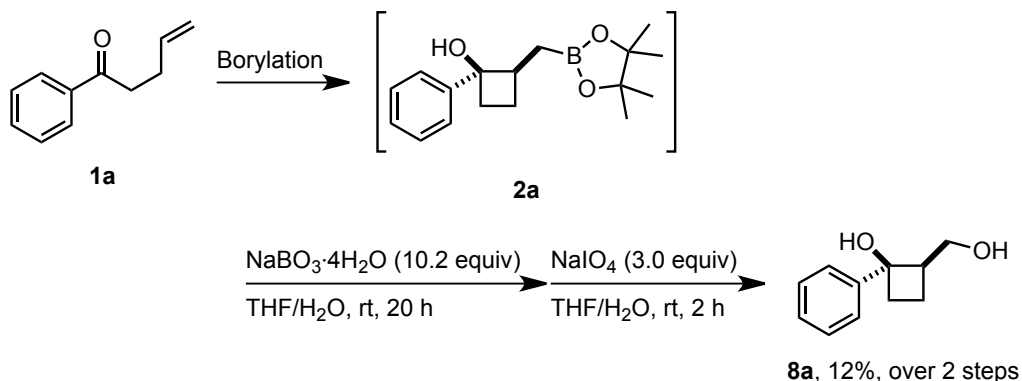
Procedure for the Synthesis of Alkyl Boronate 7a through the One-Carbon Homologation of 6a.



The one-carbon homologation was performed according to the literature procedure.²³ In an oven-dried reaction vial, **6a** (92.6 mg, 0.26 mmol, 1.0 equiv) and bromochloromethane (65.6 mg, 0.5 mmol, 1.97 equiv) were dissolved in dry THF (2 mL) in nitrogen atmosphere. After the mixture was cooled to $-78\text{ }^{\circ}\text{C}$, *n*-BuLi in hexane (1.55 M, 250 μL , 0.39 mmol, 1.51 equiv) was added dropwise. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min, then warmed to room temperature and stirred for 19 h. The reaction mixture was quenched by addition of saturated NH_4Cl aq., extracted three times with Et_2O , dried over MgSO_4 , and filtered. The crude material was purified by flash column chromatography (SiO_2 , EtOAc /hexane, 0 : 100–1.5 : 98.5) to give the corresponding alkyl boronate **7a** (65.3 mg, 0.17 mmol, 68%) as a colorless oil.

^1H NMR (392 MHz, CDCl_3 , δ): -0.07 (s, 9H), 0.68 – 0.83 (m, 2H), 1.23 (s, 12H), 1.56 – 1.68 (m, 2H), 1.78 – 1.92 (m, 2H), 2.23 – 2.33 (m, 2H), 2.54 – 2.64 (m, 1H), 7.18 – 7.23 (m, 1H), 7.27 – 7.33 (m, 2H), 7.40 – 7.45 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 1.6 (CH_3), 20.5 (CH_2), 24.1 (CH_2), 24.7 (CH_3), 24.8 (CH_3), 32.5 (CH_2), 51.1 (CH), 79.6 (C), 82.8 (C), 125.5 (CH), 126.4 (CH), 127.9 (CH), 148.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation.^{24,25} HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{35}\text{BO}_3\text{Si}$, 374.2453; found, 374.2443.

Procedure for the Synthesis of Diol **8a** through the Oxidation of **2a**.



Alkenyl ketone **1a** (80.3 mg, 0.5 mmol, 1.0 equiv) was subjected to the borylation procedure described above. In a reaction vial, the crude mixture of **2a** (81% NMR yield) was dissolved in THF/H₂O (3 : 2, 5 mL). NaBO₃·4H₂O (787.1 mg, 5.1 mmol, 10.2 equiv) was then added at room temperature. After the reaction was complete, MgSO₄ was added to the reaction mixture and the mixture was passed through a short silica gel column eluting with MeOH/CHCl₃ (5 : 95). The crude material was used directly for the next step without further purification. In a reaction vial, the crude mixture was dissolved in THF/H₂O (4 : 1, 1.3 mL). NaIO₄ (321.1 mg, 1.5 mmol, 3.0 equiv) was then added at room temperature, and then stirred at room temperature for 2 h. After the reaction was complete, MgSO₄ was added to the reaction mixture and the mixture was passed through a short silica gel column eluting with MeOH/CHCl₃ (5 : 95). The crude material was purified by flash column chromatography (SiO₂, EtOAc/hexane, 15 : 85–17 : 83) followed by GPC to give the corresponding diol **8a** (10.6 mg, 0.06 mmol, 12%) as a white solid.

¹H NMR (392 MHz, CDCl₃, δ): 1.81–1.98 (m, 2H), 2.30–2.40 (m, 1H), 2.49–2.71 (m, 2H), 2.74–2.91 (m, 2H), 3.86–4.03 (m, 2H), 7.24–7.32 (m, 1H), 7.34–7.42 (m, 2H), 7.49–7.56 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.9 (CH₂), 34.4 (CH₂), 46.6 (CH), 63.1 (CH₂), 78.6 (C), 124.9 (CH), 127.2 (CH), 128.5 (CH), 146.7 (C). HRMS–ESI (*m/z*): [M–H]⁺ calcd for C₁₁H₁₃O₂, 177.0921; found, 177.0918.

Single Crystal X-Ray Structural Analysis.

Single crystal X-ray structural analysis was carried out on a Rigaku R-Axis RAPID diffractometer using graphite monochromated Mo-K radiation. The structure was solved by direct methods and expanded using Fourier techniques. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL-97.²⁶

The relative configuration of **4a** was determined by the single crystal X-ray analysis.

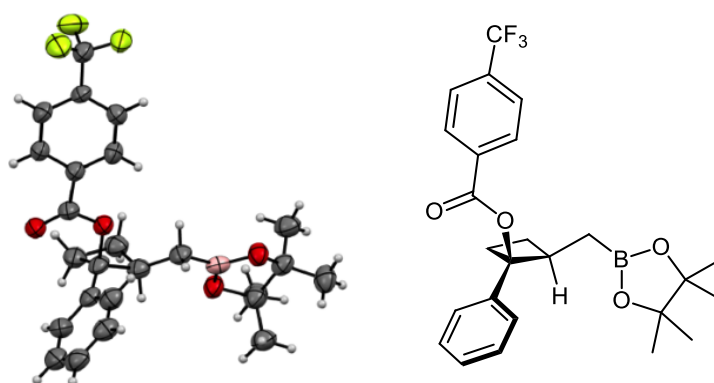


Figure S1. X-ray crystal structure of the boryl cyclization product **2a** after esterification.

Table S1. Summary of X-ray crystallographic data of **4a**.

Compound	4a
CCDC Name	CCDC 1043288
Determined Configuration	relative
Empirical Formula	C ₂₅ H ₂₈ BF ₃ O ₄
Formula Weight	460.30
Crystal System	monoclinic
Crystal Size / mm	0.510 × 0.118 × 0.096
<i>a</i> / Å	23.269(5)
<i>b</i> / Å	7.011(2)
<i>c</i> / Å	28.704(6)
<i>a</i> / °	90

$b / ^\circ$	95.65(2)
$g / ^\circ$	90
$V / \text{\AA}^3$	4660(2)
Space Group	$I2/a$ (#15)
Z value	8
$D_{\text{calc}} / \text{g cm}^{-3}$	1.312
Temperature / K	123
$2\theta_{\text{max}} / ^\circ$	55.0
μ (MoK α) / cm^{-1}	1.022
	Total : 16744
No. of Reflections	Unique :
Measured	4084
	(R_{int} =
	0.1552)
No. of Observations	4084
(All reflections)	
Residuals: R_1	
($I > 2.00\sigma(I)$)	0.0993
Residuals: wR_2	
(All reflections)	0.3234
Goodness of Fit Indicator	1.018
(GOF)	
Maximum peak in	
Final Diff. Map / $\text{\AA}^3$	0.35 e^-
Minimum peak in	
Final Diff. Map / $\text{\AA}^3$	-0.33 e^-
Flack parameter	*

*We did not obtain the Flack parameter because the purpose of this analysis is to determine the relative configuration.

References and Notes

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- (17) **Typical Procedure for Borylative Cyclization/Esterification of Aryl Alkenyl Ketones** CuCl (0.025 mmol) and (pin)B-B(pin) (0.60 mmol), Xantphos (0.025 mmol), K(O-*t*-Bu) (0.60 mmol) were placed in an oven-dried vial in a glove box. After the vial was removed from the glove box, DME (1.0 mL) was added to the vial and stirred for 30 min. Then, **1a** (0.50 mmol) was added to the mixture at 30 °C. After the reaction was complete, the reaction mixture was cooled to 0 °C. After that, DMAP [0.05 mmol in THF (1 mL)] and *i*-Pr₂NEt (0.52 mmol) were added to the mixture, and 4-trifluoromethyl benzoyl chloride (0.53 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short florisil column using eluting with Et₂O. The crude material was purified by silica gel column chromatography to give *syn*-**4a** (129.7 mg, 0.282 mmol, 56% yield) as a white solid.
- ¹H NMR (392 MHz, CDCl₃, δ): 1.25 (s, 6H), 1.26 (s, 6H), 1.36 (dd, *J* = 10.0, 15.9 Hz, 1H), 1.46 (dd, *J* = 6.3, 15.7 Hz, 1H), 1.68–1.79 (m, 1H), 2.06–2.16 (m, 1H), 2.62–2.72 (m, 1H), 2.80–2.91 (m, 1H), 2.97–3.07 (m, 1H), 7.21–7.28 (m, 1H), 7.30–7.36 (m, 2H), 7.47–7.51 (m, 2H), 7.68 (d, *J* = 7.8 Hz,

- 2H), 8.20 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 12.5 (br, B-CH₂), 23.0 (CH₂), 24.80 (CH₃), 24.86 (CH₃), 30.2 (CH₂), 44.0 (CH), 83.2 (C), 85.4 (C), 125.0 (q, $J_{\text{C-F}} = 273.8$ Hz, C), 125.1 (CH), 125.2–152.4 (m, CH), 127.2 (CH), 128.3 (CH), 130.0 (CH), 134.22 (q, $J_{\text{C-F}} = 32.7$ Hz, C), 134.28 (C), 143.1 (C), 163.8 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{28}\text{O}_4\text{BF}_3\text{Na}$, 482.1961; found, 482.1965.
- (18) Several derivatization methods were examined to improve the isolated yield, but these were not successful.
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List of Publications

Chapter 1

Stereodivergent Hydrodefluorination of *gem*-Difluoroalkenes: Selective Synthesis of (*Z*)- and (*E*)-Monofluoroalkenes

Kojima, R.; Kubota, K.; Ito, H.

Chem. Commun. **2017**, 53, 10688.

Chapter 2

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

Kojima, R.; Akiyama, S.; Ito, H.

To be submitted.

Chapter 3

Copper(I)-Catalyzed Diastereoselective Borylative *Exo*-Cyclization of Alkenyl Aryl Ketones

Yamamoto, E.; **Kojima, R.;** Kubota, K.; Ito, H.

Synlett **2016**, 27, 272–276.

Other Publications

1.

Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allyl Acylals: An Efficient Approach for Enantioenriched α -Chiral γ -Acetoxyallylboronates

Takenouchi, Y.; **Kojima, R.;** Momma, R.; Ito, H.

Synlett **2017**, 28, 270–274.

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